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Risk factors for the failure of treatment of *Pseudomonas aeruginosa* bacteremia in critically ill patients

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Pseudomonas aeruginosa bacteremia is associated with high morbidity and mortality in critically ill patients. In this study, we assessed risk factors for clinical failure of first definitive therapy for *P. aeruginosa* bacteremia in critically ill patients. All patients with *P. aeruginosa* bacteremia who entered the intensive care unit in Gifu University Hospital from January 2006 to December 2015 were retrospectively identified from electronic records. Risk factors associated with clinical failure of the first definitive therapy for *P. aeruginosa* bacteremia were analyzed by logistic regression analysis. A total of 28 patients were enrolled in the analysis. On multivariate analysis, severe burns (odds ratio [OR] = 70.9, 95% CI 2.9–1720.3; $p = 0.009$) and SOFA score ≥ 10 (OR = 28.5, 95% CI 1.1–754.3; $p = 0.045$) were significant factors in the clinical failure of first definitive therapy for *P. aeruginosa* bacteremia. The clinical success rate of first definitive therapy was significantly reduced in patients with these risk factors compared with those without them ($p < 0.001$). Severe burns and a SOFA score (≥ 10) were significant risk factors associated with the clinical failure of first definitive therapy for *P. aeruginosa* bacteremia in critically ill patients. We therefore recommend the use of therapeutic drug monitoring to optimize antibiotic dosing in these critically ill patients.

1. Introduction

*Pseudomonas aeruginos*a is a common cause of nosocomial infection and is responsible for 10–15% of hospital-acquired infections (Blance et al. 1998). Despite recent therapeutic advances, *P. aeruginosa* bacteremia is associated with a high mortality, with mortality rates ranging from 20% to 60% (Carlos 2011; Lodise et al. 2007; Osih et al. 2017; Tan et al. 2014).

Several studies have found that mortality in *P. aeruginosa* bacteremia is influenced by inappropriate selection of antibiotics in both empiric and definitive therapy and a delay in appropriate antibiotic therapy (Chamot et al. 2003; Lodise et al. 2017; Osih et al. 2007). Surviving Sepsis Campaign guidelines also recommended the administration of effective intravenous antibiotics within one hour of recognition of septic shock and severe sepsis (Dellinger et al. 2013). *P. aeruginosa* bacteremia is often accompanied by symptoms of systemic inflammatory response syndrome (Aliaga et al. 2002, Chamot et al. 2003; Osih et al. 2007). However, a recent study reported that combination antimicrobial therapy did not reduce mortality in patients with *P. aeruginosa* bacteremia compared with monotherapy (Peña et al. 2013). These findings highlight the importance of rapid and optimal selection of antibiotics *P. aeruginosa* bacteremia.

There have been several cases of *P. aeruginosa* bacteremia that did not respond to treatment despite the rapid administration of the appropriate antibiotics (Abdul-Aziz et al. 2012). The type of patients who fail to respond to antibiotic therapy for *P. aeruginosa* bacteremia despite appropriate and rapid administration of antibiotics has not been elucidated. Here, we assessed the risk factors for clinical failure of the first definitive therapy for *P. aeruginosa* bacteremia in critically ill patients.

2. Investigations and results

2.1. Patient characteristics

A total of 28 patients with bloodstream infection due to *P. aeruginosa* were enrolled (Table 1). Severe burn was the most common underlying condition (n = 8), followed by sepsis (n = 4), stroke (n = 4), postoperative status (n = 4), trauma (n = 3), pancreatitis (n = 2) and heatstroke (n = 1). Skin and soft tissue was the most common source of infection (n = 10), followed by blood stream (n = 8), respiratory system (n = 5), surgical site infection (n = 3) and urinary tract (n = 2). The most frequently used antimicrobial agent as empiric therapy was piperacillin/tazobactam in 12 patients, followed by meropenem in 10, piperacillin in 3, cefepime in 2 and ceftazidime in 1. In contrast, the most frequently used agent in definitive therapy was piperacillin in 14 patients, followed by ceftazidime in 6, meropenem in 4, piperacillin/tazobactam in 2, and cefepime and biapenem in 1 patient each.

