Antimicrobial combination treatment including ciprofloxacin decreased the mortality rate of *Pseudomonas aeruginosa* bacteraemia: a retrospective cohort study

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**Abstract** Ineffective antimicrobial therapy of *Pseudomonas aeruginosa* bacteraemia increases mortality. Recent studies have proposed the use of antimicrobial combination therapy composed of a beta-lactam with either ciprofloxacin or tobramycin. To determine if combination therapy correlates to lower mortality and is superior compared to monotherapy, we investigated the effect of antimicrobial treatment regimens on 30-day mortality in a cohort with *Pseudomonas aeruginosa* bacteraemia. All cases of *P. aeruginosa* bacteraemia (*n* = 292) in southwest Skåne County, Sweden (years 2005–2010, adult population 361,112) and the whole county (2011–2012, 966,130) were identified. Available medical and microbiological records for persons aged 18 years or more were reviewed (*n* = 235). Antimicrobial therapy was defined as empiric at admission or definitive after culture results and was correlated to 30-day mortality in a multivariate regression model. The incidence and mortality rates were 8.0 per 100,000 adults and 22.9% (67/292), respectively. As expected, multiple comorbidities and high age were associated with mortality. Adequate empiric or definitive antipseudomonal treatment was associated with lower mortality than other antimicrobial alternatives (empiric *p* = 0.02, adj. *p* = 0.03; definitive *p* < 0.001, adj. *p* = 0.007). No difference in mortality was seen between empiric antipseudomonal monotherapy or empiric combination therapy. However, definitive combination therapy including ciprofloxacin correlated to lower mortality than monotherapy (*p* = 0.006, adj. *p* = 0.003), whereas combinations including tobramycin did not. Our results underline the importance of adequate antipseudomonal treatment. These data also suggest that *P. aeruginosa* bacteraemia should be treated with an antimicrobial combination including ciprofloxacin when susceptible.

**Abbreviations**
AIDS Acquired immune deficiency syndrome
BSI Bloodstream infection
CCI Charlson comorbidity index
CF Cystic fibrosis
CI Confidence interval
COPD Chronic obstructive pulmonary disease
MIC Minimum inhibitory concentration
OR Odds ratio
SD Standard deviation

**Introduction**

Bacteraemia caused by the opportunist *Pseudomonas aeruginosa* is a serious condition that has increased in incidence [1]. It is associated with high age, multiple comorbidities and advanced or prolonged healthcare [1]. Hence, the incidence rate of *P. aeruginosa* bacteraemia is likely to continue to rise as healthcare services are advancing and life expectancy continues to increase [1, 2]. It is one of the most common Gram-negative bloodstream infections (BSI), only preceded by *Escherichia coli* and *Klebsiella* spp. However,
the mortality of P. aeruginosa BSI has consistently been reported to be higher than that of E. coli BSI (23–36%) [1, 3–8].

Treatment of pulmonary infections caused by P. aeruginosa has been the topic of several reviews [9–11]. Patients with cystic fibrosis (CF) are often colonised by P. aeruginosa, but it is rare that CF patients suffer from bacteraemia [12]. Pseudomonas aeruginosa also occasionally colonises chronic wounds and the gastrointestinal and urinary tracts, particularly in hospitalised patients or patients with indwelling catheters [13]. Pseudomonas strains causing long-term colonisation of CF patients have adapted to become less virulent, but are extremely resistant to antimicrobials due to altered efflux pumps, porins, beta-lactamases with extended substrate specificity and biofilm formation [14]. On the other hand, invasive isolates are generally more susceptible to antimicrobials, although strains with extensive antimicrobial resistance have been reported [15]. The optimal antimicrobial treatment regimens against P. aeruginosa in the airway may thus, differ from optimal treatment regimens against bacteraemia and conclusions drawn from studies on pneumonia may not be generalisable to bacteraemia.

