

## Antibiotic Therapy and Clinical Outcomes of *Pseudomonas Aeruginosa* (PA) Bacteraemia

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### Abstract

**Introduction:** *Pseudomonas aeruginosa* (PA) bacteraemia is associated with high morbidity and mortality. We assessed clinical outcomes in patients with PA bacteraemia treated with piperacillin-tazobactam (TZP) versus other antibiotics, and monotherapy versus combination, all with proven activity by disc testing without minimum inhibitory concentration (MIC) data. **Materials and Methods:** All patients with PA bacteraemia in 2007 to 2008 were reviewed for demographic, comorbidity, clinical, laboratory, treatment and outcome data. Primary outcome was 30-day mortality. Secondary outcomes included microbiological clearance, clinical response and length of stay (LOS). **Results:** Median age for 91 patients was 65 years. Median Simplified Acute Physiology Score (SAPS) II score was 30. Monotherapy was used in 77 cases: 42 on ceftazidime, 17 on TZP, 10 on carbapenems, and 8 on other antipseudomonal antibiotics. The 30-day mortality was 20.9%, and similar between ceftazidime and TZP versus other antibiotics respectively. More patients in combination versus monotherapy group had cardiovascular diseases, diabetes mellitus and vascular access as source of bacteraemia. Patients on monotherapy had higher 30-day mortality (24.7% vs 0%,  $P = 0.037$ ). Multivariate analysis identified SAPS II score (OR = 1.097, 95% CI, 1.032 to 1.166,  $P = 0.003$ ) and cancer (OR = 4.873, 95% CI, 1.235 to 19.223,  $P = 0.024$ ) as independent predictors of 30-day mortality. **Conclusion:** TZP appeared to be an effective culture-guided antibiotic for PA bacteraemia. High 30-day mortality in monotherapy might be confounded by comorbidity, illness severity and sample size. Cancer patients and a high SAPS II score were independent predictors of 30-day mortality.

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**Key words:** Bloodstream infections, Mortality

### Introduction

*Pseudomonas aeruginosa* (PA) is a virulent nosocomial pathogen and PA bacteraemia is associated with high mortality ranging from 18% to 59%.<sup>1-7</sup> It is ranked among the top 3 gram-negative bacteria associated with bacteraemia.<sup>3, 8-10</sup> It is commonly reported in patients with cancer<sup>3,11,12</sup> and in intensive care units (ICUs).<sup>8,10</sup> PA bacteraemia commonly arises from urinary source,<sup>7,12-15</sup> pneumonia<sup>7,12-15</sup> and vascular access devices.<sup>7,13</sup>

Inappropriate empirical or delayed active antibiotic worsens clinical outcomes in patients with PA bacteraemia.<sup>2-5,7,15</sup>

Mathematical modeling has shown that target attainment for optimal bacterial killing is unlikely if minimum inhibitory concentration (MIC) for piperacillin-tazobactam (TZP) exceeded 32 µg/mL.<sup>16,17</sup> Subsequently, a clinical study confirmed higher mortality for TZP if MIC exceeded 32 µg/mL in severely ill patients.<sup>16</sup> Another study showed that empirical TZP was associated with increased mortality for PA bacteraemia with MIC 32 to 64 µg/mL.<sup>6</sup> Consequently, the MIC breakpoint for non-susceptibility for TZP against PA was revised from 64 µg/mL to 16 µg/mL in 2012.

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However, MIC information was not routinely available to doctors, a situation we encountered at Tan Tock Seng Hospital (TTSH), Singapore.