Table 1: Patient characteristics

Sex, male/female	19 / 9
Age, y (range)	58.0 (21-89)
Height, cm	164.5 ± 7.9
Weight, kg	61.2 ± 14.4
Serum albumin, mg/dl	2.45 ± 0.47
Serum creatinine, mg/dl	0.91 ± 0.78
Aspartate transaminase, U/dl	34.1 ± 18.4
Hemodiafiltration (%)	5 (17.9)

SOFA score, median (range)	7.0 (3-17)
Duration of ICU stay, median (range)	39.5 (14-234)
Underlying condition n (%)	
Severe burns	8 (28.6)
Sepsis	4 (14.3)
Stroke	4 (14.3)
Postoperative status	4 (14.3)
Trauma	3 (10.7)
Pancreatitis	2 (7.2)
Heatstroke	1 (3.6)
Source of infection, n (%)	
Skin and soft tissue	10 (35.7)
Blood stream	8 (28.6)
Respiratory system	5 (17.9)
Surgical site infection	3 (10.7)
Urinary tract	2 (7.1)
Empiric therapy, n (%)	
PIPC/TAZ	12 (42.9)
MEPM	10 (35.7)
PIPC	3 (10.7)
CFPM	2 (7.1)
CAZ	1 (3.6)
First definitive therapy, n (%)	
PIPC	14 (50.0)
CAZ	6 (21.4)
MEPM	5 (17.9)
PIPC/TAZ	2 (7.1)
CFPM	1 (3.6)

PIPC, piperacillin; TAZ, tazobactam; MEPM, meropenem; CFPM, cefepime CAZ, ceftazidime, SOFA, sequential organ failure assessment

2.2. Comparison of groups with treatment success and failure of first definitive therapy

The characteristics of the 28 patients who received first definitive therapy for *P. aeruginosa* bacteremia were compared between patients with treatment success (n = 18, 64.3%) and treatment failure (n = 10, 35.7%) (Table 2). Significant differences were found in the proportion of patients with severe burns (5.6% in the treatment success group vs. 70.0% in the treatment failure group, $p = 0.01$) and patients who received piperacillin as first definitive therapy (33.3% vs. 80.0%, $p = 0.049$). In addition, weight, serum albumin and SOFA score tended to differ between the two groups (weight: 58.1±14.3 kg vs 66.7±14.3 kg, $p = 0.139$; serum albumin: 2.54±0.54 mg/dl vs 2.29±0.36 mg/dl, $p = 0.19$; and SOFA score: 7 [3–12] vs 10 [5–17], $p = 0.057$).

Table 2: Comparision of patient characteristics between the treatment success group and the treatment failure group of first definitive therapy in patients with P. aeruginosa bacteremia