The most adequate treatment regimen of P. aeruginosa bacteraemia is a matter of debate. Despite the species being often highly resistant to antimicrobials, there are normally still several antimicrobial treatment regimens to choose from, either as monotherapy or combination therapy. Ineffective empiric antimicrobial therapy has been associated with increased mortality [16, 17]. Commonly used antipseudomonal drugs include penicillins with beta-lactamase inhibitors, certain cephalosporins, carbapenems, colistin, fluoroquinolones and aminoglycosides. Combination therapy is often administered to critically ill patients and most combinations include a beta-lactam antimicrobial together with either a fluoroquinolone or an aminoglycoside. Several studies have addressed the question as to whether to use monotherapy or combination therapy and the conclusions drawn are conflicting [16–20]. The assumption that combination therapy including either fluoroquinolones or aminoglycosides would have an equivalent effect on P. aeruginosa bacteraemia is, however, not necessarily correct. Earlier studies are inconclusive due to the insufficient number of patients in each group or stratification into combined groups of both fluoroquinolones and aminoglycosides. Hence, the effect on bacteraemia of adding a fluoroquinolone or an aminoglycoside to a beta-lactam is unclear at present.

We investigated the effect on 30-day mortality of different antimicrobial treatment regimens against P. aeruginosa bacteraemia. We observed that both empiric therapy on admission and definitive therapy after culture results affected mortality. Combination therapy with a beta-lactam and ciprofloxacin was significantly associated with a lower mortality compared to monotherapy. Moreover, the design of our population-based retrospective cohort allowed us to observe unbiased incidence rates and antimicrobial susceptibility patterns.

Materials and methods

Study population and setting

The cohort comprised the adult population (aged ≥18 years) of southwest Skåne County, Sweden during a 6-year period (2005–2010; adult population 361,112) in addition to the entire county during a period of 2 years (2011–2012; adult population 966,130). The area corresponded to the catchment area of the microbiological laboratory in Malmö that was expanded in 2011 because of fusion with an adjacent laboratory. The included laboratories analysed 100% of the blood cultures sampled in the area. Hospital care was provided by Skåne University Hospital and surrounding regional hospitals.

Participants, study protocol and variables

We identified 292 unique individuals with P. aeruginosa bacteraemia. Recurrent cases were only included once. Incidence rates were calculated using yearly population data collected from Statistics Sweden [21]. Microbiological culture data were collected from the laboratory’s records (wwLab; Autonik, Sköldinge, Sweden). Data on susceptibility and concurrent infections were collected, as were the time and date of preliminary and definitive culture results. Clinical data were collected from the hospital patient records (Melior; Siemens Healthcare Services, Upplands Väsby, Sweden). Thirty-day mortality was analysed as the outcome variable for all study cases (n = 292), as presented graphically in Fig. 1. Patients with available hospital medical records were included for correlations with comorbidities (n = 235). Sixteen patients had incomplete medication charts and were excluded from correlations with treatments (n = 219). Missing data were missing at random, with more missing records during the first years of the study, gradually decreasing over the study period. Randomness was controlled by comparing sex and age for missing and non-missing files. All recorded clinical variables and healthcare-related data are presented in the supplementary data, Table A1. The Charlson comorbidity index (CCI) was calculated to estimate the level of illness prior to the current bacteraemia (supplementary data, Table A2) [22]. Compound variables included pulmonary disease [chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, asthma and cystic fibrosis] and heart disorder (congestive heart failure, ischaemic heart disease, cardiac arrhythmia and heart valve disease).
Pseudomonas aeruginosa bacteraemia was defined as the isolation of the bacterial species in a blood culture collected from a patient at a hospital out-patient unit, a hospital ward or an emergency department using standard aseptic techniques. The term ‘bacteraemia’ was considered to be equivalent to BSI.

All samples were cultured using the automated BacT/ALERT system (bioMérieux, Marcy l’Etoile, France). Isolates were identified by typical characteristics on agar plates and biochemical tests. Antimicrobial resistance was determined by disc diffusion on Mueller–Hinton agar plates, Etests (Biodisk, Solna, Sweden) or Vitek (bioMérieux) and subjected to antimicrobial susceptibility testing according to guidelines from the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [23]. Physicians were notified when preliminary results on positive blood cultures were available.

