Eur J Clin Microbiol Infect Dis (2008) 27:1219–1225
DOI 10.1007/s10096-008-0568-5

ARTICLE

Inappropriate initial antimicrobial therapy as a risk factor for mortality in patients with community-onset *Pseudomonas aeruginosa* bacteraemia

H. S. Cheong · C.-I. Kang · Y. M. Wi · K. S. Ko · D. R. Chung · N. Y. Lee · J.-H. Song · K. R. Peck

Received: 5 January 2008 / Accepted: 29 May 2008 / Published online: 25 June 2008

Abstract This study was performed to identify the risk factors for mortality and evaluate the effect of inappropriate initial antimicrobial therapy on the outcomes of patients with community-onset *Pseudomonas aeruginosa* bacteraemia in an emergency department (ER) setting. All cases with *P. aeruginosa* bacteraemia occurring within 48 h after ER visit from January 2000 to December 2005 were retrospectively analysed. A total of 106 community-onset *P. aeruginosa* bacteraemia cases in the ER were included (mean age, 57.61±14.44 years old; M:F, 58:48). Although *P. aeruginosa* bacteraemia was diagnosed in the ER, most of the cases of *P. aeruginosa* bacteraemia were healthcare-associated (88.7%). Malignancy (n=83, 78.3%) was the most common underlying disorder. Fifty patients (47.2%) were neutropaenic and 56 patients (52.8%) had septic shock. The overall 30-day mortality rate was 26.4% (28/106). In the univariate analysis, underlying malignancy, high Charlson's weighted index of comorbidity (≥3), high Pitt bacteraemia score (≥4), indwelling central venous catheter and inappropriate initial therapy were significantly associated with 30-day mortality (all P<0.05). In the multivariate analysis, high Pitt bacteraemia score (OR, 17.03; 95% CI, 4.60–63.15; P<0.001) and inappropriate initial antimicrobial therapy (OR, 4.29; 95% CI, 1.39–13.24; P=0.011) were found to be significant risk factors for 30-day mortality. The 30-day mortality rate was significantly higher in the inappropriate therapy group (18/51, 35.3%) than in the appropriate therapy group (10/55, 18.2%) (P=0.046). This study demonstrated that inappropriate initial antimicrobial therapy was significantly associated with unfavourable outcomes in patients with community-onset *P. aeruginosa* bacteraemia. As *P. aeruginosa* bacteraemia can be a fatal infection, even when community-onset, inappropriate antimicrobial therapy should be avoided in suspected cases of *P. aeruginosa* bacteraemia.

This study was presented in part at the 44th Annual Meeting of the Infectious Diseases Society of America (IDSA), 12–15 October 2006 held at the Metro Toronto Convention Centre in Toronto, Canada (abstract no. 1410)

H. S. Cheong · C.-I. Kang · Y. M. Wi · D. R. Chung · J.-H. Song · K. R. Peck (✉)
Division of Infectious Diseases, Samsung Medical Center,
Sungkyunkwan University School of Medicine,
50 Ilwon-dong, Gangnam-gu,
Seoul 135-710, Republic of Korea
e-mail: krpeck@skku.edu

N. Y. Lee
Department of Laboratory Medicine, Samsung Medical Center,
Sungkyunkwan University School of Medicine,
Seoul, Republic of Korea

K. S. Ko
Department of Molecular Cell Biology, Samsung Medical Center,
Sungkyunkwan University School of Medicine,
Seoul, Republic of Korea

K. S. Ko · J.-H. Song
Asian-Pacific Research Foundation for Infectious Diseases (ARFID),
Seoul, Republic of Korea

Background

Pseudomonas aeruginosa bacteraemia is a serious and life-threatening infection, especially in the immunocompromised and other susceptible populations [1]. Although *P. aeruginosa* is an important nosocomial pathogen, *P. aeruginosa* sepsis has also been reported in patients with community-onset infection, particularly in those with a healthcare-associated status [2, 3]. The treatment of *P. aeruginosa* infection can be

difficult because this microorganism tends to be resistant to the usual antibiotics recommended for treatment, including those in the community setting.