Many studies reported no difference in outcomes between monotherapy and combination antibiotic therapy.<sup>2,7,15,18,19</sup> A meta-analysis of randomised controlled trials in febrile neutropenia<sup>20</sup> and another in immunocompetent patients<sup>21</sup> concluded that combination antibiotics were not better than monotherapy for PA infections, although both analyses conceded that the numbers were small. Subsequently, a meta-analysis of observational studies concluded that combination therapy was more effective than monotherapy<sup>22</sup> although this was biased by aminoglycoside as monotherapy.<sup>23</sup> A review on PA pneumonia recently recommended 3 to 5 days of combination antibiotic based on the available evidence.<sup>24</sup>

Therefore we performed a 2-year retrospective study of PA bacteraemia with the objectives of: (i) determining clinical outcomes of treating PA bacteremia with various antipseudomonal antibiotics with proven activity by disc testing without MIC data, and (ii) comparing monotherapy versus combination therapy.

## Materials and Methods

### *Study Cohort*

This retrospective study was conducted in TTSH, a 1400-bed university teaching hospital in Singapore. We identified all patients with PA bacteraemia from 1 January 2007 to 31 December 2008 from our microbiology database. The study was conducted before the change in MIC breakpoint for TZP in PA from 64 to 16 µg/mL. Our inclusion criteria were: (i) patients who received at least 2 days of culture-guided antibiotics for the positive blood culture, and (ii) first episode of PA bacteraemia in the study period. Our exclusion criteria were: (i) patients with incomplete data, and (ii) patients with unavailable medical records.

### *Data Collection*

The following data were collected retrospectively from the hospital medical records: age; gender; race; comorbidities; use of devices; severity of illness in terms of Simplified Acute Physiology Score II (SAPS II)<sup>25</sup> and Pitt bacteraemia score;<sup>26</sup> whether doses of antibiotics used were appropriate; surgery in the last 30 days; prior admission to ICU; length of stay (LOS) in TTSH; other microorganisms found in blood; empirical and culture-guided antibiotics.

### *Definitions*

The presence of PA bacteraemia was defined as the identification of PA in blood culture. Severity of disease was determined by Pitt bacteraemia score<sup>26</sup> and SAPS II score.<sup>25</sup>

Parameters within each scoring system were determined within 24 to 48 hours before index culture.<sup>5</sup> If the exact Glasgow Coma Scale (GCS) score was unavailable, the GCS score would be defined by the clinician description in the case notes, for example, alert: 14 to 15, confused: 11 to 13, drowsy: 7 to 10, unresponsive: ≤6.<sup>27</sup>

Nosocomial infection was defined as infection that occurred more than 48 hours after hospital admission. Healthcare-associated infection was defined as infection that occurred in less than 48 hours after admission in patients previously admitted to other hospitals or stayed in nursing homes or other community hospitals in the past 3 months. Community-acquired infection was defined as infection that occurred in less than 48 hours without previous admission to hospitals, nursing homes or community hospitals in the past 3 months. Polymicrobial bacteraemia was defined as the presence of more than 1 micro-organism in the blood culture. Active empirical therapy was defined as antibiotic therapy active against PA given prior to culture results. Active definitive therapy was defined as the first antibiotic active against PA given for at least 2 days after culture results were available. Combination therapy was the use of 2 or more active antibiotics overlapping for more than 48 hours throughout the entire treatment duration. Doses of antibiotics ordered were checked against drug references such as Lexi-comp<sup>®</sup>. They were deemed as appropriate if the dosing adjustments were according to the renal function as per the drug reference for PA bacteraemia.

The primary outcome was 30-day mortality. Secondary outcomes included LOS, clinical and microbiological response by day 7. Clinical response was defined as defervescence, improvement in oxygen requirement, and symptoms and signs as documented in medical charts. All outcomes were measured from the day of positive blood culture.

### *Statistical Analysis*

The Pearson's chi-square test or Fisher's exact test was used to compare categorical variables while the Mann-Whitney U test was used for continuous variables. Univariate and multivariate analysis for 30-day mortality were carried out using binary logistic regression model. Variables that yielded *P* value less than or equal to 0.10 in the univariate analysis were included into the multivariate analysis. All the *P* values were 2-tailed and *P* < 0.05 indicated statistical significance. The Predictive Analytics Software (PASW) statistics, version 18.0 (SPSS Inc., Chicago, III), was used for this analysis. This study was approved by our institutional review board (DSRB 2009/00439).