Statistical analysis

All data were entered into an Excel spreadsheet (Microsoft, Redmond, WA) and exported to SPSS Statistics version 23 (IBM, Armonk, NY) and Stata 14 (StataCorp, College Station, TX) for statistical analysis. Graphs were drawn in Prism 6 (GraphPad, La Jolla, CA). The results were expressed as median and interquartile range for continuous variables and as frequencies and percentages for categorical variables. Two-tailed p-values were calculated with Wilcoxon’s and Fisher’s exact test and values ≤0.05 were considered statistically significant. Odds ratios (ORs) were determined in the univariate analysis and presented with 95% confidence intervals (CIs). The adjusted OR for mortality was determined in a multivariate logistic regression model. We used stepwise backward selection to create the multivariable model in which all variables with p-values of ≤0.1 were entered, and variables with resulting p-values exceeding 0.2 were excluded. Age was stratified into categories, with 18–49 years as the index. A propensity score-adjusted analysis was performed that included the following covariates: age, sex, pulmonary, cardiovascular, renal, hepatic, neurological and malignant comorbidities, together with healthcare indicators: catheters, surgery, intensive care and coinfections. The propensity scores of receiving ciprofloxacin as combination therapy as well as monotherapy were each introduced into separate logistic regression models using ciprofloxacin treatment as a binary regression variable.

Results

The incidence of P. aeruginosa BSI increases with high age and male sex

The average annual incidence rate of P. aeruginosa bacteraemia was 8.0 [standard deviation (SD)±1.22] cases per 100,000 adult inhabitants. The median age of the study cases was 74 years, well above the median age of the adult population (47 years, Fig. 2a) and the calculated incidence rate was highest for the oldest age groups (age ≥80 years: 31.0/100,000 adult inhabitants). As seen in previous studies, the incidence was higher for males than females (Fig. 2b) [5]. The most common infection focus was the urinary tract (94/235, 40.7%), followed by the respiratory tract (42/235, 18.2%), wounds (38/235, 16.5%) and intravenous catheters.
泌尿道焦点更常见于男性（男性77/159, 49.3% vs. 女性17/75, 22.6%, p < 0.001）。男性中，泌尿道感染持续时间超过一周的情况更多（51/77, 66.2% vs. 其他部位18/61, 22.8%, p < 0.001）。在研究的头五年，观察到发病率的年增长，然而从2010年开始，每年的发病率没有显著变化，尽管分析的血液培养的数量在整个研究期间增加（图2c）。

**Comorbidities, high age and respiratory tract focus correlate to increased mortality**

研究人群的30天死亡率是22.9%（67/292）。如预期，幸存者年龄更小（平均年龄69.8 vs. 74.4岁，p = 0.02）。基本的、合并症的和医疗相关数据在表1中呈现。为了评估合并症对30天死亡率的影响，我们计算了CCI来评估年龄及合并症。CCI和选择变量在单因素和多变量回归分析中与30天死亡率相关（表2）。女性的30天死亡率高于男性（校正后p = 0.006）和一个更高的CCI相关（survivors mean CCI 6.9 vs. non-survivors 8.5, p = 0.002）。肺部、血液或转移性恶性疾病的患者高死亡率，而糖尿病和近期化疗相关的死亡率降低。呼吸道感染焦点与较高的死亡率相关，尿路感染或泌尿道内留置导尿管与较低的死亡率相关。联合感染在90（31%）病例中被检测到。最常见的共生菌是Enterobacteriaceae，但也有不同类型的肠球菌、金黄色葡萄球菌和厌氧菌被记录。联合感染与30天死亡率增加（p = 0.02）相关。院内感染定义为在血液培养前至少住院一周的患者，与较高死亡率没有相关性。

**Antimicrobial resistance against* P. aeruginosa* did not increase during the study period**

抗感染药物对*P. aeruginosa*的耐药性在研究期间没有增加。研究中使用的细菌对的抗感染药物耐药性通常较低，与之前的报告类似。亚胺培南的耐药性为6.8%，美罗培南6.3%，哌拉西林-他唑巴坦6.2%，妥布霉素0.7%，头孢他啶5.5%和环丙沙星10.0%。除了2008年美罗培南的耐药性高峰外，抗感染药物的耐药性在研究期间没有提高（补充数据，表A3）。在单因素相关性中，只有美罗培南的耐药性与30天死亡率增加相关（6例死亡，13例，46.2%, p = 0.033）。

