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Risk factors for mortality among patients with *Pseudomonas aeruginosa* bacteraemia: a retrospective multicentre study

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ABSTRACT

This study aimed to evaluate risk factors for 30-day mortality among hospitalised patients with *Pseudomonas aeruginosa* bacteraemia, a highly fatal condition. A retrospective study was conducted between 1 January 2009 and 31 October 2015 in 25 centres (9 countries) including 2396 patients. Univariable and multivariable analyses of risk factors were conducted for the entire cohort and for patients surviving ≥48 h. A propensity score for predictors of appropriate empirical therapy was introduced into the analysis. Of the 2396 patients, 636 (26.5%) died within 30 days. Significant predictors (odds ratio and 95% confidence interval) of mortality in the multivariable analysis included patient-related factors: age (1.02, 1.01–1.03); female sex (1.34, 1.03–1.77); bedridden functional capacity (1.99, 1.24–3.21); recent hospitalisation (1.43, 1.07–1.92); concomitant corticosteroids (1.33, 1.02–1.73); and Charlson comorbidity index (1.05, 1.01–1.93). Infection-related factors were multidrug-resistant *Pseudomonas* (1.52, 1.15–2.1), non-urinary source (2.44, 1.54–3.85) and Sequential Organ Failure Assessment (SOFA) score (1.27, 1.18–1.36). Inappropriate empirical therapy was not associated with increased mortality (0.81, 0.49–1.33). Among 2135 patients surviving ≥48 h, hospital-acquired infection (1.59, 1.21–2.09), baseline endotracheal tube (1.63, 1.13–2.36) and ICU admission (1.53, 1.02–2.28) were additional risk factors. Risk factors for mortality among patients with *P. aeruginosa* were mostly irreversible. Early appropriate empirical therapy was not associated with reduced mortality. Further research should be conducted to explore subgroups that may not benefit from broad-spectrum antipseudomonal empirical therapy. Efforts should focus on prevention of infection, mainly hospital-acquired infection and multidrug-resistant pseudomonal infection.

1. Introduction

Short-term mortality following *Pseudomonas aeruginosa* bacteraemia is high, reported as 20–40% at 30 days [1,2]. Moreover, *P. aeruginosa* bacteraemia is responsible for 2–4% of hospital-acquired bloodstream infections [3,4].

Previously reported risk factors for short-term mortality in *P. aeruginosa* bacteraemia include age, co-morbidities, impaired functional capacity, immunosuppression, neutropenia, severity of clinical presentation, inappropriate or delayed empirical antibiotic therapy, and pulmonary or unknown source of infection, among others. [1,5–13]. However, the studies were either small or were published over a decade ago, and some of the risk factors were reported in only a single publication. Recent studies addressing risk factors for mortality in *P. aeruginosa* bacteraemia are mostly small series focusing on the prognosis of patients with carbapenem-resistant or multidrug-resistant (MDR) isolates [14,15].

One of the possible modifiable risk factors for mortality in severe bacterial infections is administration of appropriate empirical antibiotic therapy [16]. In the case of *P. aeruginosa* bacteraemia, some studies demonstrate appropriate empirical therapy to be a significant factor in patient survival [7,9,13,17], while others do not [2,8,12].

The aim of this study was to evaluate risk factors for 30-day mortality in a large, multicentre cohort of patients with *P. aeruginosa* bacteraemia, with an emphasis on modifiable risk factors.

2. Methods

2.1. Data collection and patient inclusion

This was a retrospective multicentre cohort study conducted in 25 centres in 9 countries across Europe, Australia and Israel during the years 2009–2015 (see Supplementary Table S1 for data on participating centres). The study was approved by the Medical Ethical Committees of each participating centre. STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines for reporting in epidemiological studies were followed. Data from the same database were used to compare different β-lactam monotherapies as definitive therapy for *P. aeruginosa* bacteraemia [18].

Consecutive adult patients (age ≥18 years) with monomicrobial *P. aeruginosa* bacteraemia during hospitalisation were included in this study. Identification of patients was performed using microbiology laboratory databases. Bacteraemia was defined as growth of *P. aeruginosa* in one or more blood culture bottles. Source of bacteraemia was defined according to US Centers for Disease Control and Prevention (CDC) guidelines [19].