## Results

### *Description of the Study Cohort*

Out of 120 patients with PA bacteraemia in the study period, 91 of them met the inclusion criteria (29 were excluded; 12 were excluded as these patients did not receive at least 2 days of definitive antibiotic treatment for bacteraemia, and 17 patients had either incomplete data or unavailable medical records). The median age was 65 years (range, 53 to 76 years). Males comprised 52 (57.1%). Combination antibiotic therapy was used in 14 patients (15.4%). Of those who used single definitive antibiotic therapy, ceftazidime (CAZ) was the most commonly used; 42 patients were on CAZ (46.2%), 17 were on TZP (18.7%), 10 were on carbapenems (CBP) (11.0%) and rest of the 8 patients were on other antipseudomonal antibiotics (8.8%) (3 on ciprofloxacin, 1 on polymyxin B, 2 on aminoglycoside, 1 on aztreonam, 1 on piperacillin).

Median SAPS II score was 30 (range, 22 to 38) and Pitt bacteraemia score 1 (range, 0 to 2). Forty-one (45.1%) patients had nosocomial, 29 (31.9%) healthcare-associated and 21 (23.1%) community-acquired infections. Forty-seven (51.6%) patients received appropriate antibiotic doses for PA bacteraemia. Forty (44.0%) patients received active empirical therapy, 15 patients received TZP, 9 received CBP, 7 received CAZ and the rest received other empirical antibiotics (5 on ciprofloxacin, 2 on aminoglycosides and 3 were on combination of empirical antipseudomonal antibiotics). Out of the 51 patients who did not receive active empirical antibiotics, only 3 of them did not receive any empirical antibiotics. Nineteen (20.9%) had polymicrobial bacteraemia.

Sources of bacteraemia were urinary (31.9%), skin and soft tissue (12.1%), respiratory (12.1%), and vascular access device (11.0%). In 19.8% of cases, no clear source of infection could be determined. ICU admission preceded 18.7% and surgical procedures 20.9% of PA bacteraemia. Mortality at 30 days was 20.9%. Median LOS was 20 days (range, 11 to 41 days). Clinical response occurred in 70.3% and microbiological response in 83.7% at 7 days.

### *Comparison of Antibiotic Treatment and Clinical Outcomes*

As shown in Table 1, out of the 19 patients who died within 30 days from index bacteraemia, there were significantly more patients with cardiovascular diseases, cancer and human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) as comorbidities, and they were significantly more ill with higher median SAPS II score. Notably, there was no significant difference for individual type of antibiotic treatment.

No patient who died at 30 days was on combination antibiotics vs 19 (24.7%) on monotherapy for definitive

treatment ( $P = 0.037$ ). Median length of hospitalisation (21 [10 to 41] vs 18 [14 to 51] days,  $P = 0.458$ ), 7-day microbiological (41 [83.7%] vs 8 [61%],  $P = 0.122$ ) and clinical (64 [83.1%] vs 13 [92.9%],  $P = 0.687$ ) response did not differ between monotherapy and combination therapy. Notably, patients on combination definitive therapy had more cardiovascular diseases ( $P = 0.014$ ), diabetes mellitus ( $P = 0.004$ ) and vascular access as a source of bacteraemia ( $P = 0.044$ ), versus monotherapy (Table 2).