**Fig. 2** *Pseudomonas aeruginosa* bacteremia incidence increases with age. Incident cases of *P. aeruginosa* bacteremia were older (a, bars, left y-axis) than the population in Skåne County (a, curve, right y-axis). In all age groups, the incidence of *P. aeruginosa* bacteremia was higher among males than females and increased with higher age (b). No increase in incidence was seen over the entire study period (c, left y-axis), even though the number of analysed blood cultures increased (c, right y-axis) (9/235, 3.9%). The remaining individuals (48, 20.8%) had unknown infection site. Urinary tract focus was more common among men (males 77/159, 49.3% vs. females 17/75, 22.6%, p < 0.001) and most men with this focus had had a urinary catheter for more than one week (51/77, 66.2% vs. other foci 18/61, 22.8%, p < 0.001). During the first five years of the study, a yearly increase was seen in incident cases. This trend, however, ceased in 2010 and, in total, we could not observe any significant change in incidence rate, although the number of analysed blood cultures increased throughout the study period (Fig. 2c).
In contrast, an increased 30-day mortality (53.3%; adj. $p = 0.01$) was observed when antimicrobials were not administered. Forty cases (18.2%) received empiric combination treatment including tobramycin, which did not decrease the mortality rate compared to monotherapy. Only five cases (2.3%) received empirical combination therapy including ciprofloxacin.

### Definitive antimicrobial therapy with ciprofloxacin combinations increases survival

Sixteen patients (7.3%) died before any culture results were available. All surviving patients ($n = 203$) were administered definitive antimicrobial treatment following positive blood culture results with *P. aeruginosa*. The majority of cases (174; 85.7%) were given an effective antipseudomonal treatment. Preliminary culture results were provided for 93.1% and the mean time to preliminary culture result was 1.96 days ($SD \pm 1.19$) and 3.68 days ($SD \pm 1.63$) to final results. More than half were treated with ciprofloxacin (50.7%), as a part of a combination therapy (38.4%) or as monotherapy (12.3%). Piperacillin–tazobactam was given to 33.0%, carbapenem to 21.2%, tobramycin to 17.2% and, finally, ceftazidime to 10.3% of the cases. Other antimicrobial regimens were administered to less than 10% of patients.

The choice of an adequate definitive antipseudomonal treatment matching the antibiogram significantly decreased 30-day mortality (adj. $p = 0.007$) when analysed in our multivariable regression model (Table 3; lower section). Targeted monotherapy was not significantly associated with decreased 30-day mortality, whereas inadequate treatment with cefotaxime or cefuroxime as monotherapy increased mortality up to 40% (4/10).

In contrast to any individual monotherapy, definitive combination therapy with ciprofloxacin decreased the 30-day mortality (adj. $p = 0.003$), whereas combinations including tobramycin did not affect the mortality. To disclose involuntary selection bias in the group receiving ciprofloxacin, a propensity score was calculated. The effect of the addition of ciprofloxacin was independent of confounders (age, sex, comorbidities and intensive care treatment, as well as choice of antimicrobial agent). With the available covariates, we did not find any evidence of selection bias to any of the ciprofloxacin/no ciprofloxacin groups. Propensity score-adjusted analyses did not change the effect on mortality for ciprofloxacin combination therapy (propensity score-adjusted OR $0.16$, 95% CI $0.05–0.53$, $p = 0.003$ vs. OR $0.16$, 95% CI $0.05–0.53$, $p = 0.003$). For ciprofloxacin monotherapy, the association remained non-significant (propensity score-adjusted OR $0.59$, 95% CI $0.04–9.9$, $p = 0.72$ vs. OR $0.32$, 95% CI $0.06–1.83$, $p = 0.20$). The lower mortality associated with ciprofloxacin combination therapy was independent of

### Empiric antimicrobial treatment and importance for mortality

Of the 219 patients with complete medication charts, almost all patients (93.2%) received antimicrobial treatment after cultures were drawn. In 47.5%, adequate empirical antimicrobial agents were given according to the antibiograms. The most common empiric treatment was cefotaxime (36.5%), followed by tobramycin (18.3%) and piperacillin (16.9%). The empiric use of any other antimicrobial was less than 10%. The administration of tobramycin was, in all cases, combined with another antimicrobial. Monotherapy was given to 125 patients (57.1%) and 79 patients received combination therapy (36.1%).