Data were retrieved from medical records of all consecutive patients identified with *P. aeruginosa* bacteraemia, including patient baseline characteristics, infection characteristics, management data, microbiological data and outcomes. The date of death was documented for each patient until the end of follow-up on 31 October 2015.

Patients with polymicrobial infection were excluded. Each patient was included only once.

2.2. Definitions

Appropriate empirical antibiotic therapy was defined as administration of an antipseudomonal antibiotic that the isolate was susceptible to by antimicrobial susceptibility testing within 24 h after blood culture collection (as determined by the local laboratories, see Supplementary Table S1).

MDR *P. aeruginosa* was defined as an isolate resistant to at least one drug from at least three groups of antibiotics (antipseudomonal penicillins, antipseudomonal cephalosporins, carbapenems, fluoroquinolones and aminoglycosides).

Combination definitive therapy was defined as >48 h of concomitant therapy with two drugs of the following groups during the first week of definitive therapy: β-lactams with fluoroquinolones/aminoglycosides/another β-lactam or any combination with colistin, only if the isolate was susceptible to both drugs.

2.3. Statistical analysis

Continuous data are expressed as the median and interquartile range (IQR) and categorical data as the number and percentage. The *t*-test was used for comparison of normally distributed variables, and the Mann–Whitney test was used for non-normally distributed variables. Comparison of categorical variables was performed using the χ^2 test or Fisher's exact test. Univariable analysis was conducted for the outcome of 30-day mortality. Variables that

were found to be statistically significant in the univariable analysis ($P < 0.05$) were included in a multivariable logistic regression analysis. Intercorrelated variables (>0.4) according to biological plausibility were excluded. Specifically, a correlation was found between variables representing instrumentation prior to infection onset, including endotracheal tube presence, central venous catheter, nasogastric tube and urinary catheter; only endotracheal tube was included in the multivariable analysis. The multiple imputation technique was used to impute missing values. Multivariable analysis was conducted using a generalised estimating equation model to control for centre as a random-effect variable. Five different models were tested, using the quasi-likelihood under the independence model criterion (QIC) in order to fit the best model. A propensity score was performed for predictors of appropriate therapy and this score was introduced into the multivariable analysis, together with an interaction variable between Sequential Organ Failure Assessment (SOFA) score and appropriate empirical therapy. Variables found to be significant in the univariable analysis were used for the propensity score. A sensitivity analysis was conducted for patients surviving ≥48 h following culture collection in order to include definitive treatment-related variables (combination therapy). All statistical analyses were conducted using IBM SPSS Statistics v.25.0 (IBM Corp., Armonk, NY, USA).

3. Results

A total of 2396 consecutive patients with documented *P. aeruginosa* bacteraemia were included in the study. The median (IQR) patient age was 67 years (56–78 years) and 882 (36.8%) were female. The most common sources of bacteraemia were pulmonary, central line-associated, urinary tract infection (UTI) and unknown source, each contributing ~20% of infections. Patient and infection characteristics of the entire cohort as well as risk factors for 30-day mortality are detailed in Table 1. Of the 2396 patients, 636 (26.5%) died within 30 days of culture collection. Patient factors associated with 30-day mortality in the univariable analysis were older age, female sex, bedridden functional capacity at baseline, recent previous hospitalisation, endotracheal tube at infection onset, immunosuppression and high Charlson comorbidity index. Infection-related factors associated with 30-day mortality included hospital-acquired infection, MDR *P. aeruginosa*, non-urinary source, admission to the intensive care unit (ICU), higher infection severity (SOFA) score at infection onset, lower total leukocyte count, neutropenia, lower albumin and higher creatinine at infection onset. Inspecting further the source of infection, non-urinary sources specifically associated with increased mortality were pulmonary and unknown sources. A vascular line source was associated with reduced mortality. (Table 1).

Risk factors remaining significant in the multivariable analysis included older age, female sex, bedridden functional capacity at baseline, previous recent hospitalisation, corticosteroid treatment, higher Charlson comorbidity index, MDR *P. aeruginosa*, non-urinary source and higher SOFA score at infection onset. Inappropriate empirical therapy (odds ratio = 1.24, 95% confidence interval 0.75–2.05) and an interaction variable between inappropriate empirical therapy and SOFA score were non-significant in the multivariable analysis (Table 2).