	Treatment success group (N=18)	Treatment failure group (N=10)	*p*-value
Sex male/female	13 / 5	6 / 4	0.677 [a]
Age, y (range)	53.7 (21-81)	60.3 (23-89)	0.265 [b]
Height, cm	165.7 ± 6.5	162.5 ± 10.3	0.319 [c]
Weight, kg	58.1 ± 14.3	66.7 ± 14.3	0.139 [c]
Serum albumin, mg/dl	2.54 ± 0.52	2.29 ± 0.36	0.190 [c]
Serum creatinine, mg/dl	0.98 ± 0.90	0.79 ± 0.52	0.545 [c]
Aspartate transaminase, U/dl	37.0 ± 21.8	29.1 ± 11.1	0.225 [c]
Hemodiafiltration (%)	2 (11.1)	3 (30.0)	0.315 [a]
SOFA score, median (range)	7 (3-12)	10 (5-17)	0.057 [b]
Duration of ICU stay, median (range)	36.0 (14-100)	61.5 (21-170)	0.080 [b]
Underlying condition n (%)			
Severe burns	1 (5.6)	7 (70.0)	0.010 [a]
Sepsis	4 (22.2)	0	0.265 [a]
Stroke	4 (22.2)	0	0.265 [a]
Postoperative status	2 (11.1)	2 (20.0)	0.601 [a]
Trauma	2 (11.1)	1 (10.0)	1.000 [a]
Pancreatitis	2 (11.1)	0	0.524 [a]
Heatstroke	1 (5.6)	0	1.000 [a]
Source of infection, n (%)			
Skin and soft tissue	6 (33.4)	4 (40.0)	0.953 [a]
Blood stream	4 (22.2)	4 (40.0)	0.575 [a]
Respiratory system	4 (22.2)	1 (10.0)	0.626 [a]
Surgical site infection	2 (11.1)	1 (10.0)	1.000 [a]
Urinary tract	2 (11.1)	0	0.524 [a]

	Treatment success group (N=18)	Treatment failure group (N=10)	*p*-value
Empiric therapy, n (%)			
PIPC/TAZ	6 (33.3)	6 (60.0)	0.333 [a]
MEPM	6 (33.3)	4 (40.0)	0.953 [a]
PIPC	3 (16.7)	0	0.533 [a]
CFPM	2 (11.1)	0	0.524 [a]
CAZ	1 (5.6)	0	1.000 [a]
First definitive therapy, n (%)			
PIPC	6 (33.3)	8 (80.0)	0.049 [a]
CAZ	5 (27.8)	1 (10.0)	0.375 [a]
MEPM	4 (22.2)	1 (10.0)	0.626 [a]
PIPC/TAZ	2 (11.1)	0	0.524 [a]
CFPM	1 (5.6)	0	1.000 [a]

PIPC, piperacillin; TAZ, tazobactam; MEPM, meropenem; CFPM, cefepime; CAZ, ceftazidime, SOFA, sequential organ failure assessment Data are mean (SD) unless otherwise specified. a) Chi square test, b) Mann-Whitney-U-test, c) Unpaired-t-test.

Table 3: Risk factors associated with clinical failure of therapy for P. aeruginosa bacteremia in critically ill patients

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Severe burns	39.7	3.5 - 449.8	0.003	70.9	2.9-1720.3	0.009
SOFA score (≥ 10)	17.0	1.6 - 181.4	0.019	28.5	1.1-754.3	0.045
Use of PIPC	8.00	1.3 - 50.0	0.026	5.20	0.3-82.6	0.245
Albumin (≤ 2.5 mg/dl)	1.80	0.4-9.6	0.456			
Weight (≤ 55 kg)	3.20	0.5-19.5	0.207			

OR, odds ratio; PIPC, piperacillin

2.3. Risk analysis of failure of first definitive therapy for P. aeruginosa bacteremia

Based on univariate logistic regression analysis, severe burns (OR = 39.7, 95% CI 3.5–449.8; $p = 0.003$), SOFA score ≥ 10 (OR = 17.0, 95% CI 1.6–181.4; $p = 0.019$) and piperacillin therapy (OR = 8.0, 95% CI, 1.3–50.0; $p = 0.026$) were significant risk factors for failure of first definitive therapy for *P. aeruginosa* bacteremia (Table 3). However, based on multivariate logistic regression analysis, severe burns (OR = 70.9, 95% CI 2.9–1720.3; $p = 0.009$) and sequential organ failure assessment (SOFA) score ≥ 10 (OR = 28.5, 95% CI 1.1–754.3; $p = 0.045$) were significant risk factors for treatment failure.

As shown in Fig. 1, both clinical success and microbiological success rates of first definitive therapy for *P. aeruginosa* bacteremia were significantly reduced in the presence of risk factors. On the other hand, there were no significant differences in either clinical success or microbiological success rates between patients who received piperacillin therapy and those who received other anti-microbiologic therapy, except for piperacillin as the first definitive therapy (Fig. 2).

