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Multidrug-resistant *Pseudomonas aeruginosa* bloodstream infections: risk factors and mortality

M. TUMBARELLO[1]*, E. REPETTO[2], E. M. TRECARICHI[1], C. BERNARDINI[2], G. DE PASCALE[1], A. PARISINI[2], M. ROSSI[1], M. P. MOLINARI[3], T. SPANU[4], C. VISCOLI[2], R. CAUDA[1] AND M. BASSETTI[2]

[1] *Institute of Infectious Diseases, Catholic University of the Sacred Heart, Roma, Italy*
[2] *Infectious Diseases Division, S. Martino Hospital and University of Genoa School of Medicine, Genoa, Italy*
[3] *Laboratory Unit, S. Martino Hospital, Genoa, Italy*
[4] *Institute of Microbiology, Catholic University of the Sacred Heart, Roma, Italy*

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SUMMARY

We retrospectively studied patients diagnosed with *P. aeruginosa* bloodstream infections (BSIs) in two Italian university hospitals. Risk factors for the isolation of multidrug-resistant (MDR) or non-MDR *P. aeruginosa* in blood cultures were identified by a case-case-control study, and a cohort study evaluated the clinical outcomes of such infections. We identified 106 patients with *P. aeruginosa* BSI over the 2-year study period; 40 cases with MDR *P. aeruginosa* and 66 cases with non-MDR *P. aeruginosa* were compared to 212 controls. Independent risk factors for the isolation of MDR *P. aeruginosa* were: presence of central venous catheter (CVC), previous antibiotic therapy, and corticosteroid therapy. Independent risk factors for non-MDR *P. aeruginosa* were: previous BSI, neutrophil count $<500/mm^3$, urinary catheterization, and presence of CVC. The 21-day mortality rate of all patients was 33·9%. The variables independently associated with 21-day mortality were presentation with septic shock, infection due to MDR *P. aeruginosa*, and inadequate initial antimicrobial therapy.

Key words: Antibiotic resistance, bloodstream infections, *Pseudomonas*.

INTRODUCTION

Bloodstream infection (BSI) caused by *Pseudomonas aeruginosa* is a serious and life-threatening condition, especially in immunocompromised hosts and populations with predisposing conditions [1–4]. *P. aeruginosa* is also one of the main organisms responsible for drug-resistant nosocomial infections, being the third most frequently isolated pathogen from blood culture among Gram-negative rods and the seventh among all pathogens [4, 5]. These infections occur more frequently in patients with severe immunodeficiency, older age, previous antimicrobial therapy, and presence of central venous catheter (CVC) or urinary device [6, 7]. In addition to being intrinsically resistant to several antimicrobial agents, *P. aeruginosa* can acquire resistance to multiple (or even all) antibiotics, and multidrug-resistant (MDR) strains, which were first reported in patients with cystic fibrosis, are increasing in frequency [5, 6, 8, 9]. The incidence of MDR *P. aeruginosa* infections is associated with increased morbidity, mortality, and cost [5]. Several studies have attempted to identify risk factors associated with

* Author for correspondence: Dr M. Tumbarello, Istituto Malattie Infettive, Università Cattolica del Sacro Cuore, Largo A. Gemelli 8, 00168 Roma, Italy.
(Email: tumbarello@rm.unicatt.it)

infections caused by antimicrobial-resistant *P. aeruginosa* strains [6, 8, 10]. However, to our knowledge, few studies have focused on risk factors for BSI caused by MDR *P. aeruginosa* [11].

We aimed to identify the factors associated with the isolation of MDR *P. aeruginosa* strains and evaluate the clinical treatment response and factors associated with mortality in patients with *P. aeruginosa* BSI.

METHODS

Setting and study design

A retrospective study was conducted in two Italian university hospitals offering a full range of clinical services and admitting about 55 000 patients per year: Catholic University Hospital, a 1600-bed hospital located in Rome, and San Martino University Hospital, a 1500-bed hospital located in Genoa.

The microbiology laboratory database was used to identify adult patients hospitalized from 1 January 2006 to 31 December 2007 with *P. aeruginosa* BSI, which was defined as the presence of at least one positive blood culture and clinical features compatible with systemic inflammatory response syndrome [12]. Each patient was included in the study only once, at the time of the initial positive blood culture.

