

## Impact of adequate empirical combination therapy on mortality in septic shock due to *Pseudomonas aeruginosa* bloodstream infections: a multicentre retrospective cohort study

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**Objectives:** To determine the association of adequate empirical combination therapy (AECT) with 30-day all-cause mortality in patients with septic shock due to *Pseudomonas aeruginosa* bloodstream infections (BSI).

**Methods:** This multicentre, retrospective cohort study analysed data from 14 public hospitals in Italy, including all consecutive adult patients admitted during 2021–2022 with septic shock due to *P. aeruginosa* BSI. We compared the outcomes of patients receiving AECT to those on adequate empirical monotherapy (AEMT) using Cox regression analyses.

**Results:** Of the 98 patients who received adequate empirical antibiotic treatment for septic shock due to *P. aeruginosa* BSI, 24 underwent AECT and 74 were given AEMT. AECT was associated with a lower 30-day all-cause mortality (25%, six out of 24) compared to AEMT (56.8%, 42 out of 74;  $P=0.007$ ). Multivariate Cox regression analysis indicated AECT as the only factor significantly associated with improved survival (aHR 0.30; 95% CI 0.12–0.71;  $P=0.006$ ). By contrast, the use of monotherapy or combination therapy in the definitive regimen did not influence mortality (aHR 0.73; 95% CI 0.25–2.14;  $P=0.568$ ).

**Conclusions:** AECT may be associated with reduced mortality compared to monotherapy in septic shock patients due to *P. aeruginosa* BSI. However, the administration of definitive adequate monotherapy or combination therapy yields similar outcomes, suggesting that once susceptibility is documented, switching to a single active *in vitro* drug is safe and feasible. Further studies are recommended to validate these findings.

## Introduction

Septic shock is a significant complication in patients with *Pseudomonas aeruginosa* bloodstream infections (BSI) because of its devastating consequences.<sup>1-3</sup>

For patients with known or suspected septic shock caused by *P. aeruginosa*, the most recent guidelines weakly recommend empirical combination therapy (i.e. administering at least two antibiotics from different antimicrobial classes to target *P. aeruginosa*) based on low-quality evidence.<sup>4-6</sup> This strategy aims to increase the likelihood that the infecting pathogen is *in vitro* susceptible to at least one of the combined antibiotics and to reduce the emergence of resistant *P. aeruginosa* strains.<sup>5-11</sup>

Another potential advantage suggested by some authors is the beneficial effect on mortality when patients empirically receive two *in vitro* active antibiotic therapies compared to monotherapy. However, information on this aspect is scarce and conflicting, with some studies failing to demonstrate a positive impact on the survival of patients treated with appropriate empirical combination therapy, which is not without drawbacks such as toxicity and increased costs.<sup>12-20</sup>

Furthermore, no studies have specifically focused on septic shock patients, a population at high risk of adverse outcomes, who may purportedly benefit the most from adequate empirical combination therapy (AECT).<sup>21</sup> The objective of the present study was to evaluate the influence of AECT versus monotherapy on the 30-day all-cause mortality in patients experiencing septic shock due to *P. aeruginosa* BSI.

## Materials and methods

### Ethics

The study was approved by the institutional review board of the coordinating centre (Comitato Etico interaziendale, City of Health and Sciences, Turin, pratica no. 202/2023, PROT.N. 0066633) and was in accordance with the declaration of Helsinki. Informed consent was deemed unnecessary due to the retrospective nature of the study.

### Study setting and design

A multicentre, retrospective cohort study was carried out in 14 public hospitals located in eight Italian regions (Liguria, Piedmont, Lombardy, Veneto, Emilia-Romagna, Lazio, Apulia and Sicily). Further details about the participating centres can be found in the [Supplementary materials](#) (available as [Supplementary data](#) at JAC Online). The computerized databases of microbiology laboratories at all participating centres were searched to identify all adult inpatients with BSI caused by *P. aeruginosa*, diagnosed between January 2021 and December 2022. In all centres, a dedicated team of infectious disease specialists continuously tracks patients with BSI, from the time of positive blood cultures until death, discharge or up to 30 days post-diagnosis, whichever occurs first.