3. Discussion

Compelling evidence has demonstrated that early and appropriate antibiotic therapy is one of the most important interventions in the

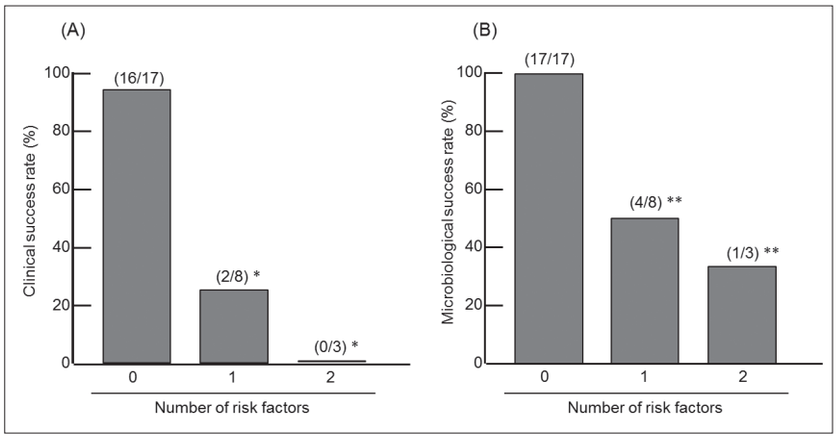

Fig. 1: Relationship between the number of risk factors and clinical (A) and microbiological success rates (B). $^{*}p < 0.01$, $^{**}p < 0.05$ by the Kruskal–Wallis test followed by Scheffe's test.

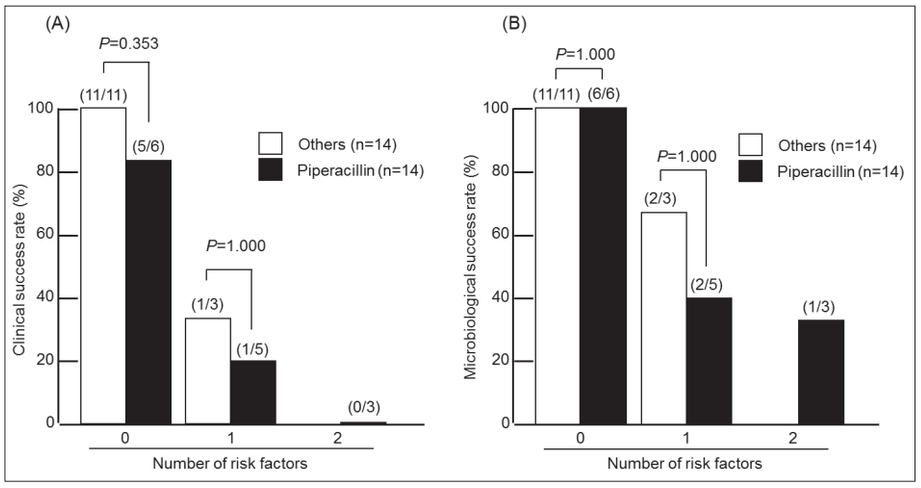

Fig. 2: Comparison of clinical (A) and microbiological success rates (B) between the piperacillin group and other antibiotics group in the presence of risk factors. Data were analyzed by the chi square test.

treatment of bacteremia in critically ill patients (Garnacho-Montero et al. 2003; Harbarth et al. 2003; Kollef et al. 1999). In our present series, however, despite the appropriate selection and administration of antibiotics in both empirical and first definitive therapy, 21.4% (6/28) of patients with *P. aeruginosa* bacteremia failed to respond despite first definitive therapy. We therefore examined the risk factors for clinical failure of first definitive therapy in these critically ill patients by logistic regression analysis, and found that both severe burns (OR = 70.9, 95% CI 2.9–1720.3; $p = 0.009$) and SOFA score ≥ 10 (OR = 28.5, 95% CI 1.1–754.3; $p = 0.045$) were risk factors.