In an emergency department (ER) setting, the initiation of treatment with antimicrobial agents is almost always empirical, requiring knowledge of the likely pathogen and their usual antimicrobial susceptibility patterns. Resistance among *P. aeruginosa* has become increasingly common, making empirical therapy decisions more difficult.

The hospital mortality associated with *P. aeruginosa* bacteraemia is reported to be greater than 20%, and is the highest among patients receiving inappropriate initial antimicrobial treatment [4–6]. Numerous studies of *P. aeruginosa* bacteraemia have been reported [1, 4–9]. However, there are limited data regarding community-onset bacteraemia caused by *P. aeruginosa*. Furthermore, prior studies of *P. aeruginosa* bacteraemia did not evaluate the influence of inappropriate antimicrobial therapy on mortality caused by community-onset *P. aeruginosa* bacteraemia.

Thus, in the present study, we describe a recent six-year survey of *P. aeruginosa* bacteraemia, concentrated exclusively on community-onset infections, and the clinical-epidemiological features of patients. We conducted this study to identify the risk factors for mortality and evaluate the effect of inappropriate initial antimicrobial therapy on outcome in patients with community-onset *P. aeruginosa* bacteraemia.

Materials and methods

Study population

The database at our clinical microbiology laboratory was reviewed in order to identify patients with *P. aeruginosa* bacteraemia. Patients were included in the study if they had blood drawn for cultures within 48 h of admission in the ER and if their culture results had been positive for *P. aeruginosa*. Patients with polymicrobial bloodstream infection were excluded. The study period extended from January 2000 to December 2005 at the Samsung Medical Center, Seoul, Republic of Korea, a 1,350-bed tertiary care university hospital. The annual ER census in this hospital is approximately 55,000 visits. Only the first bacteraemic episode for each patient was included in the analysis.

Study design and data collection

A retrospective observational cohort study was conducted. We reviewed the medical records of the patients. The data collected included age, gender, underlying disease, site of infection, severity of illness (as calculated by the Pitt bacteraemia score and Charlson's weighted index of morbidity) and antimicrobial regimen. Severity status on admission could be assessed by the Pitt bacteraemia score. The comorbidity index developed by Charlson et al. is a validated method of classifying comorbidity to predict short- and long-term mortality from medical records [10, 11]. The presence of the following comorbid conditions was also documented: neutropaenia, presentation with septic shock, the receipt of immunosuppressive agents within 30 days prior to the onset of bacteraemia and the presence of a central venous catheter. As this study was retrospective, the patients' physicians, not researchers, had chosen the antimicrobial therapy regimens. The main outcome measure used was the 30-day mortality rate.

Definitions

P. aeruginosa bacteraemia was defined as a finding of *P. aeruginosa* in a blood culture specimen. Clinically significant bacteraemia was defined as at least one positive blood culture, together with two or more of the following conditions: fever (temperature >38°C) or hypothermia (<36°C), tachypnea (>24 breaths/min), tachycardia (heart rate >90 beats/min) and leukocytosis (white cell count >12,000 cells/mm^3) or leucopaenia (white cell count <4,000 cells/mm^3) [12].

Community-onset bacteraemia was defined as a positive blood culture taken on or within 48 h of admission. Episodes of community-onset bacteraemia were further classified as "healthcare-associated" if any of the following criteria were present [13]: >48 h hospital admission during the previous 90 days, receipt of haemodialysis, receipt of intravenous medication or home wound care in the previous 30 days, and residence in a nursing home or long-term care facility. Otherwise, cases without healthcare-associated risk factors were considered to be "community-acquired."

The initial empirical antimicrobial therapy was considered to be "appropriate" if the initial antibiotics, which were administered within 24 h after the acquisition of a blood culture sample, included at least one antibiotic that was active in vitro and when the dosage and route of administration were confirmed with current medical standards. Otherwise, the initial antimicrobial therapy was considered as "inappropriate" [14].