A sensitivity analysis of patients surviving ≥48 h included 2135 patients, of whom 375 (17.6%) died within 30 days. Patient and infection characteristics of this cohort as well as risk factors for 30-day mortality are detailed in Table 3. Patient factors associated with 30-day mortality in the univariable analysis were bedridden functional capacity at baseline, previous recent hospitalisation, corticosteroid use and higher Charlson comorbidity index. Infection-related factors associated with 30-day mortality included hospital-acquired infection, MDR *P. aeruginosa*, non-urinary source, admission to the ICU, higher infection severity (SOFA) score at infection onset, lower albumin and higher creatinine at infection onset. Inappropriate empirical therapy within 24 h and combination therapy as definitive treatment were not significantly associated with increased mortality in the univariable analysis. Risk factors remaining significant in the multivariable analysis included bedridden functional capacity at baseline, previous hospitalisation, endotracheal tube at time of infection, higher Charlson comorbidity index, hospital-acquired infection, MDR *P. aeruginosa*, non-urinary source, ICU admission and higher SOFA score at infection onset (Table 4).

There was no significant difference in Charlson comorbidity index or rate of immunosuppression in patients with a MDR isolate ($n = 335$) compared with those without a MDR isolate. However, patients with a MDR isolate were more likely to be hospitalised in the ICU at time of infection onset, have invasive devices at the time of infection onset (intubated/endotracheal tube, arterial or central venous line, nasogastric tube and urinary catheter), have had surgery within 90 days prior to bacteraemia, to have acquired their infection in the hospital, to have a non-urinary source and to present with a higher SOFA score. They were more likely to receive inappropriate empirical therapy (69.6% received appropriate therapy within 24 h vs. 76.6% of non-MDR patients).

These patients had worse outcomes with 38.5% (129/335) 30-day mortality compared with 24.6% (507/2061) among patients with a non-MDR isolate (see Supplementary Table S2 for details).

4. Discussion

In this study, risk factors for all-cause 30-day mortality among 2396 patients with *P. aeruginosa* bacteraemia, including data from 25 centres in nine countries, were assessed. Overall 30-day mortality in the entire cohort reached 26.5%. Older age, female sex, bedridden functional capacity, higher Charlson comorbidity index, MDR *P. aeruginosa* and higher SOFA score were identified as significant risk factors for 30-day mortality. Urinary source of bacteraemia was significantly associated with decreased mortality. A sensitivity analysis of 2135 patients surviving ≥48 h demonstrated similar risk factors for mortality, excluding age and sex, and including previous hospitalisation, instrumentation, hospital-acquired infection and ICU admission.

The finding of increased mortality among women has not been described previously for this infection. In general, *P. aeruginosa* bacteraemia is more common in men, however sex differences in mortality have not been previously described [20]. Female sex is considered protective against sepsis in general, although studies have demonstrated increased mortality among females specifically in *Staphylococcus aureus* bacteraemia [21,22] and in ICU patients with nosocomial pneumonia [23]. The reason for the increased mortality is not thoroughly understood and is attributed to multifactorial mechanisms, including hormonal factors in addition to behavioural and physiological ones [21]. Female sex has also been associated with more frequent and virulent *P. aeruginosa* infections in cystic fibrosis patients [21]. In the present cohort, women were more likely than men to receive chemotherapy or steroids and to have neutropenia. In addition, they were less likely to have UTI as their source of bacteraemia compared with men, a source associated with lower mortality. These findings may provide some explanation for the higher mortality demonstrated in women.

Overall, 14.0% of the cohort (335/2396 patients) had bacteraemia caused by MDR *P. aeruginosa* and had significantly increased mortality. Previous studies have demonstrated conflicting results. In a small cohort, Buehrle et al. demonstrated no significant difference in 30-day mortality between patients with MDR *P. aeruginosa* bacteraemia and those with non-MDR isolates [14]. Lee et al. demonstrated higher mortality among 25 patients with carbapenem-only-resistant *P. aeruginosa* versus all-susceptible

Table 1
Univariable analysis of risk factors for 30-day all-cause mortality [a]