Data were extracted from patients' medical records and computerized hospital databases according to a pre-defined questionnaire. Patients were compared regarding demographics, medical history, clinical and laboratory findings, treatment, and outcome of infection. The impact of comorbidities was determined by the Charlson Comorbidity Index [13], and the overall severity of the patient's illness was rated by the Acute Physiology and Chronic Health Evaluation (APACHE) III score [14] calculated on the basis of available clinical data for the first 24 h following BSI onset. A case-case-control study design was used. The first case group was composed of patients from whom MDR *P. aeruginosa* strains were isolated (the MDR *P. aeruginosa* group); the second case group contained patients from whom non-MDR *P. aeruginosa* were isolated (the non-MDR *P. aeruginosa* group). The same control group was used for both case groups. The control group consisted of patients (total of cases : controls = 1 : 2) with no evidence of BSI or positive clinical cultures for *P. aeruginosa* during their hospitalization and chosen at random from lists of patients admitted to the same ward during the same time period.

Patients were included only if a complete data series could be obtained from their medical records. The distributions of the case and control admissions throughout the study period were similar.

We conducted a two-part analysis. First, a case-case-control study [15, 16] in which groups 1 and 2 were compared to controls to determine factors associated with the isolation of MDR and non-MDR strains of *P. aeruginosa*, respectively. Second, a cohort study including all patients with *P. aeruginosa* BSI (group 1 plus group 2) was performed to identify factors associated with in-hospital mortality associated with *P. aeruginosa* BSI using death within 21 days of the first positive blood culture as the outcome and comparing survivors and non-survivors.

Definitions

Prior to data analysis, MDR *P. aeruginosa* BSI was defined by blood-culture positivity (at least one specimen) for a strain of *P. aeruginosa* resistant to at least one drug of $\geqslant 3$ of the following anti-pseudomonal agents: β-lactams/inhibitors (piperacillin-tazobactam), cephalosporins (cefepime, ceftazidime), carbapenems (imipenem, meropenem), quinolones (ciprofloxacin, levofloxacin), and aminoglycosides (amikacin, gentamicin). Polymyxins-only-susceptible (POS) *P. aeruginosa* BSI was defined as being caused by a *P. aeruginosa* strain resistant to all commercially available drugs except colistin.

BSI onset was the date of collection of the first blood culture yielding the study isolate (index culture). BSI source was an infection at a distant site caused by a microbial strain identical to the bloodstream isolate documented by microbiological and physician findings. Infections were defined as nosocomial if the index blood culture had been drawn more than 48 h after admission [17]. Early-onset infections (i.e. cultures drawn within the first 48 h of hospitalization) were classified as healthcare-associated or community-acquired in accordance with the definitions of Friedman *et al.* [18].

Septic shock was defined as sepsis associated with organ dysfunction, accompanied by persistent hypotension following volume replacement [12]. An absolute neutrophil count (ANC) < 500 neutrophils/μl at the onset of infection was defined as neutropenia.

An in-patient stay of $\geqslant 2$ days during the 12 months preceding the index hospitalization was considered prior hospitalization. The use of any antimicrobial for more than 48 h during the 3 months preceding the

index admission was considered prior antimicrobial therapy. Antibiotic use was examined, both in terms of whether any antibiotics were used and by aggregate classes (fluoroquinolones, oxyimino-cephalosporins, aminoglycosides, carbapenems, β-lactam-β-lactamase inhibitors). Antibiotic treatment empirically prescribed before *in vitro* susceptibility test results were available was defined as initial antibiotic treatment and considered 'inadequate' [inadequate initial antibiotic treatment (IIAT)] when treatment with an antibiotic possessing *in vitro* activity against the isolated pathogen was absent.

Microbiology analysis

Bloodstream isolates were identified at the species level using the VITEK 2 (bioMérieux Inc., USA) and/or Phoenix (Becton Dickinson Microbiology Systems, USA) systems. Minimum inhibitory concentrations (MICs) of amikacin, cefepime, ceftazidime, ciprofloxacin, colistin, gentamicin, imipenem, levofloxacin, meropenem, and piperacillin-tazobactam were determined by E-test (AB Biodisc, Sweden). *P. aeruginosa* (ATCC 27853) and *Escherichia coli* (ATCC 25922 and 35218) were included as quality-control strains in all sessions. The MICs were classified according to the Clinical Laboratory Standards Institute (CLSI) guidelines [19].