Neutropaenia was defined as an absolute neutrophil count below 500/mm^3. Septic shock was defined as sepsis associated with evidence of organ hypoperfusion and a systolic blood pressure <90 or >30 mm Hg less than the baseline, or a need for the use of a vasopressor to maintain blood pressure.

Microbiological tests

The recovery of *P. aeruginosa* isolates from blood was accomplished by the processing of blood cultures in a BACTEC Model 9240 (BD Diagnostic Instrument Systems,

Sparks, MD) or BacT/ALERT 3D (bioMerieux Inc., Hazelwood, MO). The identification of *P. aeruginosa* and antibiotics susceptibility testing were performed on the VITEK II automated system (bioMerieux Inc., Hazelwood, MO). Interpretations and quality control measures were performed according to the protocol of the manufacturer and compared to the standards of the Clinical and Laboratory Standards Institute [15].

Statistical analysis

Student's *t*-test was used to compare continuous variables and χ^2 or Fisher's exact test was used to compare categorical variables. In identifying the risk factors for mortality, a stepwise logistic regression analysis was used to control for the effects of confounding variables. Variables with a *P*-value of <0.05 in the univariate analysis were candidates for multivariate analysis. The Kaplan-Meier method was used for the survival analysis. We used backward elimination of any variable that did not contribute to the model on the grounds of the likelihood ratio test, using a significance cutoff of 0.05. All *P*-values were two-tailed, and *P*-values of <0.05 were considered to be statistically significant. The SPSS for Windows software package (version 11.5; SPSS Inc., Chicago, IL) was used for this analysis.

Results

Clinical characteristics of the study population

A total of 330 patients with *P. aeruginosa* bacteraemia were identified during the study period in our hospital, and, of these, 129 (39.1%) patients had a community-onset infection. Among these patients, 106 patients were enrolled and the remaining 23 patients (17.8%) were excluded from the analysis because of transfer to another hospital, incomplete medical records or unevaluable medical records. The mean (±standard deviation) age of the patients was 57.61±14.4 years and 58 (54.7%) of the patients were male. The demographic and clinical features are described in Table 1. The most common underlying diseases were solid tumour (*n*=56, 52.8%), haematologic malignancy (*n*=27, 25.5%) and benign pancreatobiliary tract disease (*n*=6, 5.7%). However, four patients (3.8%) showed no underlying disease. As for the primary sites of infection, the most common primary sites were the pancreatobiliary tract (*n*=21, 19.8%) and the lung (*n*=19, 17.9%). The primary site of infection was unknown in 36.8% (39 patients) of the patients. Fifty-six patients (52.8%) presented with septic shock and 50 patients (47.2%) were neutropaenic. Ninety-four patients (88.7%) were classified as having healthcare-associated infection and 12 patients (11.3%) had community-acquired bacteraemia.

Table 1 Clinical characteristics of the study population

Characteristics	Value (*n*=106)
Age, years (mean±SD)	57.61±14.44
Sex	
Male	58 (54.7)
Female	48 (45.3)
Underlying disease	
Solid tumour	56 (52.8)
Haematologic malignancy	27 (25.5)
Benign pancreatobiliary disease	6 (5.7)
End-stage renal disease	6 (5.7)
Others	7 (6.6)
None	4 (3.8)
Primary site of infection	
Unknown	39 (36.8)
Pancreatobiliary tract	21 (19.8)
Lung	19 (17.9)
Catheter-related infection	10 (9.4)
Soft tissue	5 (4.7)
Gastrointestinal tract	5 (4.7)
Urinary tract	3 (2.8)
Others	2 (1.9)
Neutropaenia	50 (47.2)
Presentation with septic shock	56 (52.8)
Use of immunosuppressive agents	49 (46.2)
Indwelling central venous catheter	31 (29.2)

SD=standard deviation
Note. Unless otherwise indicated, the data represent patient numbers (percentage in parentheses)

The antimicrobial susceptibilities of the *P. aeruginosa* blood isolates obtained during the study period are presented in Table 2. Resistance rates to ceftazidime, piperacillin/tazobactam, ciprofloxacin and imipenem were 16.3%, 11.5%, 17.0% and 8.6%, respectively.