Characteristic	Entire cohort (N = 2396)	30-day mortality		*P*-value
		Dead (n = 636)	Alive (n = 1760)	
Patient characteristics				
Age (years)	67 (56–78)	69 (59–78)	67 (55–77)	0.004
Sex female	882/2394 (36.8)	263/636 (41.4)	619/1758 (35.2)	0.000
Functional capacity: bedridden	116/2110 (5.5)	44/586 (7.5)	72/1524 (4.7)	0.000
Previous hospitalisation (<90 days)	1282/2342 (54.7)	376/621 (60.5)	906/1721 (52.6)	0.001
Endotracheal tube	425/2378 (17.9)	181/632 (28.6)	244/1746 (14.0)	0.000
Arterial line	436/2374 (18.4)	154/631 (24.4)	282/1743 (16.2)	0.000
Central venous line	1092/2374 (46.0)	321/628 (51.1)	771/1746 (44.2)	0.003
Nasogastric tube	414/2126 (19.5)	170/592 (28.7)	244/1534 (15.9)	0.000
Urinary catheter	984/2372 (41.5)	310/631 (49.1)	674/1741 (38.7)	0.000
Any foreign device	544/2364 (23.0)	138/629 (21.9)	406/1735 (23.4)	0.456
Chemotherapy previous 30 days	608/2377 (25.6)	191/632 (30.2)	417/1745 (23.9)	0.002
Corticosteroids	456/2365 (19.3)	147/624 (23.6)	309/1741 (17.7)	0.002
Previous surgery (<90 days)	627/2380 (26.3)	160/634 (25.2)	467/1746 (26.7)	0.46
Chronic dialysis	116/2377 (4.9)	25/633 (3.9)	91/1744 (5.2)	0.205
Intravenous drug use	63/2377 (2.7)	20/635 (3.1)	43/1742 (2.5)	0.36
Neutropenia	478/2382 (20.1)	156/632 (24.7)	322/1750 (18.4)	0.001
Charlson comorbidity index	3 (1–6)	4 (2–6)	3 (1–6)	0.001
Infection-related characteristics				
Hospital-acquired infection	1283/2389 (53.7)	382/636 (60.1)	901/1753 (51.4)	0.000
MDR *Pseudomonas*	335/2396 (14.0)	129/636 (20.3)	206/1760 (11.7)	0.000
UTI bacteraemia	458/2396 (19.1)	55/636 (8.6)	403/1760 (22.9)	0.000
Other source of infection				
Pneumonia	472/2396 (19.7)	192/636 (30.2)	280/1760 (15.9)	0.001
Line infection	498/2396 (20.8)	94/636 (14.8)	404/1760 (23.0)	0.001
Intra-abdominal infection	166/2396 (6.9)	43/636 (6.8)	123/1760 (7.0)	0.927
Unknown	516/2396 (21.5)	178/636 (28.0)	338/1760 (19.2)	0.001
Other	244/2396 (10.2)	62/636 (9.7)	182/1760 (10.3)	0.702
ICU admission	526/2386 (22.0)	208/636 (32.7)	318/1750 (18.2)	0.000
SOFA score (n = 687)	4 (2–6)	7 (4–11)	3 (1–5)	0.000
Leukocytes ($\times 10^9$/L) (n = 742)	10.09 (2.8–16.85)	8.82 (1.3–17.3)	10.3 (3.8–16.8)	0.022
Albumin (g/dL) (n = 476)	2.7 (2.2–3.2)	2.4 (1.9–2.9)	2.8 (2.3–3.3)	0.000
Creatinine (mg/dL) (n = 739)	1.1 (0.75–1.85)	1.31 (0.8–2.17)	1.05 (0.72–1.72)	0.000
Appropriate empirical treatment (<24 h)	1846/2345 (78.7)	523/616 (84.9)	1323/1729 (76.5)	0.000

MDR, multidrug-resistant; UTI, urinary tract infection; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment.
[a] Categorical variables are presented as number (percentage) and continuous variables as median (interquartile range).

Table 2
Multivariate logistic regression analysis of risk factors for 30-day all-cause mortality: multivariate generalised linear model (generalised estimating equation), β = 0.326 (N = 2345)