### Inclusion and exclusion criteria

To be included in the final analysis, patients with *P. aeruginosa* BSI, defined as at least one peripheral blood culture testing positive for *P. aeruginosa* obtained from a patient with signs and/or symptoms of infection, had to:

- (i) be aged  $\geq 18$  years old;
- (ii) develop septic shock [according to the Third International Consensus Definition for Sepsis and Septic Shock (Sepsis-3)] within the first 24 hours of *P. aeruginosa* BSI onset;<sup>22</sup>

(iii) receive an adequate empirical antibiotic therapy, defined as (a) that administered within the first 24 hours of BSI onset; (b) before the reporting of the antimicrobial susceptibility testing, and (c) subsequently verified to be *in vitro* active against *P. aeruginosa* isolate.

Exclusion criteria were:

- (i) polymicrobial BSI;
- (ii) failure to receive *in vitro* active empirical therapy against the *P. aeruginosa* isolate;
- (iii) recurrent *P. aeruginosa* BSI (only the first episode per patient was included in our analysis).

### Data collection

Medical charts were retrospectively reviewed according to a pre-established protocol including the following variables: age, gender and underlying diseases, including the Charlson comorbidity index.<sup>23</sup> Additional variables considered were immunosuppression (chemotherapy, radiotherapy and/or other immunosuppressive therapy before BSI onset), the presence of neutropenia (defined as an absolute granulocyte count of  $<500/\mu\text{L}$ ) and any invasive procedures the patient underwent either during hospitalization or in the 30 days before the onset of *P. aeruginosa* BSI. These included: placement of urinary catheter, central venous catheter (CVC) or surgery. Infection related characteristics included previous *P. aeruginosa* colonization within the previous 90 days; antimicrobial susceptibility of the *P. aeruginosa* isolate; infection source and adequate source control; antibiotic therapy against *P. aeruginosa* and outcomes including 30-day all-cause mortality.

### Variable exposure

The primary variable exposure was the number of *in vitro* active antibiotics administered as empirical antibiotic therapy. According to our study protocol, patients were classified into two groups based on the number of *in vitro* active empirical antibiotics: an AECT group that received simultaneously at least two active antibiotics with a different mechanism of action against the isolated pathogen and adequate empirical monotherapy group (AEMT) that received only one active *in vitro* antibiotic. If a patient received two antipseudomonal agents, but only one was adequate, empirical antibiotic therapy was considered as AEMT. Empirical aminoglycoside monotherapy was considered as adequate only when administered for BSI originating from the urinary tract.<sup>15</sup>

### Endpoint

The primary endpoint was all-cause mortality within 30 days following the first positive blood culture for *P. aeruginosa*.

### Other definitions

Definitions for the following variables were established before data analysis. BSI onset was defined as the date of collection of the first blood culture yielding the study isolate. As for the source of BSI, diagnosis and classification of infection were defined according to the criteria of the US Centers for Disease Control and Prevention.<sup>24</sup> The source of BSI was divided into two categories: low-risk (CVC, skin and soft tissue infections, and urinary tract) and high risk (all other sources). Early adequate source control was defined as the removal of pre-existing infected hardware or drainage of an infected fluid collection thought to be the origin of the *P. aeruginosa* BSI, performed within 24 hours from the BSI onset.<sup>25</sup> Definitive therapy was considered to be any treatment that continued or started on the day that the antimicrobial susceptibility tests were known by the physicians in charge of the patients. All definitive therapies were deemed adequate based on *in vitro* susceptibility testing. They were categorized as follows: (i) adequate definitive monotherapy (ADMT) when a single active antibiotic was administered, or (ii) adequate definitive

combination therapy (ADCT) when two active antimicrobials were administered.

### Microbiological studies

Blood cultures, organism identification and susceptibility tests were conducted at each participating centre based on standard operating procedures. Antimicrobial susceptibility interpretations were provided by the local laboratories according to the EUCAST recommendations.<sup>26</sup> The criteria for categorizing *P. aeruginosa* as multidrug resistant (MDR), extremely drug resistant (XDR) or pandrug resistant were derived from the standardized international definitions proposed by Magiorakos et al.<sup>27</sup>