The choice of empiric treatment was associated with 30-day mortality in our cohort in direct correlations and when entered into a multivariable regression model (Table 3, upper section). Treatment with any effective antipseudomonal significantly decreased the 30-day mortality to 15.4% (adj. $p = 0.03$). In contrast, an increased 30-day mortality (53.3%;

| Characteristic | Male ($n = 159$) | Female ($n = 76$) |
|---------------|-----------------|------------------|
| Age           | 74 (63–80)      | 74 (63–83)       |
| Charlson score| 7 (5–9)         | 6 (5–9)          |
| Pulmonary disease* | 34 (21.4) | 15 (19.7)       |
| COPD          | 17 (10.7)       | 7 (9.2)          |
| Cystic fibrosis | 1 (0.6)      | 0 (0.0)          |
| Heart disorder* | 62 (39.0)    | 25 (32.9)        |
| Peripheral vascular disease | 40 (25.2) | 15 (19.7)       |
| Vascular graft | 11 (6.9)       | 4 (5.3)          |
| Diabetes mellitus | 50 (31.4)   | 22 (28.9)        |
| Renal failure | 36 (22.6)       | 6 (7.9)          |
| Chronic liver disease | 4 (2.5)     | 4 (5.3)          |
| Neurological paresis | 4 (2.5)     | 0 (0.0)          |
| Immunosuppression | 35 (22.0)  | 17 (22.4)        |
| Chemotherapy in the last 6 months | 30 (18.9) | 22 (28.9)       |
| Solid malignancy | 45 (28.3)   | 28 (36.8)        |
| Metastasis    | 24 (15.1)       | 15 (19.7)        |
| Haematological disease | 26 (16.4) | 10 (13.2)        |
| Neutropaenia  | 24 (15.1)       | 14 (18.4)        |
| AIDS          | 1 (0.6)         | 0 (0.0)          |
| Burn wounds   | 4 (2.5)         | 2 (2.6)          |
| Urinary catheter >1 week | 70 (44.0) | 18 (23.7)        |
| Hospitalised >1 week | 58 (36.5) | 24 (31.6)        |
| Surgery in the last month | 34 (21.4) | 14 (18.4)       |
| Resident at nursing home | 26 (16.4) | 7 (9.2)          |

*Age for all cases (n = 292) and characteristics for cases with full medical records (n = 235). Continuous variables are expressed as median (interquartile range) and categorical variables as observed numbers (percentage). Compound variables are marked with *
### Table 2 Thirty-day mortality correlated to selected characteristics