Risk factor	OR	95% CI	*P*-value
Propensity score			0.745
Age (per 1 year)	1.02	1.01–1.03	**0.000**
Sex female	1.34	1.03–1.77	**0.031**
Functional capacity: bedridden	1.99	1.24–3.21	**0.005**
Previous hospitalisation (<90 days)	1.43	1.07–1.92	**0.016**
Endotracheal tube	1.29	0.9–1.83	0.154
Corticosteroid treatment	1.33	1.02–1.73	**0.034**
Neutropenia	1.12	0.45–2.78	0.811
Charlson comorbidity index	1.05	1.01–1.93	**0.012**
Hospital-acquired infection	1.28	0.97–1.69	0.070
MDR *Pseudomonas*	1.52	1.15–2.1	**0.004**
UTI bacteraemia	0.41	0.26–0.65	**0.000**
ICU admission	0.98	0.48–2.01	0.973
SOFA score	1.27	1.18–1.36	**0.000**
Appropriate empirical treatment (<24 h)	1.24	0.75–2.05	0.408
Appropriate empirical treatment × SOFA score interaction	0.97	0.88–1.06	0.546

OR, odds ratio; CI, confidence interval; MDR, multidrug-resistant; UTI, urinary tract infection; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment.

P. aeruginosa [15]. The largest study evaluating the impact of carbapenem resistance on 30-day mortality by Peña et al. demonstrated carbapenem resistance to be associated with significantly increased mortality [24]. However, this association was in correlation with baseline condition, with the highest risk observed among patients with higher Charlson comorbidity index [24]. In the current study, no correlation was found between MDR *P. aeruginosa* and Charlson comorbidity index, however patients with MDR *Pseudomonas* were more likely to be hospitalised in the ICU at the time of infection, have a hospital-acquired infection, have a higher SOFA score at presentation and receive inappropriate empirical therapy. These may imply that baseline patient characteristics and management may be more influential than the resistant bacterium itself. Nevertheless, in the absence of molecular analysis, it is difficult to determine whether the increased mortality is the result of a more virulent pathogen or simply the association with a

Table 3
Risk factors for 30-day all-cause mortality among patients alive for ≥48 h after culture collection ($N = 2135$)[a]

Characteristic	All cohort ($N = 2135$)	30-day mortality		*P*-value
		Dead ($N = 375$)	Alive ($N = 1760$)	
Patient characteristics				
Age	67 (55–78)	68 (58–79)	67 (55–77)	0.074
Sex female	755/2133 (35.4)	136/375 (36.3)	619/1758 (35.2)	0.698
Functional capacity: bedridden	104/1869 (5.6)	32/345 (9.3)	72/1524 (4.7)	0.001
Previous hospitalisation (<90 days)	1136/2087 (54.4)	230/366 (62.8)	906/1721 (52.6)	0.000
Endotracheal tube	354/2119 (16.7)	110/373 (29.5)	244/1746 (14.0)	0.000
Arterial line	375/2115 (17.7)	93/372 (25.0)	282/1743 (16.2)	0.000
Central venous line	972/2115 (46.0)	201/369 (54.5)	771/1746 (44.2)	0.000
Nasogastric tube	355/1884 (18.8)	111/350 (31.7)	244/1534 (15.9)	0.000
Urinary catheter	870/2113 (41.2)	196/372 (52.7)	674/1741 (38.7)	0.000
Any foreign body	488/2106 (23.2)	82/371 (22.1)	406/1735 (23.4)	0.591
Chemotherapy previous 30 days	521/2117 (24.6)	104/372 (28.0)	417/1745 (23.9)	0.099
Corticosteroids	392/2107 (18.6)	83/366 (22.7)	309/1741 (17.7)	0.028
Previous surgery (<90 days)	578/2120 (27.3)	111/374 (29.7)	467/1746 (26.7)	0.248
Chronic dialysis	109/2116 (5.2)	18/372 (4.8)	91/1744 (5.2)	0.764
Intravenous drug use	403/2123 (19.0)	81/373 (21.7)	322/1750 (18.4)	0.097
Neutropenia	403/2123 (19.0)	81/373 (21.7)	322/1750 (18.4)	0.138
Charlson comorbidity index	3 (1–6)	5 (2–7)	3 (1–6)	0.000
Infection-related characteristics				
Hospital-acquired infection	1151/2128 (54.1)	250/375 (66.7)	901/1753 (51.4)	0.000
MDR *Pseudomonas*	291/2135 (13.6)	85/375 (22.7)	206/1760 (11.7)	0.000
UTI bacteraemia	448/2135 (21.0)	45/375 (12.0)	403/1760 (22.9)	0.000
ICU admission	424/2125 (20.0)	106/375 (28.3)	318/1750 (18.2)	0.000
SOFA score ($n = 687$)	3 (2–6)	5 (3–9)	3 (1–5)	0.000
Leukocytes ($\times 10^9$/L) ($n = 742$)	10.3 (3.5–16.98)	10.35 (2.02–17.6)	10.3 (3.8–16.8)	0.863
Albumin (g/dL) ($n = 476$)	2.7 (2.2–3.2)	2.4 (1.9–2.9)	2.8 (2.3–3.3)	0.000
Creatinine (mg/dL) ($n = 739$)	1.07 (0.72–1.8)	1.17 (0.75–2.1)	1.05 (0.72–1.72)	0.050
Appropriate empirical treatment (<24 h)	1605/2094 (76.6)	282/365 (77.3)	1323/1729 (76.5)	0.761
Combination therapy	405/2135 (19.0)	78/375 (20.8)	327/1760 (18.6)	0.319