Statistical analysis

Continuous variables were compared by Student's *t* test if normally distributed and the Mann–Whitney *U* test if non-normally distributed. Categorical variables were evaluated using χ^2 or the two-tailed Fisher's exact test. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to evaluate the strength of any association. Values for continuous and categorical variables are expressed as mean $\pm$ standard deviation (S.D.) or percentage of the group from which it is derived, respectively.

Logistic regression was used to identify independent risk factors. Variables associated with BSI caused by MDR *P. aeruginosa* in the univariate analysis ($P \leqslant 0{\cdot}1$) were included at model entry, and a backward stepwise approach was used to identify independent risk factors. Variables were retained in the final model if the *P* value was $\leqslant 0{\cdot}05$. With the same methodology a second multivariate model was performed for BSI caused by non-MDR *P. aeruginosa*. The Kaplan–Meier method was used for the survival analysis. Two-tailed tests were used to determine significance; $P < 0{\cdot}05$ was considered significant. All statistical analyses were performed using the Intercooled Stata program, version 8 for Windows (Stata Corporation, USA).

RESULTS

Incidence and population characteristics

P. aeruginosa BSI was diagnosed in 109 of the 212 658 patients hospitalized in our centres (111 907 in Rome, 100 751 in Genoa) over the 2 years of the study (overall incidence 0·51/1000 admissions). Three patients were not included in the analysis because of a lack of sufficient data, resulting in a final number of 106 cases. There were 212 patients included as controls.

Antimicrobial susceptibility

Of the 106 strains of *P. aeruginosa* evaluated, 50 (47·2%) displayed resistance to ceftazidime, 48 (45·3%) to cefepime, 47 (44·3%) to levofloxacin, 46 (43·4%) to ciprofloxacin, 44 (41·5%) to imipenem, 42 (37·7%) to meropenem, 38 (35·8%) to gentamicin, 20 (18·8%) to piperacillin-tazobactam, eight (7·5%) to amikacin, and none to colistin. Forty-six strains (12·5%) were classified as MDR *P. aeruginosa*. Eight isolates (7·5%) were POS.

Risk factors for MDR and non-MDR *P. aeruginosa* BSIs

Descriptive characteristics of patients with MDR and non-MDR *P. aeruginosa* BSI are shown in Table 1. The results of a comparison of the case groups with the controls by univariate analysis are shown in Table 2. MDR and non-MDR *P. aeruginosa* cases had longer hospital stays and previous BSI; previous surgery was more common in these groups. Compared to controls, patients were more likely to have undergone invasive procedures: mechanical ventilation, urinary catheterization, CVC, nasogastric tube, surgical drainage tube, total parenteral nutrition, and have a neutrophil count $< 500/mm^3$; previous treatment with corticosteroid and antibiotic therapy with β-lactam/β-lactamase inhibitors, oxyimino-cephalosporins, and carbapenems was more frequent in the patient group.

Isolation of MDR *P. aeruginosa* was also associated with previous use of fluoroquinolones or aminoglycosides, previous hospitalization and prior use of anti-neoplastic chemotherapy. The non-MDR

Table 1. *Clinical characteristics of patients*

Characteristic	MDR ($n=40$)	Non-MDR ($n=66$)	P
Nosocomial onset of infection	38 (95)	54 (81·8)	0·05
Hospital location at time of index blood culture			
Medicine	10 (25)	20 (30·3)	0·55
Surgery	3 (7·5)	17 (25·7)	0·01
Intensive care unit	27 (67·5)	29 (43·9)	0·01
Primary site of infection			
Urinary tract	5 (12·5)	12 (18·1)	0·43
Lower respiratory tract	7 (17·5)	7 (10·6)	0·30
Surgical wound	3 (7·5)	6 (9·1)	0·77
Central venous catheter	11 (27·5)	16 (24·2)	0·70
Biliary tract	3 (7·5)	2 (3)	0·29
Unknown	12 (30)	21 (31·8)	0·84
Previous antimicrobials*			
Aminoglycosides	4 (10)	5 (7·6)	0·66
β-lactam-β-lactamase inhibitors	11 (27·5)	17 (25·7)	0·84
Fluoroquinolones	14 (35)	9 (13·6)	0·009
Oxyimino-cephalosporins	25 (62·5)	30 (45·4)	0·08
Carbapenems	7 (17·5)	12 (18·1)	0·92
Charlson Comorbidity Index (mean ± S.D.)	3·55 ± 2·24	2·46 ± 1·78	0·01
APACHE score >15	31 (77·5)	45 (68·2)	0·30
Time at risk (mean ± S.D., days)†	24 ± 27	19 ± 20	0·24
Time to hospital discharge (mean ± S.D., days)‡	27 ± 14	17 ± 13	0·01
21-day mortality	20 (50)	16 (24·2)	0·006

MDR, Multidrug resistant.
Values are *n* (%) unless otherwise noted.
* Within the 30 days preceding infection onset.
† Duration of hospitalization prior to the date of collection of the first blood culture yielding the study isolate (index culture), calculated only for patients with nosocomial infections.
‡ For patients alive at day 21 ($n=70$) and calculated from the date of collection of the first blood culture yielding the study isolate (index culture).