Baseline characteristics were similar between those patients who received CAZ versus those who did not, as well as TZP vs non-TZP treatment groups (Tables 4 and 5). There was no statistically significant difference in 30-day mortality (12 [28.6%] vs 7 [20.0%],  $P = 0.436$ ), median length of hospitalisation (18 [9 to 31] vs 25 [11 to 64] days,  $P = 0.072$ ), 7-day microbiological (23 [92%] vs 18 [75%],  $P = 0.138$ ) and clinical response (33 [78.6%] vs 31 [88.6%],  $P = 0.243$ ) in CAZ versus non-CAZ treatment groups. Similarly 30-day mortality (4 [23.5%] vs 15 [25.0%],  $P = 0.901$ ), median length of hospitalisation (20 [10 to 40] vs 21 [11 to 41] days,  $P = 0.927$ ), 7-day microbiological (7 [63.6%] vs 34 [89.5%],  $P = 0.063$ ) and clinical response (15 [80.2%] vs 49 [81.7%],  $P = 0.721$ ) did not differ significantly between TZP and non-TZP treatment groups. Notably, there was no significant difference in proportions of patients who received active empirical antibiotic in monotherapy vs combination therapy, CAZ vs non-CAZ, and TZP vs non-TZP treatment groups.

### *Risk Factors for 30-day Mortality*

Univariate analysis identified risk factors for 30-day mortality as cardiovascular disease (OR = 0.320, CI, 0.113 to 0.905,  $P = 0.032$ ), cancer (OR = 7.200, CI, 2.252 to 23.023,  $P = 0.001$ ), HIV/AIDS (OR = 6.133, CI, 1.241 to 30.309,  $P = 0.026$ ) and median SAPS II score (OR = 1.091, CI, 1.040 to 1.146,  $P = \leq 0.001$ ). On multivariate analysis, only cancer as comorbidity (OR = 4.873, CI, 1.235 to 19.223,  $P = 0.024$ ) and median SAPS II score (OR = 1.097, CI, 1.032 to 1.166,  $P = 0.003$ ) remained as independent predictors of 30-day mortality (Table 3).

## Discussion

Studies have reported severe sepsis or shock,<sup>2,13,15</sup> severity of illness,<sup>1,2,4-6,13,14,28</sup> pneumonia as source,<sup>2,7</sup> ineffective empirical or definitive antibiotic therapy,<sup>2,4,15</sup> admission to ICU<sup>13,15</sup> and age<sup>5,13,28</sup> as independent risk factors for mortality. Differences in independent risk factors might be due to definition of outcome<sup>1,4-7,13,15,28,29</sup> and study populations.<sup>14</sup> In addition to published risk factors, our study also found cancer and SAPS II score as independent predictors of 30-day mortality.

Table 1. Baseline Characteristics and Antibiotic Therapy for 91 Patients with *Pseudomonas Aeruginosa* Bacteraemia with and without 30-day Mortality\*