| Characteristic                        | Died (%) | OR (95% CI)     | p-value | adj. OR (95% CI) | adj. p-value |
|---------------------------------------|----------|-----------------|---------|-----------------|--------------|
| Male sex                              | 40 (19.9)| 0.59 (0.33–1.04)| 0.07    | 0.35 (0.17–0.74)| 0.006        |
| Age 18–49 years                       | 2 (9.1)  | 1.00            |         |                 |              |
| Age 50–59 years                       | 6 (16.7) | 2.00 (0.37–10.92)| 0.42    | 2.72 (0.39–19.08)| 0.31         |
| Age 60–69 years                       | 14 (22.6)| 2.92 (0.61–14.03)| 0.18    | 3.21 (0.51–20.03)| 0.21         |
| Age 70–79 years                       | 20 (24.1)| 3.17 (0.68–14.78)| 0.14    | 3.58 (0.58–22.17)| 0.17         |
| Age ≥80 years                         | 25 (28.1)| 3.91 (0.85–17.95)| 0.08    | 6.60 (1.13–38.49)| 0.04         |
| Comorbidity (n = 235)                 |          |                 |         |                 |              |
| Pulmonary disease                     | 18 (36.7)| 2.58 (1.29–5.14)| 0.01    | 3.05 (1.34–6.94)| 0.008        |
| COPD                                  | 8 (33.3) | 1.89 (0.76–4.69)| 0.20    | 0.61 (0.16–2.37)| 0.47         |
| Cystic fibrosis                       | 0 (0.0)  |                 |         |                 |              |
| Heart disorder                        | 22 (25.3)| 1.33 (0.71–2.49)| 0.42    | 1.50 (0.64–3.51)| 0.35         |
| Peripheral vascular disease           | 13 (23.6)| 1.14 (0.56–2.34)| 0.71    | 2.26 (0.96–5.30)| 0.06         |
| Vascular graft                         | 1 (6.7)  | 0.24 (0.03–1.83)| 0.20    | 0.18 (0.02–1.69)| 0.13         |
| Diabetes mellitus                     | 9 (14.3) | 0.49 (0.22–1.08)| 0.08    | 0.46 (0.22–0.96)| 0.04         |
| Renal failure                         | 10 (23.8)| 1.12 (0.51–2.46)| 0.84    | 1.96 (0.74–5.17)| 0.18         |
| Chronic liver disease                 | 3 (33.3) | 1.79 (0.43–7.40)| 0.42    | 1.27 (0.22–7.21)| 0.79         |
| Neurological paresis                  | 1 (33.3) | 1.16 (0.12–11.36)| 1.00   | 7.61 (0.45–128.36)| 0.16         |
| Immunosuppression                     | 11 (21.2)| 0.91 (0.43–1.93)| 0.85    | 0.75 (0.26–2.18)| 0.59         |
| Chemotherapy in the last 6 months     | 12 (23.1)| 1.05 (0.50–2.19)| 1.00    | 0.21 (0.07–0.66)| 0.007        |
| Solid malignancy                      | 20 (27.4)| 1.55 (0.81–2.94)| 0.23    | 0.99 (0.37–2.68)| 0.98         |
| Metastasis                            | 14 (35.9)| 2.33 (1.11–4.90)| 0.03    | 7.12 (2.32–21.79)| 0.001        |
| Haematologic disease                  | 11 (26.2)| 1.63 (0.74–3.59)| 0.28    | 5.47 (1.85–16.17)| 0.002        |
| Neutropeaemia                         | 11 (28.9)| 1.51 (0.69–3.30)| 0.30    | 1.33 (0.41–4.28)| 0.63         |
| AIDS                                  | 0 (0.0)  |                 |         |                 |              |
| Burn wounds                           | 2 (33.3) | 1.77 (0.32–9.95)| 0.62    | 4.08 (0.45–36.68)| 0.21         |
| Composite comorbidity score (n = 235) |         |                 |         |                 |              |
| Charlson score ≤4                     | 4 (9.1)  | 1.00            |         |                 |              |
| Charlson score 5–8                    | 27 (22.7)| 2.93 (0.96–8.94)| 0.06    | 2.91 (0.95–8.92)| 0.06         |
| Charlson score 9–12                   | 13 (26.5)| 3.61 (1.08–12.08)| 0.04  | 3.67 (1.09–12.41)| 0.04         |
| Charlson score ≥13                    | 21 (38.1)| 6.15 (1.59–23.82)| 0.009  | 7.05 (1.79–27.86)| 0.005        |
| Healthcare-related (n = 235)          |         |                 |         |                 |              |
| Urinary catheter >1 week              | 18 (20.5)| 0.87 (0.45–1.65)| 0.75    | 1.09 (0.50–2.39)| 0.82         |
| Surgery last month                    | 18 (18.8)| 0.76 (0.34–1.69)| 0.56    | 0.98 (0.38–2.51)| 0.96         |
| Hospitalised >1 week                  | 20 (24.4)| 1.21 (0.64–2.29)| 0.62    | 1.61 (0.76–3.41)| 0.22         |
| Resident at nursing home              | 8 (24.2) | 1.15 (0.48–2.72)| 0.82    | 1.16 (0.41–3.32)| 0.78         |
| Polymicrobial infection               | 22 (24.4)| 1.13 (0.62–2.02)| 0.68    | 2.52 (1.18–5.40)| 0.02         |
| Origin of infection (n = 235)         |         |                 |         |                 |              |
| Urinary tract                         | 12 (14.6)| 0.37 (0.18–0.75)| 0.005   | 0.28 (0.12–0.65)| 0.003        |
| Respiratory tract                     | 17 (38.6)| 2.81 (1.38–5.70)| 0.003   | 2.81 (1.13–7.01)| 0.03         |
| Wound                                 | 12 (31.6)| 1.81 (0.84–3.90)| 0.13    | 1.99 (0.81–4.92)| 0.13         |
| Central venous catheter               | 0 (0.0)  |                 |         |                 |              |
| Other/unknown                         | 11 (22.0)| 0.99 (0.47–2.11)| 0.98    | 1.16 (0.47–2.83)| 0.75         |