### Statistical analysis

Demographic, clinical characteristics and outcomes for patients receiving AECT were compared to those for patients given AEMT. Continuous variables were presented as median with the first and third quartile (Q1–Q3), while categorical variables were described by count and percentage. Categorical variables underwent comparison via the  $\chi^2$  test or Fisher's exact test, while the Wilcoxon rank sum test was employed for continuous variables, as appropriate. The independent impact of variables on survival was assessed through both unadjusted and multivariate adjusted hazard ratios (aHRs) using Cox proportional hazards regressions. Variables with a *P* value < 0.1 in the unadjusted models were incorporated into the multivariate analysis, along with the characteristics associated with the type of adequate empirical therapy (Model A). A second multivariate model was built starting from the first, selecting the variables with a backward stepwise procedure (Model B). Variables considered in this model were incorporated in a final model that also included the centre as shared frailty (Model C). A sensitivity analysis, focused on patients who survived the first 24 hours, was conducted in the same way. A further multivariate Cox regression analysis was conducted considering patients who received definitive therapy. This analysis included the relevant variable (type of adequate definitive therapy) and variables with a *P* < 0.1 in the corresponding unadjusted analyses. For each fixed Cox model, the proportional hazards assumption was verified and for each variable, aHRs and their 95% confidence intervals (CIs) were determined. A *P* ≤ 0.05 was deemed statistically significant, all tests were two-sided and no missing data were present. Analyses were conducted with SPSS version 28.0.1.0 (SPSS Software, Chicago, IL, USA) and SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

## Results

During the 2-year study period, a total of 639 patients aged ≥18 years old with *P. aeruginosa* BSI were detected. Overall, 119 of the 639 patients (18.6%) fulfilled the criteria for septic shock within the first 24 h after blood culture was drawn. Eight patients died before receiving any antibiotic therapy and 13 patients were excluded because they received inadequate empirical therapy. Thus, 98 episodes of septic shock due to *P. aeruginosa* BSI were included in the final analysis and represent the object of the present study.

Table 1 shows demographics, clinical characteristics and outcomes of the study population. Patients were classified according to the empirical therapy as AECT [24 out of 98 patients (24.5%)] and AEMT [74 out of 98 patients (75.5%)]. Among the 74 patients who received AEMT, only two (2.7%) were treated with two drugs simultaneously, but only one was *in vitro* active. Carbapenems (35/74; 47.3%) and piperacillin-tazobactam (29/74; 39.2%) were the most frequently used treatments in the AEMT group. Among the 24 patients treated with AECT, meropenem and

aminoglycoside together with piperacillin-tazobactam and aminoglycoside (5/24; 20.8% each) were the most frequent antimicrobial combinations. Further details on antimicrobials prescribed as empirical therapy are provided in the Table S1.

### Thirty-day all-cause mortality according to empirical antibiotic therapy

The 30-day all-cause mortality rate was 49.0% (48/98), with a median hospital stay from BSI onset to death being 2.0 days (Q1–Q3 1.0–9.5). As detailed in Table 1, the AECT group showed a lower 30-day all-cause mortality rate in comparison to the AEMT group [six out of 24 (25.0%) versus 42 out of 74 (56.8%), *P* = 0.007]. Patients receiving AECT were younger and more commonly had a BSI due to a MDR or XDR *P. aeruginosa* strain. No other significant differences were observed between groups in terms of underlying diseases, invasive procedures, source of BSI and early adequate source control of the infection.

### Predictors of 30-day all-cause-mortality

Unadjusted Cox analysis determined the variables associated with 30-day all-cause mortality (Table 2). The multivariate Cox regression analysis (Table 3, Model A) confirmed only a high-risk source BSI as associated with increasing 30-day all-cause mortality (aHR 2.51; 95% CI 1.10–5.73; *P* = 0.029). By contrast, receiving an AECT was the only variable associated with improved survival (aHR 0.38; 95% CI 0.15–0.95; *P* = 0.039). An additional multivariate model (Model B) performed with stepwise backward selection procedure confirmed AECT as a protective factor from mortality (aHR 0.32; 95% CI 0.14–0.76; *P* = 0.010). Similar results were observed in the final model (Model C), also including centre as shared frailty (aHR 0.30; 95% CI 0.12–0.71; *P* = 0.006). The results of sensitivity analysis for patients who survived the first 24 hours are available in the Table S2 and are consistent with the primary analysis. When excluding the only patient treated empirically with aminoglycoside monotherapy for a BSI originating from the urinary tract, as well as the two patients with AEMT due to the inadequacy of one of the two administered agents, results remained unchanged (data not shown). Figure 1 shows the cumulative survival of septic shock patients receiving AECT compared to those on AEMT (logrank test, *P* = 0.009). The Kaplan–Meier survival curves, performed after excluding patients who died within the first 24 hours of BSI onset, support the decreased mortality associated with AECT (logrank test, *P* = 0.040). These curves are provided in the Figure S1.