30-day Mortality	Yes n = 19	No n = 72	P Value
Age, median years (range)	66 (53 – 73)	65 (53.5 – 76.25)	0.689
Male	14 (73.7%)	38 (52.8%)	0.123
<b>Site of Acquisition</b>			
Nosocomial	11 (57.9%)	30 (41.7%)	0.300
Healthcare-associated	5 (26.3%)	24 (33.3%)	0.783
Community	3 (15.8%)	18 (25.0%)	0.397
<b>Comorbidity</b>			
Cardiovascular	8 (42.1%)	50 (69.4%)	0.034
Diabetes mellitus	5 (26.3%)	29 (40.3%)	0.300
Cancer	9 (47.4%)	8 (11.1%)	<0.001
Renal	2 (10.5%)	19 (26.4%)	0.144
HIV/AIDS	4 (21.1%)	3 (4.2%)	0.014
Respiratory	1 (5.3%)	9 (12.5%)	0.370
<b>Source of Bacteraemia</b>			
Urinary system	5 (26.3%)	24 (33.3%)	0.783
Unknown	6 (31.6%)	12 (16.7%)	0.147
Respiratory	4 (21.1%)	7 (9.7%)	0.178
Skin and soft tissue	2 (10.5%)	9 (12.5%)	0.814
Vascular access	0 (0.0%)	10 (13.9%)	0.085
Hepatobiliary	1 (5.3%)	5 (6.9%)	0.793
Intra-abdominal	1 (5.3%)	3 (4.2%)	0.836
Others	0 (0.0%)	2 (2.8%)	0.463
<b>Severity of Illness</b>			
Median SAPS II score (range)	39 (30 – 52)	28 (20.75 – 37.25)	0.010
Median Pitt bacteraemia score (range)	1 (0.5 – 2)	1 (0 – 2)	0.485
Device used†	10 (52.6%)	50 (69.4%)	0.184
Surgery in past 30 days	2 (10.5%)	17 (23.6%)	0.212
Intensive care admission	3 (15.8%)	14 (19.4%)	0.716
Polymicrobial	5 (26.3%)	14 (19.4%)	0.512
Appropriate dose	12 (63.2%)	35 (48.6%)	0.259
Active empirical therapy	11 (57.9%)	29 (40.3%)	0.200
Ceftazidime	3 (15.8%)	4 (5.6%)	0.136
Piperacillin-tazobactam	3 (15.8%)	11 (15.3%)	0.956
Carbapenems	3 (15.8%)	6 (8.3%)	0.333
Ciprofloxacin	1 (5.3%)	4 (5.6%)	0.960
Aminoglycosides	0 (0.0%)	2 (2.8%)	0.463
Combination‡	1 (5.3%)	2 (2.8%)	0.589
<b>Definitive Antibiotic Therapy</b>			
Ceftazidime	12 (63.2%)	30 (41.7%)	0.123
Piperacillin-tazobactam	4 (21.1%)	13 (18.1%)	0.766
Carbapenems	3 (15.8%)	7 (9.7%)	0.452
Others§	0 (0.0%)	8 (11.1%)	0.128
Combination antibiotics	0 (0.0%)	14 (19.4%)	0.037

HIV/AIDS: Human immunodeficiency virus/ Acquired immune deficiency syndrome

\*Data are number of patients (%), unless stated otherwise.

†Device used included central venous catheter, peripherally inserted central catheter, arterial line, prosthetic heart valves, urinary catheter, permanent catheter for dialysis, tracheostomy tube, percutaneous transhepatic cholangiogram and percutaneous nephrostomy tube.

‡1 was on imipenem + amikacin, 1 was on ceftazidime + ciprofloxacin, 1 was on piperacillin-tazobactam + amikacin.

§Ciprofloxacin = 3, polymyxin = 1, aminoglycoside = 2, piperacillin = 1, aztreonam = 1.

|| Carbapenem + aminoglycoside = 2, ceftazidime + aminoglycoside = 4, ceftazidime + ciprofloxacin = 3, piperacillin-tazobactam + aminoglycoside = 1, piperacillin-tazobactam + ciprofloxacin = 2, aminoglycoside + ciprofloxacin = 1, carbapenem + aminoglycoside + ciprofloxacin = 1.

Table 2. Baseline Characteristics of Patients with *Pseudomonas Aeruginosa* Bacteraemia Who Received Active Definitive Therapy (Monotherapy versus Combination Antibiotic Therapy)\*