P. aeruginosa cases were also significantly older than the controls and were more likely to have diabetes.

In logistic regression analysis, the only three variables independently associated with the isolation of MDR *P. aeruginosa* were: presence of CVC, previous antibiotic therapy, and corticosteroid use. Independent significant risk factors for the isolation of non-MDR *P. aeruginosa* were previous BSI, neutrophil count $<500/mm^3$, urinary catheterization, and the presence of CVC (Table 3).

Treatment and outcome

Forty patients with MDR *P. aeruginosa* BSI were empirically treated with the following antimicrobials: oxyimino-cephalosporins (ceftazidime or cefepime; $n=7$, 17·5%), β-lactam/β-lactamase inhibitor combination (amoxicillin-clavulanic acid or piperacillin-tazobactam; $n=15$, 37·5%), carbapenems (imipenem or meropenem; $n=11$, 27·5%), aminoglycosides (amikacin or gentamicin; $n=5$, 12·5%), fluoroquinolones (ciprofloxacin or levofloxacin; $n=7$, 17·5%), or others ($n=1$, 2·5%). Patients infected with non-MDR *P. aeruginosa* were empirically treated with oxyimino-cephalosporins ($n=17$, 25·7%), β-lactam/β-lactamase inhibitor combination ($n=16$, 24·2%), carbapenems ($n=15$, 22·7%), aminoglycosides ($n=8$, 12·1%), fluoroquinolones ($n=16$, 24·2%), or others ($n=2$, 3·1%). In some cases, the antimicrobials were used in combination therapy. In most cases, the choice in empirical regimen was made by the physician in charge of the patient, and protocols were not used.

In vitro susceptibility testing revealed that the initial therapy was inadequate in 33·9% of the cases (36/106), 12 of which received oxyimino-cephalosporins (33·3%), six fluoroquinolones (16·6%), eight carbapenems (22·2%), nine β-lactam/β-lactamase inhibitor combination (25%), and two aminoglycosides (5·5%). Three patients (8·3%) did not receive antibiotic therapy within 48 h of the blood culture draw.