### Clinical outcome according to definitive therapy

Of the 98 patients, 27 (27.6%) died before antimicrobial susceptibility tests were available. Thus, 71 patients received definitive antimicrobial therapy: 25/71 (35.2%) received ADCT and 46/71 (64.8%) received ADMT. As shown in Table 2, univariate analysis revealed that ADCT had a similar risk of death in comparison to ADMT (HR 0.48; 95% CI 0.17–1.31; *P* = 0.152). Multivariate Cox regression analysis showed that 30-day all-cause mortality did not significantly differ between patients receiving ADCT and those who received ADMT (aHR 0.73; 95% CI 0.25–2.14; *P* = 0.568; data not shown).

**Table 1.** Demographics and clinical characteristics and outcomes of 98 septic shock patients with *P. aeruginosa* BSI, categorized by empirical therapy type

Variable	Total (n=98)	AEMT (n=74)	AECT (n=24)	P value
Age (years), median (Q1–Q3)	68.0 (58.0–76.0)	70.0 (59.8–78.0)	60 (49.8–69.7)	0.006
Male sex, n (%)	63 (64.3)	46 (62.2)	17 (70.8)	0.441
Underlying diseases, n (%)				
Cardiovascular disease	33 (33.7)	26 (35.1)	7 (29.2)	0.591
Solid malignancy	24 (24.5)	18 (24.3)	6 (25.0)	0.947
Neurological disease	23 (23.5)	19 (25.7)	4 (16.7)	0.366
Diabetes mellitus	17 (17.3)	15 (20.3)	2 (8.3)	0.228 <sup>f</sup>
Chronic obstructive pulmonary disease	14 (14.3)	12 (16.2)	2 (8.3)	0.507 <sup>f</sup>
Gastrointestinal disease	13 (13.3)	7 (9.5)	6 (25.0)	0.079 <sup>f</sup>
Chronic renal failure	13 (13.3)	11 (14.9)	2 (8.3)	0.511 <sup>f</sup>
Haematological malignancy	13 (13.3)	8 (10.8)	5 (20.8)	0.296 <sup>f</sup>
Charlson comorbidity index (median, Q1–Q3)	4.0 (2.0–6.0)	4.0 (2.0–4.0)	2 (3.5–6.0)	0.389
Immunosuppression, n (%)	44 (44.9)	31 (41.9)	13 (54.2)	0.294
Neutropenia, n (%)	10 (10.2)	5 (6.8)	5 (20.8)	0.062 <sup>f</sup>
Invasive procedures <sup>a</sup> , n (%)				
Urinary catheter	66 (67.3)	50 (67.6)	16 (66.7)	0.935
CVC	63 (64.3)	47 (63.5)	16 (66.7)	0.779
Any surgery	32 (32.7)	26 (35.1)	6 (25.0)	0.358
Previous <i>P. aeruginosa</i> colonization <sup>b</sup> , n (%)	29 (29.6)	21 (28.4)	8 (33.3)	0.644
Median hospital stays until BSI onset, days (Q1–Q3)	9.5 (2.0–31.0)	9 (2.0–33.5)	13(2.2–26.0)	0.852
Susceptibility profile, n (%) <sup>c</sup>				
Non-MDR	90 (91.8)	71 (95.9)	19 (79.2)	0.020 <sup>f</sup>
MDR-XDR <sup>c</sup>	8 (8.2)	3 (4.1)	5 (20.8)	
Low-risk BSI, n (%)	25 (25.5)	19 (25.7)	6 (25.0)	Ref.
CVC-associated BSI	17 (17.3)	11 (14.9)	6 (25.0)	0.351 <sup>f</sup>
Skin and soft tissue infection	5 (5.1)	5 (6.8)	0 (0.0)	0.330 <sup>f</sup>
Urinary tract	3 (3.1)	3 (4.1)	0 (0.0)	1.000 <sup>f</sup>
High-risk BSI, n (%)	73 (74.5)	55 (74.3)	18 (75.0)	0.947
Respiratory tract	35 (35.7)	25 (33.8)	10 (41.7)	0.484
Primary origin	32 (32.7)	27 (36.5)	5 (20.8)	0.155
Abdominal	6 (6.1)	3 (4.1)	3 (12.5)	0.155 <sup>f</sup>
Early adequate source control <sup>d</sup> , n (%)	9/23 (39.1)	7/16 (43.8)	2/7 (28.6)	0.657 <sup>f</sup>
Definitive therapy <sup>e</sup> , n (%)				
Monotherapy	46/71 (64.8)	38/50 (76.0)	8/21 (38.1)	0.002
Combination therapy	25/71 (35.2)	12/50 (24.0)	13/21 (61.9)	
Outcomes, n (%)				
Need for CRRT after <i>P. aeruginosa</i> septic shock	13 (13.3)	9 (12.2)	4 (16.7)	0.729 <sup>f</sup>
30-day all-cause mortality	48 (49.0)	42 (56.8)	6 (25.0)	0.007