Table 2 Antimicrobial resistance rate of *Pseudomonas aeruginosa* isolates

Antimicrobial agents	R/T (%)
Amikacin	5/103 (4.9)
Aztreonam	19/105 (18.1)
Ceftazidime	17/104 (16.3)
Ciprofloxacin	18/106 (17.0)
Gentamicin	21/106 (19.8)
Imipenem	9/105 (8.6)
Piperacillin/tazobactam	12/104 (11.5)

R=number of resistant isolates; T=total number of tested isolates

Thirty-day mortality and predictors of mortality

The overall 30-day mortality rate of *P. aeruginosa* bacteraemia was 26.4% (28/106). The factors associated with 30-day mortality are shown in Table 3. According to the univariate analysis, the factors associated with 30-day mortality in *P. aeruginosa* bacteraemia were high Charlson's weighted index of comorbidity, underlying malignancy, high Pitt bacteraemia score, indwelling central venous catheter and inappropriate therapy (Table 3).

Multivariate analysis using a logistic regression model including the variables associated with mortality by univariate analysis ($P<0.05$) showed that the significant independent risk factors for mortality were high Pitt bacteraemia score and inappropriate therapy (Table 4).

Impact of inappropriate therapy on the outcome of community-acquired *P. aeruginosa* bacteraemia

Fifty-one patients (48.1%) received inappropriate initial antimicrobial therapies. Of these, 40 patients received cephalosporins, four patients received aminoglycosides (with/without cephalosporins), one received carbapenem and four received ciprofloxacin. Two patients did not receive any antimicrobial agents.

Of 55 patients (51.9%) who received appropriate initial antimicrobial therapy, 23 patients received cefepime, 20 received ceftazidime (with/without aminoglycosides), eight received ciprofloxacin, two carbapenems and two received piperacillin/tazobactam.

When the clinical characteristics of the appropriate therapy group were compared with those of the inappropriate therapy group, there were no significant differences between both of the groups for the variables associated with mortality (i.e. underlying malignancy and severity of illness). When compared with patients who received appropriate therapy, the mortality of patients who received inappropriate therapy was significantly higher (35.3% [18/51] vs. 18.2% [10/55], $P=0.046$; Table 5). The survival curve also showed that the inappropriate therapy group had a lower probability of survival than the appropriate therapy group (Fig. 1).

Discussion

In this study, we present our recent experiences related to community-onset *P. aeruginosa* bacteraemia and described their clinical characteristics. We found that the severity of illness (Pitt bacteraemia score), severity of underlying disease (Charlson's weighted index of comorbidity) and inappropriate antimicrobial therapy were strong prognostic factors of mortality. Inadequately treated patients had significantly higher mortality than adequately treated patients, and inappropriate initial antimicrobial therapy was identified as an independent predictor for mortality by multivariate analysis after adjusting for confounding variables.

Previous investigations have also demonstrated that inappropriate initial antimicrobial therapy was associated with higher mortality in patients with serious infection, including *P. aeruginosa* bacteraemia [4, 6, 14, 16–19]. However, previous reports have focussed on all cases of *P. aeruginosa* bacteraemia, including nosocomial bacteraemia [4, 14], and limited data are available regarding community-onset bacteraemia in an ER setting. Here, we concentrated exclusively on community-onset infections

Table 3 Risk factors associated with 30-day mortality in community-onset *P. aeruginosa* bacteraemia based on the univariate analysis