Table 2. *Univariate analysis of risk factors for* P. aeruginosa *infection*

Variable	No. of subjects (%)			Univariate analysis			
		Cases		MDR *vs.* control		Non-MDR *vs.* control	
	Controls ($n=212$)	MDR ($n=40$)	Non-MDR ($n=66$)	*P*	OR (95% CI)	*P*	OR (95% CI)
Demographics							
Male sex	122 (57·5)	23 (57·5)	39 (59·1)	0·99	0·99 (0·47–2·11)	0·82	1·06 (0·58–1·95)
Age, years (mean ± S.D.)	63 ± 17	62 ± 16	67 ± 12	0·72	—	0·04	—
Length of hospitalization, days (mean ± S.D.)	20 ± 29	41 ± 23	35 ± 26	<0·001	—	<0·001	—
Previous hospitalization*	115 (54·2)	30 (75)	38 (57·6)	0·01	2·53 (1·12–6·08)	0·63	1·14 (0·63–2·08)
Previous BSI†	3 (1·4)	7 (17·5)	14 (21·2)	<0·001	14·77 (3·12–91·23)	<0·001	18·75 (4·91–104·01)
Invasive procedures							
Central venous catheter	45 (21·2)	35 (87·5)	42 (63·6)	<0·001	25·97 (9·25–88·40)	<0·001	6·49 (3·41–12·39)
Mechanical ventilation	22 (10·3)	21 (52·5)	24 (36·3)	<0·001	9·54 (4·14–21·84)	<0·001	4·93 (2·38–10·14)
Nasogastric tube	27 (12·7)	14 (35)	27 (40·9)	<0·001	3·68 (1·56–8·34)	<0·001	4·74 (2·38–9·38)
Urinary catheterization	56 (26·4)	24 (60)	42 (63·6)	<0·001	4·17 (1·95–9·02)	<0·001	4·87 (2·60–9·17)
Comorbidities							
Solid tumour	46 (21·7)	13 (32·5)	14 (21·2)	0·13	1·73 (0·75–3·81)	0·93	0·97 (0·45–1·97)
Haematological malignancy	30 (14·1)	8 (20)	10 (15·1)	0·34	1·51 (0·54–3·78)	0·83	1·08 (0·44–2·45)
Diabetes	33 (15·5)	10 (25)	19 (28·8)	0·14	1·80 (0·71–4·25)	0·01	2·19 (1·07–4·37)
Liver disease	32 (15·1)	3 (7·5)	5 (7·6)	0·19	0·45 (0·08–1·57)	0·11	0·45 (0·13–1·26)
Chronic renal failure	25 (11·8)	2 (5)	5 (7·5)	0·20	0·39 (0·04–1·69)	0·33	0·61 (0·17–1·73)
Previous surgery†	30 (23·6)	15 (37·5)	31 (46·9)	0·06	1·94 (0·87–4·17)	<0·001	2·86 (1·54–5·31)
Surgical drainage tube	24 (11·3)	14 (35)	19 (28·8)	<0·001	4·21 (1·77–9·72)	<0·001	3·16 (1·49–6·58)
Total parenteral nutrition	24 (11·3)	14 (35)	19 (28·8)	<0·001	4·21 (1·77–9·72)	<0·001	3·16 (1·49–6·58)
Anti-neoplastic chemotherapy†	26 (12·2)	13 (32·5)	12 (18·2)	0·001	3·44 (1·43–7·93)	0·22	1·58 (0·68–3·52)
Neutrophil count $<500/mm^3$	5 (2·3)	8 (20)	6 (9·1)	<0·001	10·35 (2·74–42·18)	0·01	4·14 (1·00–17·66)
Corticosteroid therapy	27 (12·7)	19 (47·5)	19 (28·8)	<0·001	6·19 (2·74–13·80)	0·002	2·76 (1·32–5·66)
Previous antibiotic therapy†	83 (39·1)	31 (77·5)	45 (68·2)	<0·001	5·35 (2·32–13·36)	<0·001	3·33 (1·78–6·30)
Aminoglycosides	7 (3·3)	4 (10)	5 (7·5)	0·05	3·25 (0·65–13·50)	0·13	2·40 (0·57–9·11)
β-lactam-β-lactamase inhibitors	24 (11·3)	11 (27·5)	17 (25·7)	0·006	2·97 (1·17–7·09)	0·003	2·71 (1·25–5·73)
Fluoroquinolones	29 (13·6)	14 (35)	9 (13·6)	0·001	3·39 (1·45–7·66)	0·99	0·99 (0·39–2·32)
Oxyimino-cephalosporins	36 (16·9)	25 (62·5)	30 (45·4)	<0·001	8·14 (3·68–18·21)	<0·001	4·07 (2·12–7·76)
Carbapenems	3 (2·7)	7 (17·5)	12 (18·1)	0·001	7·56 (1·58–47·06)	<0·001	7·92 (1·99–45·04)

BSI, Bloodstream infection; MDR, multidrug resistant; OR, odds ratio; CI, confidence interval.
Values are *n* (%) unless otherwise noted.
* Within the 12 months preceding infection onset.
† Within the 30 days preceding infection onset.

Table 3. *Logistic regression analysis of risk factors for* P. aeruginosa *infection*

Risk factor	*P*	OR (95% CI)
MDR *P. aeruginosa*		
Central venous catheter	<0·001	17·99 (6·46–50·09)
Previous antibiotic therapy	0·03	2·79 (1·10–7·07)
Corticosteroid therapy	0·03	2·73 (1·06–7·00)
Non-MDR *P. aeruginosa*		
Previous bloodstream infection	0·001	9·91 (2·47–39·64)
Neutrophil count <500/mm^3	0·02	4·98 (1·18–21·02)
Urinary catheterization	0·002	3·20 (1·53–6·70)
Central venous catheter	0·002	3·03 (1·49–6·18)

MDR, Multidrug resistant; OR, odds ratio; CI, confidence interval.

The percentages of patients receiving IIAT were 52·5% (21/40) and 24·2% (16/66) in those with MDR and non-MDR *P. aeruginosa* BSIs, respectively (P = 0·003).