CRRT, continuous renal replacement therapy; CVC, central venous catheter; ICU, intensive care unit.

<sup>a</sup>Within the 30 days before *P. aeruginosa* BSI onset.

<sup>b</sup>Within the 90 days before *P. aeruginosa* BSI onset.

<sup>c</sup>Overall, *P. aeruginosa* strains were identified as MDR in five episodes and XDR in three episodes. Of the five MDR cases, two received AEMT and three underwent AECT. Of the three XDR cases, one was treated with AEMT and two with AECT.

<sup>d</sup>Only 23 out of 98 patients had an infection requiring source control.

<sup>e</sup>Overall, 71 out of 98 patients received definitive adequate therapy.

<sup>f</sup>Fisher's exact test.

## Discussion

The key findings of the present multicentre cohort study can be summarized as follows: (i) mortality rate in patients with septic shock due to *P. aeruginosa* BSI is notably high; (ii) empirical combination therapy incorporating at least two *in vitro* active

antibiotics significantly reduces the 30-day all-cause mortality risk compared to monotherapy and (iii) the administration of definitive adequate monotherapy or combination therapy yields similar outcomes, suggesting that once susceptibility is documented, switching to a single active *in vitro* drug is safe and feasible.

**Table 2.** Univariate Cox models for 30-day all-cause mortality in patients with septic shock due to *P. aeruginosa* BSI

Variable	Alive (n=50)	Dead (n=48)	HR	95% CI	P value
Age (years), median (Q1–Q3)	66.0 (56.0–73.0)	69.0 (58.0–79.0)	1.02	1.00–1.04	0.082
Male sex, n (%)	34 (68.0)	29 (60.4)	0.84	0.47–1.50	0.550
Underlying diseases, n (%)					
Cardiovascular disease	15 (30.0)	18 (37.5)	1.44	0.80–2.58	0.226
Solid malignancy	14 (28.0)	10 (20.8)	0.75	0.37–1.51	0.421
Neurological disease	13 (26.0)	10 (20.8)	0.89	0.44–1.79	0.741
Diabetes mellitus	11 (22.0)	6 (12.5)	0.65	0.28–1.53	0.324
Chronic obstructive pulmonary disease	4 (8.0)	10 (20.8)	1.81	0.90–3.65	0.095
Gastrointestinal disease	9 (18.0)	4 (8.3)	0.51	0.18–1.42	0.195
Chronic renal failure	5 (10.0)	8 (16.7)	1.65	0.77–3.52	0.200
Haematological malignancy	7 (14.0)	6 (12.5)	0.95	0.41–2.24	0.913
Charlson comorbidity index, median (Q1–Q3)	4.0 (2.0–6.0)	4.0 (3.0–6.0)	1.02	0.92–1.13	0.701
Immunosuppression, n (%)	23 (46.0)	21 (43.8)	0.93	0.53–1.64	0.800
Neutropenia, n (%)	5 (10.0)	5 (10.4)	1.02	0.40–2.58	0.967
Invasive procedures <sup>a</sup> , n (%)					
Urinary catheter	35 (70.0)	31 (64.6)	0.91	0.50–1.65	0.755
CVC	38 (76.0)	25 (52.1)	0.49	0.28–0.87	0.015
Any surgery	18 (36.0)	14 (29.2)	0.84	0.45–1.56	0.576
Previous <i>P. aeruginosa</i> colonization <sup>b</sup> , n (%)	18 (36.0)	11 (22.9)	0.65	0.33–1.28	0.214
Median hospital stays until BSI onset, days (Q1–Q3)	7.5 (2.0–24.0)	10.0 (4.0–36.0)	1.00	0.99–1.01	0.964
Susceptibility profile, n (%)					
Non-MDR	45 (90.0)	45 (93.8)	Ref.	Ref.	Ref.
MDR-XDR <sup>c</sup>	5 (10.0)	3 (6.3)	0.64	0.20–2.06	0.454
Low-risk BSI, n (%)	18 (36.0)	7 (14.6)	Ref.	Ref.	Ref.
CVC-associated BSI	12 (24.0)	5 (10.4)	0.45	0.18–1.13	0.089
Skin and soft tissue infection	4 (8.0)	1 (2.1)	0.30	0.04–2.20	0.238
Urinary tract	2 (4.0)	1 (2.1)	0.71	0.10–5.15	0.736
High-risk BSI, n (%)	32 (64.0)	41 (85.4)	2.54	1.14–5.68	0.023
Respiratory tract	15 (30.0)	20 (41.7)	1.34	0.76–2.38	0.316
Primary origin	14 (28.0)	18 (37.5)	1.50	0.83–2.71	0.176
Abdominal	3 (6.0)	3 (6.3)	0.95	0.30–3.06	0.934
Empirical therapy, n (%)					
AEMT	32 (64.0)	42 (87.5)	Ref.	Ref.	Ref.
AECT	18 (36.0)	6 (12.5)	0.34	0.15–0.80	0.014
Early adequate source control <sup>d</sup> , n (%)	6/13 (49.2)	3/10 (33.3)	0.65	0.16–2.62	0.549
Definitive therapy, n (%) <sup>e</sup>					
Adequate monotherapy	30 (60.0)	16/21 (76.2)	Ref.	Ref.	Ref.
Adequate combination therapy	20 (40.0)	5/21 (23.8)	0.48	0.17–1.31	0.152
Need for CRRT after <i>P. aeruginosa</i> septic shock	6 (12.0)	7 (14.6)	1.06	0.47–2.35	0.896