The SOFA score, which is an indicator of multiple organ dysfunction, is understood to reflect the condition of critically ill patients (Vincent et al. 1998) and can also predict their mortality (Kajdacsy-Balla Amaral et al. 2005). Routsi et al. (2007) reported that SOFA score on the day of bacteremia was significantly higher in patients who did not survive compared with those who did (10±3.4 vs 7.3±3.2, $p < 0.001$) and that it is an independent prognostic factor for the outcome of bacteremia in critically ill patients. In our present study, 62.5% (5/8) patients with a SOFA score ≥10 failed to respond to first definitive therapy for *P. aeruginosa* bacteremia, and the SOFA score was identified as an independent risk factor for therapy failure. Accordingly, the SOFA score can be used as a predictor of not only mortality but also the efficacy of antibiotic therapy in critically ill patients and may be one of the most important assessments in emergency settings.

Blood concentrations of hydrophilic antibiotics such as b-lactams, aminoglycosides and glycopeptides in critically ill patients can be influenced by increases in Vd and CL (Roberts et al. 2009). In a systematic review, all subjects in a study of b-lactam antibiotics showed an increase in Vd compared with healthy volunteers (Gonçalves-Pereira et al. 2011). Similarly, physiological changes in critically ill patients, such as increased cardiac output, hypoalbuminemia and enhanced blood flow to major organs, were shown to increase kidney perfusion and consequently increase creatinine clearance of hydrophilic antibiotics (Roberts et al. 2009). Notably, supraphysiologic clearance with values over 120 ml/min is defined as augmented renal clearance (ARC), and creatinine clearance levels over 130 ml/min have been associated with subtherapeutic antibiotic concentration and a worse patient outcome (Claus et al., 2013, Udy et al. 2011, 2012).

The pharmacokinetic change of increased Vd is associated with fluid resuscitation and the physiologic derangements that occur with increased severity of illness in critically ill patients (Roberts et al. 2014). Marik et al. (1993) reported that the hydrophilic antibiotic volume of distribution correlated well with APACH II score ($r = 0.70$, $P < 0.001$), and the degree of increase in Vd may be associated with the severity of critical illness. Thus, patients with a higher SOFA score might also have an increased Vd. Similarly, both increased Vd and CL were observed in patients with burns (Roberts et al. 2009), which the present study found was a risk factor for clinical failure. In a population pharmacokinetic analysis, the Vd and/or CL of b-lactam was higher than those reported in patients without burns (Doh et al. 2010; Jeon et al. 2014). Based on their population pharmacokinetic analysis of piperacillin in burns patients, Jeon et al. (2014) recommended that a higher daily dose of piperacillin or longer duration of infusion should be considered for these patients. These findings suggest that patients with a higher SOFA score and/or severe burns might have an increased Vd and/or CL; if correct, this might have led to subtherapeutic antibiotic concentrations in the present study. We therefore recommend the use of therapeutic drug monitoring to optimize antibiotic dosing in critically ill patients.

Another finding of our study was that piperacillin was a risk factor associated with clinical failure of therapy for *P. aeruginosa* bacteremia on univariate logistic regression analysis only. Although the rate of risk factors was higher in patients in the piperacillin groups than the other antibiotics groups in our study, several studies have reported that piperacillin concentration varies among critically ill patients (Udy et al. 2012; Huttner et al. 2015). These reports also showed that piperacillin concentration is associated with creatinine clearance and is frequently below the therapeutic concentration in patients with augmented renal clearance (ARC). Unfortunately, we did not measure the 24-hour creatinine clearance to assess involvement of ARC in this study.

Limitations of this study were its retrospective design and restriction to a single medical institution. Accordingly, the patient population was limited and the sample size was small. In addition, we were unable to incorporate all possible risk factors for the clinical failure of therapy for *P. aeruginosa* bacteremia.