Variables	No. of survivors (%), $n=78$	No. of non-survivors (%), $n=28$	OR (95% CI)	P-value
Old age (≥65 years)	25 (32.1)	11 (39.3)	1.37 (0.56~3.35)	0.488
Sex (M/F)	39/39	19/9	0.47 (0.19~1.18)	0.103
Charlson's WIC				
0~2	48 (61.5)	11 (39.3)		
≥3	30 (38.5)	17 (60.7)	2.47 (1.02~5.99)	0.049
Underlying malignancy	57 (73.1)	26 (92.9)	4.79 (1.05~21.96)	0.033
Infection site				
Hepatobiliary infection	16 (16.7)	4 (14.3)	0.65 (0.20~2.13)	0.581
Lung infection	14 (18.0)	7 (25.0)	1.52 (0.54~4.28)	0.420
Pitt bacteraemia score				
0~3	73 (93.6)	14 (50.0)		
≥4	4 (5.1)	14 (50.0)	14.60 (4.53~47.06)	<0.001
Neutropaenia	35 (44.9)	15 (53.6)	1.42 (0.60~3.37)	0.510
Indwelling CVC	27 (34.6)	4 (14.3)	0.32 (0.10~1.00)	0.042
Inappropriate therapy	33 (42.3)	18 (64.3)	2.46 (1.00~6.00)	0.046

OR=odds ratio; Charlson's WIC=Charlson's weighted index of comorbidity; CVC=central venous catheter

Table 4 Independent risk factors associated with 30-day mortality in community-onset *P. aeruginosa* bacteraemia based on multivariate analysis

Variables	No. of survivors (%), *n*=78	No. of non-survivors (%), *n*=28	Adjusted OR (95% CI)	*P*-value
Charlson's WIC				
0~2	48 (61.5)	11 (39.3)		
≥3	30 (38.5)	17 (60.7)	2.92 (0.97~8.83)	0.058
Indwelling CVC	27 (34.6)	4 (14.3)	0.40 (0.11~1.48)	0.168
Pitt bacteraemia score				
0~3	73 (93.6)	14 (50.0)		
≥4	4 (5.1)	14 (50.0)	17.03 (4.60~63.15)	<0.001
Inappropriate therapy	33 (42.3)	18 (64.3)	4.29 (1.39~13.24)	0.011

OR=odds ratio; Charlson's WIC=Charlson's weighted index of comorbidity; CVC=central venous catheter

over a large time frame. Thus, we analysed a relatively large population of patients with community-onset *P. aeruginosa* bacteraemia. To our knowledge, this is the largest study carried out thus far to assess the impact of inappropriate therapy on the outcomes of patients with community-onset *P. aeruginosa* bacteraemia after adjustment for other variables.

Recently, episodes of community-onset bacteraemia were further classified as healthcare-associated and community-acquired [13]. According to this definition, 88.7% of patients in this study experienced healthcare-associated bacteraemia. However, we also found four previously healthy patients out of 12 patients with community-acquired *P. aeruginosa* bacteraemia. Moreover, as the number of patients with a healthcare-associated status in the ER setting has increased, clinicians have frequently faced *P. aeruginosa* infection in the ER. The present data provide information regarding the clinical features of patients infected with *P. aeruginosa* and allow us to predict the particular risk of a patient and, therefore, to select an individual initial empirical antimicrobial therapy more judiciously.

In another study regarding community-onset *P. aeruginosa* bacteraemia [3], the common underlying diseases were also solid tumour (41%) and haematologic malignancy (18%). The demographic characteristics of the patients in this study were similar to those indicated by previous data [2, 3, 20–22]. Although inappropriate initial antimicrobial therapy failed to be an independent predictor of death in a previous study, this may simply have been due to the limited number of cases included in the study [3].

Patients are increasingly being admitted to the hospital with infections caused by antibiotic-resistant bacteria, including *P. aeruginosa*, thus, increasing the likelihood that inappropriate antimicrobial therapies will be administered [23]. In other words, optimising antimicrobial treatment is a crucial step in the initial management of patients possessing risk factors for *P. aeruginosa* bacteraemia [18]. However, using these results to help derive recommendations for the empirical use of anti-pseudomonal therapy might require knowledge of the likelihood that *P. aeruginosa* bacteraemia is a cause of a particular infection syndrome.