The overall 21-day mortality rate of all patients was 33·9% (36/106). The mortality rate was significantly higher in the MDR *P. aeruginosa* BSI group than the non-MDR group (55·5% *vs.* 28·5%, P = 0·006). The survival curve also shows that the MDR *P. aeruginosa* BSI group had a lower probability of survival than the non-MDR group (Fig. 1).

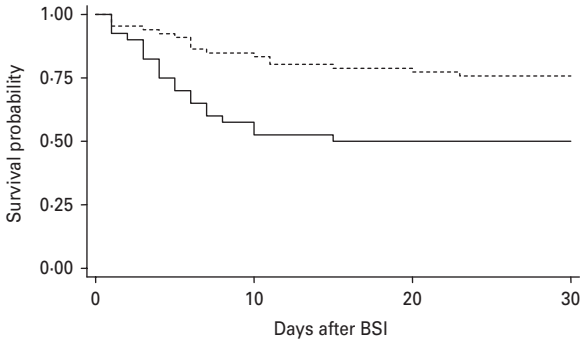

Fig. 1. Survival curve using the Kaplan–Meier method for patients with bloodstream infections (BSI) caused by multidrug-resistant (MDR) *P. aeruginosa* compared to those with non-MDR *P. aeruginosa*. The MDR group (——) has lower probability of survival than the non-MDR group (- - -) (P = 0·003).

Risk factors for mortality

The results of the univariate and multivariate analyses of risk factors for mortality are shown in Table 4. Univariate analysis revealed significant differences between the survivor and non-survivor subgroups. A significantly higher percentage of non-survivors were older, had a higher mean Charlson Comorbidity Index score, received prior antibiotic and corticosteroid therapy, and had nosocomial infections. Non-survivors were also more frequently in the intensive care unit (ICU), had BSI presentation that included septic shock, and their infections were more frequently caused by MDR *P. aeruginosa*. A higher percentage of non-survivors received IIAT.

In logistic regression analysis, the variables independently associated with 21-day mortality were presentation with septic shock, infection due to MDR *P. aeruginosa*, and IIAT.

DISCUSSION

In the present study, we found *P. aeruginosa* BSI to be a relatively rare condition with an overall incidence of 0·51/1000 admissions, which is similar to that recently reported by Marchaim *et al.* [20].

The prevalence of antimicrobial-resistant *P. aeruginosa* is increasing in ICU patients [6]. A large proportion (67·5%) of our patients with MDR *P. aeruginosa* BSIs were in the ICU at the time of BSI onset. In general, one out of every four cases included in our study was hospitalized in the ICU. This fact may have contributed to the high rate of MDR *P. aeruginosa* observed in our patients.

Schechner *et al.* recently demonstrated that independent predictors of *P. aeruginosa* bacteraemia were severe immunodeficiency, age >90 years, antimicrobial therapy within the previous 30 days, and presence of a CVC or urinary device [7], but the risk factors for MDR *P. aeruginosa* were not separately reported. In our study, a case-case-control study design was used, which involves two parallel case-control studies with a common control group,