Variable	Monotherapy n = 77	Combination n = 14	P Value
Age, median years (range)	65 (52 – 76)	67 (57 – 76)	0.552
Male	46 (59.7%)	6 (42.9%)	0.240
<b>Site of Acquisition</b>			
Nosocomial	35 (45.5%)	6 (42.9%)	0.857
Healthcare-associated	24 (32.2%)	5 (35.7%)	0.761
Community	18 (23.4%)	3 (21.4%)	1.000
<b>Comorbidity</b>			
Cardiovascular	45 (58.4%)	13 (92.9%)	0.014
Diabetes mellitus	24 (31.2%)	10 (71.4%)	0.004
Cancer	15 (19.5%)	2 (14.3%)	1.000
Renal	15 (19.5%)	6 (42.9%)	0.082
HIV/AIDS	7 (9.1%)	0 (0.0%)	0.590
Respiratory	8 (10.4%)	2 (14.3%)	0.649
<b>Source of Bacteraemia</b>			
Urinary system	25 (32.5%)	4 (28.6%)	1.000
Unknown	18 (23.4%)	0 (0.0%)	0.064
Respiratory	11 (14.3%)	0 (0.0%)	0.203
Skin and soft tissue	7 (9.1%)	4 (28.6%)	0.062
Vascular access	6 (7.8%)	4 (28.6%)	0.044
Hepatobiliary	5 (6.5%)	1 (7.1%)	1.000
Intra-abdominal	3 (3.9%)	1 (7.1%)	0.494
Others	2 (2.6%)	0 (0.0%)	1.000
<b>Severity of Illness</b>			
Median SAPS II score (range)	30 (22 – 39)	32 (24 – 38)	0.912
Median Pitt bacteraemia score (range)	1 (0 – 2)	1 (0 – 2)	0.300
Device used†	49 (63.6%)	11 (78.6%)	0.366
Surgery in past 30 days	17 (22.1%)	2 (14.3%)	0.726
Intensive care admission	14 (18.2%)	3 (21.4%)	0.721
Polymicrobial	15 (19.5%)	4 (28.6%)	0.480
Active empirical therapy	34 (44.2%)	6 (42.9%)	0.928

HIV/AIDS: Human immunodeficiency virus/ Acquired immune deficiency syndrome

\*Data are number of patients (%), unless stated otherwise.

†Device used included central venous catheter, peripherally inserted central catheter, arterial line, prosthetic heart valves, urinary catheter, permanent catheter for dialysis, tracheostomy tube, percutaneous transhepatic cholangiogram and percutaneous nephrostomy tube.

Table 3. Multivariate Analysis of Risk Factors for 30-day Mortality in *Pseudomonas Aeruginosa* Bacteraemia

Variable	Univariate Analysis		Multivariate Analysis	
	Odds Ratio (95% CI)	P Value	Adjusted Odds Ratio (95% CI)	P Value
Cardiovascular (comorbidity)	0.320 (0.113 – 0.905)	0.032	-	-
Cancer	7.200 (2.252 – 23.023)	0.001	4.873 (1.235 – 19.223)	0.024
HIV/AIDS	6.133 (1.241 – 30.309)	0.026	-	-
Median SAPS II score	1.091 (1.040 – 1.146)	<0.001	1.097 (1.032 – 1.166)	0.003
Ceftazidime (definitive monotherapy)	2.400 (0.846 – 6.812)	0.100	-	-

HIV/AIDS: Human immunodeficiency virus/ Acquired immune deficiency syndrome

Table 4. Baseline Characteristics of Patients with *Pseudomonas Aeruginosa* Bacteraemia Who Received Active Definitive Therapy (CAZ versus Non-CAZ Treatment)\*

Variable	CAZ n = 42	Non-CAZ n = 35	P Value
Age, median years (range)	65 (53 – 74)	65 (51 – 77)	0.918
Male	24 (57.1%)	22 (62.9%)	0.611
<b>Site of Acquisition</b>			
Healthcare-associated	14 (33.3%)	10 (28.6%)	0.653
Nosocomial	16 (38.1%)	19 (54.3%)	0.155
Community	12 (28.6%)	6 (17.1%)	0.238
<b>Comorbidity</b>			
Cardiovascular	24 (57.1%)	21 (60.0%)	0.800
Diabetes mellitus	14 (33.3%)	10 (28.6%)	0.653
Respiratory	3 (7.1%)	5 (14.3%)	0.457
Cancer	11 (26.2%)	4 (11.4%)	0.103
Renal	8 (19.0%)	7 (20.0%)	0.916
HIV/AIDS	4 (9.5%)	3 (8.6%)	1.000
<b>Source of Bacteraemia</b>			
Hepatobiliary	3 (7.1%)	2 (5.7%)	1.000
Intra-abdominal	1 (2.4%)	2 (5.7%)	0.588
Vascular access	2 (4.8%)	4 (11.4%)	0.402
Respiratory	7 (16.7%)	4 (11.4%)	0.513
Skin and soft tissue	3 (7.1%)	4 (11.4%)	0.695
Urinary system	17 (40.5%)	8 (22.9%)	0.100
Unknown	9 (21.4%)	9 (25.7%)	0.658
Others	0 (0.0%)	2 (5.7%)	0.203
<b>Severity of Illness</b>			
Median SAPS II score (range)	29 (22 – 39)	30 (22 – 44)	0.846
Median Pitt bacteraemia score (range)	1 (0 – 2)	2 (0 – 3)	0.167
Device used†	26 (61.9%)	23 (65.7%)	0.729
Surgery in past 30 days	8 (19.0%)	9 (25.7%)	0.483
Intensive care admission	8 (19.0%)	6 (17.1%)	0.829
Polymicrobial	5 (11.9%)	10 (28.6%)	0.066
Active empirical therapy	19 (45.2%)	15 (42.9%)	0.834