Patient characteristics correlated to 30-day mortality and presented with odds ratio (OR), adjusted odds ratio (adj. OR) and 95% confidence interval (95% CI). The multivariable model contained age, sex, pulmonary disease, vascular graft, peripheral vascular disease, chemotherapy in the last 6 months, haematological diseases including malignancies, metastasis, diabetes mellitus and neurological paresis. Significant values are in **bold font**

Age, CCI and origin of infection (Fig. 3a–c). Importantly also, patients in intensive care units that were treated with ciprofloxacin had a lower 30-day mortality than those receiving other antimicrobials (0 dead of 9 treated: 0% vs. other: 7/19, 36.8%, adj. p = 0.035).

### Discussion

In this retrospective cohort study, we provide evidence that the choice of antimicrobial treatment affected the 30-day mortality in patients suffering from *P. aeruginosa* bacteraemia.
Despite the average time to culture results being as short as 48 h, inadequate empiric antimicrobial treatment on admission negatively affected mortality rates. Similarly, inadequate definitive treatment after blood culture results was also associated with higher mortality rates. Particularly, definitive combination treatment that included ciprofloxacin favourably affected the 30-day mortality.

In total, we identified 292 patients with *P. aeruginosa* bacteraemia between 2005 and 2012. The overall 30-day mortality in this study was 22.9% and the annual incidence was 8 per 100,000 inhabitants, with higher rates among men and with increasing age. This was in line with previous studies, which have reported 30-day mortality rates ranging from 23% to 36.5% and incidence rates in the range 3.6–10.8 cases per 100,000 inhabitants and year [1, 3–8]. The incidence was higher for males than females, which was accounted for by the higher incidence among males with urinary catheter. Although the number of blood cultures steadily increased during the study period, no increase in the incidence of *P. aeruginosa* bacteraemia was seen over the entire study period. However, in parallel to the increase reported in the UK, the incidence rate in our study rose between 2005 and 2009 [1]. The explanation for the rising incidence during the first several years of the study and the concurrent increase in the UK is, at present, unclear and no epidemiological link is known.

The importance of correct empiric therapy on admission has been debated and, in the present study, the initial antimicrobial choice was important, as patients who received adequate antipseudomonal treatment had significantly lower mortality rates [3, 17, 24]. No individual empirical antimicrobial monotherapy or combination therapy was associated with changes in mortality. The large number of different administered antimicrobials resulted in low statistical power for all but the most commonly used drugs and only five patients received empirical ciprofloxacin combination treatment.

After positive blood cultures with *P. aeruginosa*, adequate definitive antipseudomonal treatment decreased the 30-day mortality. In contrast to ciprofloxacin combinations, combination therapy including tobramycin was not superior to monotherapy, similarly to that previously reported [20]. To find the potential influence of selection bias on our results, a propensity score was calculated to ensure comparability of the cohort receiving ciprofloxacin and those receiving other treatments, but no such bias could be identified. A few previous studies have investigated whether combination therapy was favourable against *P. aeruginosa* bacteraemia. For example, Kim et al.
showed that adequate combination therapy of any sort was beneficial for a subgroup of bacteraemic patients with febrile neutropaenia [18]. Peña et al. reported, however, that the choice between combination therapy and single-drug therapy did not affect outcome [17]. Furthermore, in a recent meta-analysis focusing on empiric treatment, no difference in mortality was seen between the study groups, but in contrast to the present investigation, no analysis was made separately for aminoglycoside and ciprofloxacin combination therapy [19]. Our results are supported by DiMondi et al., who investigated the short-term outcome of bacteraemia and pneumonia; ciprofloxacin combinations comprised 90% of the combination therapies that were associated with favourable outcome [16]. Both beta-lactams and ciprofloxacin are highly efficient against *P. aeruginosa* in vitro. The reason for the favourable outcome for ciprofloxacin combination-treated patients in the present study is unknown. Combination therapy broadens the antimicrobial spectrum and synergy between antimicrobial drugs has been described, but synergy between ciprofloxacin and beta-lactams has not been reported [25].