Table 4. *Risk factors associated with 21-day mortality*

Variable	Non-survivors ($n=36$)	Survivors ($n=70$)	P	OR (95% CI)
Univariate analysis				
Demographics				
Male sex	23 (63·9)	39 (55·7)	0·41	1·40 (0·57–3·53)
Mean age, years (±S.D.)	69±11	63±15	0·02	—
Primary site of infection				
Urinary tract	3 (8·3)	4 (5·7)	0·60	1·50 (0·20–9·39)
Lower respiratory tract	7 (19·4)	7 (10)	0·17	2·17 (0·58–7·95)
Surgical wound	0	1 (1·4)	0·47	—
Central venous catheter	0	7 (10)	0·04	—
Biliary tract	0	5 (7·1)	0·10	—
Unknown	27 (75)	44 (62·8)	0·20	1·77 (0·67–4·94)
Comorbidities				
Liver disease	3 (8·3)	5 (7·1)	0·82	1·18 (0·17–6·49)
Chronic renal insufficiency	3 (8·3)	4 (5·7)	0·60	1·50 (0·20–9·39)
Diabetes mellitus	10 (27·8)	19 (27·1)	0·94	1·03 (0·37–2·74)
Haematological malignancy	8 (22·2)	10 (14·3)	0·30	1·71 (0·52–5·40)
Solid tumour	10 (27·8)	17 (24·3)	0·69	1·19 (0·42–3·23)
Neutrophil count $<500/mm^3$	7 (19·4)	7 (10)	0·17	2·17 (0·58–7·95)
Charlson Comorbidity index (mean±S.D.)	3·55±2·02	2·52±2·02	0·01	—
History				
Previous surgery*	14 (38·9)	32 (45·7)	0·50	0·75 (0·30–1·84)
Previous antibiotic therapy*	30 (83·3)	46 (65·7)	0·05	2·60 (0·89–8·66)
Prior hospital admission†	25 (69·4)	43 (61·4)	0·41	1·42 (0·56–3·74)
Corticosteroid therapy	19 (52·8)	19 (27·1)	0·009	3·00 (1·19–7·56)
Epidemiological category				
Nosocomial	35 (97·2)	57 (81·4)	0·02	7·98 (1·09–348·69)
Healthcare-associated	0	5 (7·1)	0·10	—
Community-acquired	1 (2·7)	8 (11·4)	0·13	0·22 (0·01–1·78)
Ward at BSI onset				
Medicine	10 (27·8)	20 (28·5)	0·93	0·96 (0·34–2·54)
Surgery	1 (2·8)	19 (27·1)	0·002	0·07 (0·01–0·53)
Intensive care unit	25 (69·4)	31 (44·3)	0·01	2·85 (1·13–7·43)
Clinical presentation				
APACHE score >15	29 (80·5)	47 (67·1)	0·14	2·02 (0·71–6·28)
Septic shock	16 (44·4)	13 (18·5)	0·004	3·50 (1·30–9·41)
Bloodstream isolate characteristics				
Multidrug resistant	20 (55·5)	20 (28·5)	0·006	3·12 (1·24–7·86)
Polymyxins-only-susceptible	5 (13·9)	3 (4·2)	0·07	3·60 (0·64–24·34)
Inadequate initial antimicrobial treatment	20 (55·5)	17 (24·2)	0·001	3·89 (1·52–9·99)
Combination antibiotic definitive therapy	6 (16·66)	21 (30)	0·13	0·46 (0·13–1·38)
Multivariate analysis				
Presentation with septic shock	—	—	0·007	3·99 (1·47–10·87)
Infection due to multidrug-resistant isolate	—	—	0·01	3·31 (1·27–8·59)
Inadequate initial antimicrobial treatment	—	—	0·03	2·73 (1·08–6·85)

OR, Odds ratio; CI, confidence interval.
Values are n (%) unless otherwise noted.
$n=106$ patients with *P. aeruginosa* bloodstream infection (BSI).
* During the 30 days preceding the index blood culture.
† During the 12 months preceding the index hospitalization.

providing a more precise estimate of the risk of a particular *P. aeruginosa* isolate being MDR. This information is useful as a guide for selecting empirical antibiotic treatments and early institution of contact precautions. By logistic regression, we found that MDR *P. aeruginosa* BSIs are associated with previous antibiotic therapy, corticosteroid therapy, and CVC.

Exposure to antibiotics predisposes patients to colonization with *P. aeruginosa* strains that are intrinsically resistant to these agents. *P. aeruginosa* also has the capacity to rapidly become resistant during the course of anti-pseudomonal drug treatment [21]. Therefore, previous therapies increase the risk of infection with selected resistant strains [6, 22, 23]. In our experience, MDR strains are isolated more frequently from patients previously treated with different classes of antibiotics: cephalosporins, carbapenems, fluoroquinolones, and β-lactam/β-lactamase inhibitor combinations. In contrast, carbapenems and fluoroquinolones were the antibiotics most frequently related to MDR resistance in previous studies [6]. Previous exposure to a particular antibiotic is not only associated with the acquisition of resistance to that antibiotic [24], but also to antibiotics belonging to a different class [25]. This concept is particularly true for *P. aeruginosa* as a pathogen harbouring multiple mechanisms of resistance [26]. Moreover, antibiotic pressure could play a lesser role because horizontal transmission would be the main mechanism of acquisition in some cases [27].

Concern has also been expressed about the promotion of infection by corticosteroids: recent studies have reported that corticotherapy is an independent predictor of nosocomial pneumonia sustained by Gram-negative pathogens and infection with antibiotic-resistant Gram-negative rods [28, 29].

The presence of CVC was confirmed in our analysis as an important risk factor for *P. aeruginosa* BSI [7, 30]. Interestingly, our study is the first to separately analyse the impact of this variable in MDR and non-MDR infections, demonstrating that it increases the risk of MDR *P. aeruginosa* BSI by almost 18 times.