MDR, multidrug-resistant; UTI, urinary tract infection; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment.
[a] Categorical variables are presented as number (percentage) and continuous variables as median (interquartile range).

Table 4
Multivariate logistic regression analysis of risk factors for 30-day all-cause mortality: multivariate generalised linear model (generalised estimating equation) ($N = 2135$)

Risk factor	OR	95% CI	*P*-value
Functional capacity: bedridden	2.29	1.41–3.74	**0.001**
Previous hospitalisation	1.42	1.09–1.83	**0.007**
Endotracheal tube	1.63	1.13–2.36	**0.01**
Corticosteroids	1.17	0.87–1.59	0.291
Charlson comorbidity index	1.07	1.03–1.13	**0.001**
Hospital-acquired infection	1.59	1.21–2.09	**0.001**
MDR *Pseudomonas*	1.72	1.26–2.33	**0.001**
UTI bacteraemia	0.66	0.46–0.94	**0.021**
ICU admission	1.53	1.02–2.28	**0.038**
SOFA score	1.19	1.13–1.26	**0.000**

OR, odds ratio; CI, confidence interval; MDR, multidrug-resistant; UTI, urinary tract infection; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment.

severely ill patient. Virulence factors of carbapenem-resistant *P. aeruginosa* have previously been described in association with higher mortality [25].

Increased risk of infection is a well-known adverse event of long-term high-dose corticosteroid use. However, an association between such use and increased mortality from bacteraemia is not well documented. Possible explanations for the increased mortality in the current cohort might include reduced inflammatory response and delayed diagnosis due to blunted clinical presentation, severe underlying disease, increased risk for secondary infections and higher risk for cardiovascular complications [26,27].

Appropriate empirical therapy was significantly associated with mortality in the univariable analysis of the entire cohort. This association was not significant in the multivariable analysis using a propensity score for receiving appropriate empirical therapy. In addition, excluding from the analysis patients who died within 48 h, no association between appropriate empirical therapy and mortality was demonstrated. Analysing predictors of receiving appropriate therapy, a significantly higher SOFA score was found among patients receiving appropriate empirical therapy. Thus, we assume that the association between appropriate therapy and mortality represents earlier and broader-range antibiotic therapy administered to more severely ill patients. This observation of a higher likelihood of receiving early appropriate therapy among patients with poor prognostic factors has previously been found by Horino et al. [2]. Similarly, Wiggers et al. raised the possibility of bias-by-indication to explain their finding of no association between appropriate therapy and time to cure among patients with bacteraemic UTI [28]. Additional recent studies also demonstrated no association between appropriateness of therapy and mortality among patients with extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae bacteraemia. The most common source of infection in these studies was UTI [29,30]. The rate of active empirical therapy in this study in general was similar to that reported by previous studies evaluating *P. aeruginosa* bacteraemia (~60–70%) [10,24].

Combination definitive therapy was not associated with mortality in this cohort. This finding is in line with the previous lack of strong evidence to support combination therapy for *P. aeruginosa* bacteraemia [31].

This study was a multicentre study including data from 25 centres. On the one hand, this carries the advantage of a large sample size of 2396 patients. On the other hand, multicentre studies might be associated with between-centre differences, creating heterogeneity in the results. To overcome this potential limitation, the analysis was performed using the generalised estimating equation model [32]. Nevertheless, the results are limited by the retrospective design, compromising the robustness of the data collected.

Unmeasured confounders may have affected the results, and these could explain the finding of significantly increased mortality with MDR *P. aeruginosa*, for example, as discussed above.