CAZ: Ceftazidime; HIV/AIDS: Human immunodeficiency virus/ Acquired immune deficiency syndrome

\*Data are number of patients (%), unless stated otherwise.

†Device used included central venous catheter, peripherally inserted central catheter, arterial line, prosthetic heart valves, urinary catheter, permanent catheter for dialysis, tracheostomy tube, percutaneous transhepatic cholangiogram and percutaneous nephrostomy tube.

Table 5. Baseline Characteristics of Patients with *Pseudomonas Aeruginosa* Bacteraemia who Received Active Definitive Therapy (TZP versus Non-TZP Treatment)\*

Variable	TZP n = 17	Non-TZP n = 60	P Value
Age, median years (range)	74 (52 – 81)	64 (53 – 73)	0.185
Male	10 (58.8%)	36 (60.0%)	0.930
<b>Site of Acquisition</b>			
Healthcare-associated	8 (47.1%)	16 (26.7%)	0.109
Nosocomial	6 (35.3%)	29 (48.3%)	0.341
Community	3 (17.6%)	15 (25.0%)	0.748
<b>Comorbidity</b>			
Cardiovascular	10 (58.8%)	35 (58.3%)	0.971
Diabetes mellitus	5 (29.4%)	19 (31.7%)	0.859
Respiratory	2 (11.8%)	6 (10.0%)	1.000
Cancer	2 (11.8%)	13 (21.7%)	0.499
Renal	4 (23.5%)	11 (18.3%)	0.73
HIV/AIDS	1 (5.9%)	6 (10.0%)	1.000
<b>Source of Bacteraemia</b>			
Hepatobiliary	1 (5.9%)	4 (6.7%)	1.000
Intra-abdominal	1 (5.9%)	2 (3.3%)	0.532
Vascular access	1 (5.9%)	5 (8.3%)	1.000
Respiratory	4 (23.5%)	7 (11.7%)	0.247
Skin and soft tissue	2 (11.8%)	5 (8.3%)	0.646
Urinary system	4 (23.5%)	21 (35.0%)	0.373
Unknown	2 (11.8%)	16 (26.7%)	0.331
Others	2 (11.8%)	0 (0.0%)	0.046
<b>Severity of Illness</b>			
Median SAPS II score (range)	34 (22 – 44)	29 (22 – 38)	0.363
Median Pitt bacteraemia score (range)	2 (1 – 2)	1 (0 – 2)	0.464
Device used†	9 (52.9%)	40 (66.7%)	0.299
Surgery in past 30 days	3 (17.6%)	14 (23.3%)	0.749
Intensive care admission	1 (5.9%)	13 (21.7%)	0.173
Polymicrobial	4 (23.5%)	11 (18.3%)	0.730
Active empirical therapy	4 (23.5%)	30 (50.0%)	0.052

HIV/AIDS: Human immunodeficiency virus/ Acquired immune deficiency syndrome; TZP: Piperacillin-tazobactam

\*Data are number of patients (%), unless stated otherwise.