In addition to the presence of CVC, the other risk factors associated with non-MDR *P. aeruginosa* BSI in our study were previous bacteraemia, neutropenia, and presence of urinary catheter.

To our knowledge, none of previous studies have reported an independent association between prior bacteraemia and *P. aeruginosa* BSI, this might be a marker for several other variables (such as previous use of antimicrobials, severe disease, invasive procedures), and not a risk factor by itself.

P. aeruginosa is one of the most common aetiological agents of Gram-negative bacteraemia in neutropenic patients, in particular in those with haematological malignancies [31, 32]; in addition, neutropenia has been found to be independently associated to community-onset *P. aeruginosa* BSI by other authors [30].

Regarding urinary catheterization, as mentioned above, Schechner *et al.* demonstrated that the presence of a urinary device was an independent predictor of *P. aeruginosa* bacteraemia upon hospital admission [7]. All of these three factors were not found to be related to the onset of BSI caused by MDR *P. aeruginosa* in our study.

The all-cause 21-day mortality of 34% in patients with monomicrobial *P. aeruginosa* bacteraemia found here is in line with previous observations [3, 8]. In addition, we highlight the high mortality associated with MDR *P. aeruginosa* BSIs. Twenty-one days after infection onset, 50% of the patients with MDR *P. aeruginosa* infections had died, whereas non-MDR *P. aeruginosa* mortality was 24·2%.

The first prognostic indicator of an unfavourable clinical outcome is presentation with septic shock, which is an obvious result because the mortality for septic shock is usually more than double the mortality for severe sepsis, both in ICU and non-ICU patients [33].

Inadequate therapy emerged as another independent predictor of mortality in our patients. These findings are consistent with those of Lodise *et al.* [2], who suggested that delaying appropriate therapy for approximately 2 days significantly increases the risk of mortality in patients with *P. aeruginosa* BSI. In addition, they found that antibiotic resistance in more than three classes was independently associated with a >52 h delay of appropriate therapy. Although the impact of appropriate empirical antimicrobial therapy for *P. aeruginosa* BSIs on patients' outcomes has not been clearly established, analogous findings have been reported by others [34–36]. Nevertheless, some studies suggest that the use of appropriate initial empirical therapy is not critical to patients' outcomes [3, 37].

Multivariate analysis revealed that isolation of a MDR strain of *P. aeruginosa* is an independent predictor of mortality in *P. aeruginosa* BSIs. Although a recent review showed high mortality rates in association with infections caused by antibiotic-resistant

Gram-negative bacteria [5], the causal link between antibiotic resistance and poor outcome remains unclear, and inadequate therapy, which is more likely to occur in BSI caused by antibiotic-resistant bacteria, could be hypothesized. However, previous studies have reported significantly higher rates of mortality in patients with infections caused by antimicrobial-resistant Gram-negative rods [8, 16, 38]; although Blot *et al*. [39] reported no association between antimicrobial resistance and poor outcome in critically ill patients with nosocomial bacteremia caused by Gram-negative bacteria. In addition, Tam and colleagues [36] have recently reported that isolation of a MDR strain of *P. aeruginosa* was an independent predictor of mortality in *P. aeruginosa* BSIs.

Our study has certain limitations that must be acknowledged. First, the clonality of the isolates was not investigated (so that possible outbreaks could not be ruled out); in addition, the mechanisms of resistance were not analysed, and risk factors and prognosis might be different. Finally, some episodes could have been misclassified as having an unknown source, because a microbiological confirmation of a clinically suspected source was not requested.

In conclusion, decisions regarding the empirical treatment of *P. aeruginosa* BSIs must be based on sound knowledge of the local distribution of pathogens and their susceptibility patterns. In settings similar to ours, where MDR *P. aeruginosa* is fairly common, it is not easy to suggest empirical treatment of nosocomial BSIs due to the difficulty of ideally including drugs effective against these pathogens; in addition, preventive strategies (such as antibiotic policy, infection control measures, etc.) should be implemented in order to reduce the spread of these bacterial isolates. However, in patients at high risk for MDR *P. aeruginosa* BSI, empirical therapy including more than one anti-pseudomonal agent or a drug with high activity against the most resistant *P. aeruginosa* isolates (i.e. colistin) could be considered until susceptibility results become known.

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DECLARATION OF INTEREST

None.

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