5. Conclusions

All of the risk factors for a fatal outcome were not dependent on the management of infection. Early appropriate empirical therapy and definitive combination therapy were not associated with reduced mortality. In patients with non-severe clinical presentation, especially those with a suspected urinary source, using a narrow-spectrum antibiotic as an empirical strategy may be reasonable while awaiting susceptibility results. Owing to the irreversibility of these risk factors, efforts should probably focus on prevention of infection, mainly hospital-acquired and MDR infections.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2019.11.004.

References

[1] Kang CI, Kim SH, Kim HB, Park SW, Choe YJ, Oh MD, et al. *Pseudomonas aeruginosa* bacteremia: risk factors for mortality and influence of delayed receipt of effective antimicrobial therapy on clinical outcome. Clin Infect Dis 2003;37:745—51.
[2] Horino T, Chiba A, Kawano S, Kato T, Sato F, Maruyama Y, et al. Clinical characteristics and risk factors for mortality in patients with bacteremia caused by *Pseudomonas aeruginosa*. Intern Med 2012;51:59–64.
[3] Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. Clin Infect Dis 2004;39:309–17.
[4] Ammerlaan HS, Harbarth S, Buiting AG, Crook DW, Fitzpatrick F, Hanberger H, et al. Secular trends in nosocomial bloodstream infections: antibiotic-resistant bacteria increase the total burden of infection. Clin Infect Dis 2013;56:798–805.
[5] Aliaga L, Mediavilla JD, Cobo F. A clinical index predicting mortality with *Pseudomonas aeruginosa* bacteraemia. J Med Microbiol 2002;51:615–19.
[6] Lee CC, Lee CH, Hong MY. Risk factors and outcome of *Pseudomonas aeruginosa* bacteremia among adults visiting the ED. Am J Emerg Med 2012;30:852–60.
[7] Micek ST, Lloyd AE, Ritchie DJ, Reichley RM, Fraser VJ, Kollef MH. *Pseudomonas aeruginosa* bloodstream infection: importance of appropriate initial antimicrobial treatment. Antimicrob Agents Chemother 2005;49:1306–11.
[8] Vidal F, Mensa J, Almela M, Martínez JA, Marco F, Casals C, et al. Epidemiology and outcome of *Pseudomonas aeruginosa* bacteremia, with special emphasis on the influence of antibiotic treatment. Analysis of 189 episodes. Arch Intern Med 1996;156:2121–6.
[9] Cheong HS, Kang CI, Wi YM, Ko KS, Chung DR, Lee NY, et al. Inappropriate initial antimicrobial therapy as a risk factor for mortality in patients with community-onset *Pseudomonas aeruginosa* bacteraemia. Eur J Clin Microbiol Infect Dis 2008;27:1219–25.
[10] Joo EJ, Kang CI, Ha YE, Kang SJ, Park SY, Chung DR, et al. Risk factors for mortality in patients with *Pseudomonas aeruginosa* bacteremia: clinical impact of antimicrobial resistance on outcome. Microb Drug Resist 2011;17:305–12.
[11] Kim YJ, Jun YH, Kim YR, Park KG, Park YJ, Kang JY, et al. Risk factors for mortality in patients with *Pseudomonas aeruginosa* bacteremia; retrospective study of impact of combination antimicrobial therapy. BMC Infect Dis 2014;14:161.
[12] Schechner V, Gottesman T, Schwartz O, Korem M, Maor Y, Rahav G, et al. *Pseudomonas aeruginosa* bacteremia upon hospital admission: risk factors for mortality and influence of inadequate empirical antimicrobial therapy. Diagn Microbiol Infect Dis 2011;71:38–45.
[13] Su TY, Ye JJ, Hsu PC, Wu HF, Chia JH, Lee MH. Clinical characteristics and risk factors for mortality in cefepime-resistant *Pseudomonas aeruginosa* bacteremia. J Microbiol Immunol Infect 2015;48:175–82.
[14] Buehrle DJ, Shields RK, Clarke LG, Potoski BA, Clancy CJ, Nguyen MH. Carbapenem-resistant *Pseudomonas aeruginosa* bacteremia: risk factors for mortality and microbiologic treatment failure. Antimicrob Agents Chemother 2017;61 pii: e01243-16.