†Device used included central venous catheter, peripherally inserted central catheter, arterial line, prosthetic heart valves, urinary catheter, permanent catheter for dialysis, tracheostomy tube, percutaneous transhepatic cholangiogram and percutaneous nephrostomy tube.

As a recent study with mathematical modeling<sup>17</sup> and a subsequent clinical study<sup>16</sup> demonstrated that the effectiveness of TZP for PA infection were related to MIC and illness severity, we were concerned that our use of TZP might be associated with increased adverse outcomes as we did not have MIC data to guide clinical practice. Our study was reassuring as patients treated with TZP did not do worse compared with other antibiotics, as long as activity was demonstrated by disc susceptibility testing. Additionally, TZP use was not a predictor of 30-day mortality.

Our study was performed in 2007 and 2008 before the revision of MIC breakpoint for TZP and PA by the Clinical Laboratory Standards Institute in 2012. In addition, we did not administer TZP by prolonged infusion for PA infections in 2007 and 2008. One possible reason for the effectiveness of TZP might be because the MIC for TZP for PA in our hospital was less than 16 µg/mL. It might also be due to lower illness severity as only 18.7% of our patients were admitted to ICU. In Lodise's study, prolonged infusion of TZP to achieve optimal target attainment was only shown to be associated with lower 30-day mortality in a subgroup of patients with Acute Physiological and Chronic Health Evaluation 2 score exceeding 17.<sup>16</sup>

Combination antibiotic therapy appeared to be associated with lower mortality versus monotherapy in our study. Few of our monotherapy group was treated with aminoglycoside alone, which was the main bias that previously suggested the benefit of combination antibiotic for PA infections.<sup>22,29</sup> The difference in 30-day mortality between monotherapy and combination therapy might be due to the larger number of pneumonia cases (14.3% vs 0%) and infections with unknown source (23.4% vs 0%) in the monotherapy group. Respiratory infections were associated with higher risk of mortality in previous PA bacteraemia studies.<sup>2,7</sup> Vascular access device infections were commonly associated with lower mortality.<sup>7</sup> There were significantly lesser vascular access device infections in the monotherapy group (7.8% vs 28.6%). This might explain the lower mortality rate in combination therapy group. However, this observed benefit of combination antibiotic was not borne out by the only 2 independent predictors of 30-day mortality, which were cancer and illness severity. While empiric combination antibiotics for infections where PA is a likely pathogen may be indicated by virtue of multidrug resistance, we do not believe with current evidence, proven PA infections need to be treated with more than 1 active antibiotic, as meta-analyses of randomised controlled trials showed toxicity without any advantage.<sup>20,21</sup>

We did not find inactive empiric antibiotic to be associated with higher 30-day mortality. The impact of inactive or inappropriate empiric antibiotic on mortality in PA infections was variable. Some studies reported increased

risk of mortality<sup>4,30</sup> while no difference in mortality had been reported in others.<sup>2,5,7</sup> This might be contributed by illness severity as increased risk of mortality was often shown in critically ill patients<sup>1,2,4,6,13,14</sup> or time to active culture-guided antibiotic.<sup>4,30</sup> During the study period, all patients with bacteraemia were reviewed by a blood culture notification and advisory service, which was set up by the Infectious Diseases department from 2007, to ensure active antibiotics were given within 2 days.

The limitations of our study included its retrospective study design, thus accurate data on recent admission to hospitals or non-affiliated community hospitals might be limited. The relatively small sample size limited statistical power to detect small differences in treatment outcomes. Results from the subgroup analyses comparing different antibiotics used in this study might be confounded by type 2 errors in view of the small sample sizes. More importantly, we did not have MIC data for TZP in our retrospective cohort, which might have added to evidence for or against the impact of MIC for TZP on clinical outcomes.

## Conclusion

We found that cancer as comorbidity and higher median SAPS II score were independent predictors of 30-day mortality. The choice of culture-guided antipseudomonal antibiotic did not seem to affect clinical outcome in this study, however a larger sample size will be needed to confirm this finding.

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