In conclusion, we found that severe burns and a high SOFA score ≥ 10 were significant risk factors associated with clinical failure of first definitive therapy for *P. aeruginosa* bacteremia in critically ill patients. Even though first definitive therapy was used, clinical success rates in these patients were decreased. We therefore recommend the use of therapeutic drug monitoring to optimize antibiotic dosing in these patients.

4. Experimental

4.1. Study design and patients

The effectiveness of first definitive therapy with anti-pseudomonal antibiotics for *P. aeruginosa* bacteremia in critically ill patients who entered the intensive care units of Gifu University Hospital from January 2006 to December 2015 was retrospectively analyzed. All data were obtained from the electronic medical records. Patients aged

under 18 years and those who died within 3 days after the start of definitive therapy were excluded. The presence of *P. aeruginosa* bacteremia was defined as the identification of *P. aeruginosa* in a blood culture.

4.2. Antimicrobial therapy

'Empiric therapy' was defined as antibiotics administered within the first 24 h following blood culture, whereas 'definitive therapy' was defined as antibiotics that were selected and administered based on the results of susceptibility testing of blood cultures in this study. In particular, piperacillin was selected as an empiric or definitive therapy for *P. aeruginosa* in preference to other anti-pseudomonal antibiotics in the study period. We evaluated the efficacy of the first definitive therapy of anti-pseudomonal antibiotics based on susceptibility testing of blood cultures. All patients included in this study received commonly used doses of antibiotics for appropriate treatment durations, in concordance with various guidelines (Gilbert et al. 2016).

4.3. Risk analysis of failure of treatment of P. aeruginosa bacteremia

Patient characteristics between those with treatment success and treatment failure with use of first definitive therapy were compared, and risk factors for treatment failure were then determined by univariate and multivariate logistic regression analyses. Odds ratios (OR) and 95% confidence intervals (CI) were determined. Cut-off age was determined by the Youden index method in the receiver operating characteristic curve (ROC) analysis, calculated as the maximum value of (sensitivity + specificity − 1) according to previously described methods (Akobeng et al. 2007; Hajian-Tilaki et al. 2013).

4.4. Efficacy of first definitive therapy for P. aeruginosa bacteremia

Microbiological success was defined as the disappearance of *P. aeruginosa* from blood samples during targeted antibiotic treatment. Clinical success of definitive therapy was defined as the absence of infection relapse within two weeks after the completion of targeted antibiotic therapy without switching to other antibiotics.

4.5. Definition

Clinically significant bloodstream infection was defined according to the modified criteria of the United States Centers for Disease Control and Prevention, as follows: ≥ 1 positive blood culture for all bacterial pathogens, except for common skin contaminants, which required ≥ 2 positive blood cultures within a 48-h period (Horan et al. 2008). The day the first positive blood culture was sampled was designated as the date of onset of the bloodstream infection (day 0). Catheter-related bloodstream infection was considered when clinical signs of catheter infection, positive culture results from the catheter tip, or both, were present with no evidence of an alternative source of bloodstream infection. Primary bloodstream infection was diagnosed when an infectious focus was not identified. The source of secondary bloodstream infection was determined from clinical, radiological, and microbiological evidence consistent with the Centers for Disease Control and Prevention criteria.

4.6. Statistical analysis

Data were analysed using SPSS version 11 (SPSS, Chicago, IL, USA). Parametric variables were analysed using the *t*-test, while non-parametric variables were analysed using the Mann–Whitney *U*-test. *P*-values < 0.05 were considered statistically significant.

4.7. Ethical approval

This study was carried out in accordance with the guidelines for human studies adopted by the ethics committee of Gifu University Graduate School of Medicine, and notified by the Japanese government (Institutional review board approval No. 26-372). In view of the retrospective nature of the study, the need for the informed consent of subjects was not mandated.

Conflicts of interest: None declared.

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