In our cohort, 10.0% of the bacterial strains had reduced susceptibility for ciprofloxacin. This should be compared to three BSI studies from the USA that reported varying resistance levels (range 4.7–31%), with the highest levels from Maryland, where a majority of cases had been hospitalised for more than three days at inclusion [3, 4, 24]. Local knowledge of resistance levels is important, but it may be difficult to derive current resistance levels from surveillance programmes, as BSI may not be reported and, often, bacteraemia-causing bacteria are more susceptible. For comparison, the fluoroquinolone resistance in Skåne County of *P. aeruginosa* bacteraemia strains was 9.8% in 2011, whereas in the same year, 88.1% of *P. aeruginosa* strains from the respiratory tract of patients with CF were resistant to fluoroquinolones (unpublished data). Hence, combinations of antimicrobials including ciprofloxacin may be the most effective antipseudomonal treatment against bacteraemia, but the results are not, however, generalisable to pneumonia.

Patients suffering from BSI were of higher age than the general population and had multiple comorbidities, which also correlated to higher 30-day mortality, as did pulmonary disease (and infectious foci in the respiratory tract), malignant disease with metastasis and haematological malignancies. As inadequate antimicrobial therapy increased mortality, the likelihood of *P. aeruginosa* BSI should be considered at the choice of empiric antimicrobial therapy. Not all septic patients need empiric antipseudomonal treatment at admission, but it could be considered for patients with increased risk of *Pseudomonas* bacteraemia and with high risk of mortality. In addition to critically ill patients, these results suggest that patients with neoplasia and the elderly with multiple comorbidities could be eligible for such treatment. However, laboratory tests in vitro have shown that the use of ciprofloxacin at sub-MIC concentrations lead to bacterial mutations, causing resistance against both ciprofloxacin and beta-lactam antimicrobials [26]. Hence, any decisions to use ciprofloxacin should
be made wisely in order to limit further resistance development and monotherapy with ciprofloxacin should probably be avoided.

Our study cohort had a minimised population selection bias and, consequently, allowed for observation of, in total, 4.2 million adult person-years. The records at the microbiology laboratories allowed us to identify every occurrence of *P. aeruginosa* bacteraemia. This population-based approach allowed for a valid analysis of the incidence rate. We were not able to use a scoring system for severity of disease; instead this was determined by treatment at an intensive care unit. In the future, a prospective randomised interventional study to examine the effects of treatment regimens would be of high value, although the relative infrequency of *P. aeruginosa* bacteraemia would make this challenging in practice. An alternative would be a larger retrospective trial with emphasis on markers of acute severe disease.

In conclusion, this study gives an indication that *P. aeruginosa* bacteraemia should be treated with definitive antimicrobial drug combination regimens including ciprofloxacin when susceptible. Inadequate empiric antipseudomonal treatment on admission or inadequate definitive therapy after notification of positive blood cultures was associated with increased mortality. These results are of particular importance to those at the greatest risk for *P. aeruginosa* bacteraemia, the elderly patients with multiple comorbidities and patients with malignancy. Appropriate antipseudomonal treatment should be considered for these patients as early as possible to minimise the risk of death.

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**Compliance with ethical standards**

**Conflict of interest** Dr Jonas Ahl has received speaker honorarium from Pfizer, AstraZeneca, Meda and MSD, and research grants from Pfizer for a study not related to the present work. All remaining authors declare that they have no conflicts of interest.

**Ethical approval** Informed consent was not relevant to this retrospective study according to the Regional Ethical Review Board in Lund, Sweden, who granted approval of the present study (Dnr 2014/10).

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