[15] Lee CH, Su TY, Ye JJ, Hsu PC, Kuo AJ, Chia JH, et al. Risk factors and clinical significance of bacteremia caused by *Pseudomonas aeruginosa* resistant only to carbapenems. J Microbiol Immunol Infect 2017;50:677—83.
[16] Paul M, Shani V, Muchtar E, Kariv G, Robenshtok E, Leibovici L. Systematic review and meta-analysis of the efficacy of appropriate empiric antibiotic therapy for sepsis. Antimicrob Agents Chemother 2010;54:4851–63.
[17] Lodise P Jr, Patel N, Kwa A, Graves J, Furuno JP, Graffunder E, et al. Predictors of 30-day mortality among patients with *Pseudomonas aeruginosa* bloodstream infections: impact of delayed appropriate antibiotic selection. Antimicrob Agents Chemother 2007;51:3510–15.
[18] Babich T, Naucler P, Valik JK, Giske CG, Benito N, Cardona R, et al. Ceftazidime, carbapenems, or piperacillin–tazobactam as single definitive therapy for *Pseudomonas aeruginosa* bloodstream infection—a multi-site retrospective study. Clin Infect Dis 2019 Jul 17 [Epub ahead of print]. doi:10.1093/cid/ciz668.
[19] Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control 2008;36:309–32.
[20] Parkins MD, Gregson DB, Pitout JD, Ross T, Laupland KB. Population-based study of the epidemiology and the risk factors for *Pseudomonas aeruginosa* bloodstream infection. Infection 2010;38:25–32.
[21] Humphreys H, Fitzpatick F, Harvey BJ. Gender differences in rates of carriage and bloodstream infection caused by methicillin-resistant *Staphylococcus aureus*: are they real, do they matter and why? Clin Infect Dis 2015;61:1708–14.
[22] Mansur N, Hazzan R, Paul M, Bishara J, Leibovici L. Does sex affect 30-day mortality in *Staphylococcus aureus* bacteremia? Gend Med 2012;9:463–70.
[23] Combes A, Luyt CE, Trouillet JL, Nieszkowska A, Chastre J. Gender impact on the outcomes of critically ill patients with nosocomial infections. Crit Care Med 2009;37:2506–11.
[24] Peña C, Suarez C, Gozalo M, Murillas J, Almirante B, Pomar VSpanish Network for Research in Infectious Diseases (REIPI). Prospective multicenter study of the impact of carbapenem resistance on mortality in *Pseudomonas aeruginosa* bloodstream infections. Antimicrob Agents Chemother 2012;56:1265–72.
[25] Jeong SJ, Yoon SS, Bae IK, Jeong SH, Kim JM, Lee K. Risk factors for mortality in patients with bloodstream infections caused by carbapenem-resistant *Pseudomonas aeruginosa*: clinical impact of bacterial virulence and strains on outcome. Diagn Microbiol Infect Dis 2014;80:130–5.
[26] Ni YN, Chen G, Sun J, Liang BM, Liang ZA. The effect of corticosteroids on mortality of patients with influenza pneumonia: a systematic review and meta–analysis. Crit Care 2019;23:99.
[27] Cutolo M, Seriolo B, Pizzorni C, Secchi ME, Soldano S, Paolino S, et al. Use of glucocorticoids and risk of infections. Autoimmun Rev 2008;8:153–5.
[28] Wiggers JB, Sehgal P, Pinto R, MacFadden D, Daneman N. The association of adequate empirical treatment and time to recovery from bacteraemic urinary tract infections: a retrospective cohort study. Clin Microbiol Infect 2019;25:1253–8.
[29] Frakking FN, Rottier WC, Dorigo-Zetsma JW, van Hattem JM, van Hees BC, Kluytmans JA, et al. Appropriateness of empirical treatment and outcome in bacteremia caused by extended-spectrum-β-lactamase-producing bacteria. Antimicrob Agents Chemother 2013;57:3092–9.
[30] Lim CL, Spelman D. Mortality impact of empirical antimicrobial therapy in ESBL- and AmpC-producing Enterobacteriaceae bacteremia in an Australian tertiary hospital. Infect Dis Health 2019;24:124–33.
[31] Paul M, Leibovici L. Editorial commentary: combination therapy for *Pseudomonas aeruginosa* bacteremia: where do we stand? Clin Infect Dis 2013;57:217–20.
[32] Kahan BC. Accounting for centre-effects in multicentre trials with a binary outcome—when, why, and how? BMC Med Res Methodol 2014;14:20.