Table 5 Comparison of clinical characteristics between appropriate therapy group and inappropriate therapy group

Variables	Appropriate therapy (*n*=55)	Inappropriate therapy (*n*=51)	*P*-value
Charlson's WIC			
0~2	31 (56.4)	28 (54.9)	
≥3	24 (43.6)	23 (45.1)	0.880
Underlying malignancy	47 (85.5)	36 (70.6)	0.064
Pitt bacteraemia score			
0~3	46 (83.6)	41 (80.4)	
≥4	9 (16.4)	10 (19.6)	0.663
30-day mortality	10 (18.2)	18 (35.3)	0.046

Charlson's WIC=Charlson's weighted index of comorbidity
Note. The data represent patients numbers (percentage in parentheses)

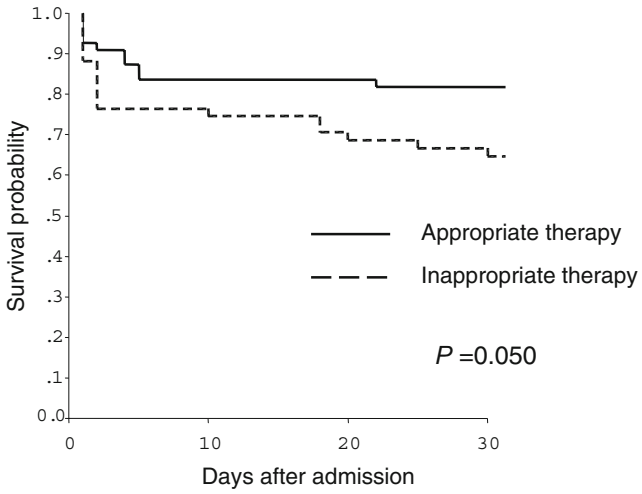

Fig. 1 Survival curve using the Kaplan-Meier method of appropriate and inappropriate therapy in community-onset *Pseudomonas aeruginosa* bacteraemia (by the log-rank method, *P*=0.050)

There are some limitations to our study. First, nearly 20% of patients were excluded in this study because of transfer to other hospital or incomplete or unevaluable medical records. This is could be a source of selection bias. Second, we did not identify risk factors for other treatment factors that may have contributed to adverse outcomes, such as improper dosing, a delay in treatment and other procedures [24]. Third, we used all causes of mortality of *P. aeruginosa* bacteraemia. We had difficulty in determining if these deaths were directly related to *P. aeruginosa* bacteraemia. The majority of patients had conditions which would shorten their life span. Fourth, there was a limitation of the used scoring system, such as Pitt bacteraemia score and Charlson's weighted index of morbidity, on retrospectively collected data, with the potential for inaccuracy. Fifth, our study was performed at a single institute, and the results may not be applicable to other settings [4]. Finally, other outcome parameters, such as time to the resolution of bacteraemia or combination therapy, were not evaluated because our data were incomplete and insufficient for analysing the exact population. As this study was of a retrospective nature, the possibility that these limitations precluded accurate comparisons should be kept in mind. In our hospital, combination therapy was usually administered for specialised cases, such as neutropaenic fever or septic shock.

In conclusion, we found that inappropriate initial antimicrobial therapy for community-onset *P. aeruginosa* bacteraemia was significantly associated with adverse outcomes. Clinicians must be aware that, if bacteraemia due to a resistant organism such as *Pseudomonas* is suspected based on the epidemiology of the patient, empiric therapy should be with an agent suitable for covering *Pseudomonas*, which will act to prevent or minimise the occurrence of inappropriate antimicrobial therapy. Future studies are warranted to define the optimal strategy for the empirical treatment of patients at risk for community-onset *P. aeruginosa* bacteraemia and identify clinical predictors for *P. aeruginosa* infection in community-onset bacteraemia.

Funding: None.

Transparency declarations: None to declare.

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