CRRT, continuous renal replacement therapy; CVC, central venous catheter; ICU, intensive care unit.

<sup>a</sup>Within the 30 days before *P. aeruginosa* BSI onset.

<sup>b</sup>Within the 90 days before *P. aeruginosa* BSI onset.

<sup>c</sup>Overall, *P. aeruginosa* strains were identified as MDR in five episodes and XDR in three episodes. Of the five MDR cases, three patients survived and two died. Of the three XDR cases, two patients survived and one died.

<sup>d</sup>Only 23 out of 98 patients had an infection requiring source control.

<sup>e</sup>Overall, 71 out of 98 patients received definitive adequate therapy.

To the best of our knowledge, this is the first study that evaluates the effect of AECT on septic shock due to *P. aeruginosa* BSI, using the Sepsis-3 criteria.<sup>22</sup> In addition, the multicentre approach strengthens its external validity, making our results more widely applicable.

Recent guidelines recommend administering empirical combination therapy in all patients with septic shock with known or

suspected MDR Gram-negative BSI, including *P. aeruginosa*.<sup>4–6</sup> However, the quality of the evidence supporting this recommendation is very low, as it based on the clinical judgement of the expert panel members. This weakness in the recommendation provided in the guidelines is reflected by the low rates of patients with septic shock receiving empirical combination

**Table 3.** Multivariate Cox models for 30-day all-cause mortality in patients with septic shock due to *P. aeruginosa* BSI

Variable <sup>b</sup>	Model A <sup>a</sup>		Model B <sup>a</sup>		Model C <sup>a</sup>	
	aHR (95% CI)	P value	aHR (95% CI)	P value	aHR (95% CI)	P value
AECT <sup>c</sup>	0.38 (0.15–0.95)	0.039	0.32 (0.14–0.76)	0.010	0.30 (0.12–0.71)	0.006
Age <sup>e</sup>	1.01 (0.99–1.04)	0.266				
CVC <sup>c</sup>	0.57 (0.32–1.03)	0.064	0.54 (0.30–0.97)	0.038	0.57 (0.30–1.09)	0.088
Chronic obstructive pulmonary disease <sup>c</sup>	1.61 (0.79–3.29)	0.189				
High-risk BSI <sup>c</sup>	2.51 (1.10–5.73)	0.029	2.27 (1.00–5.15)	0.050	2.52 (1.10–5.79)	0.030
MDR-XDR <sup>d</sup>	1.05 (0.31–3.57)	0.933				

CVC, central venous catheter.

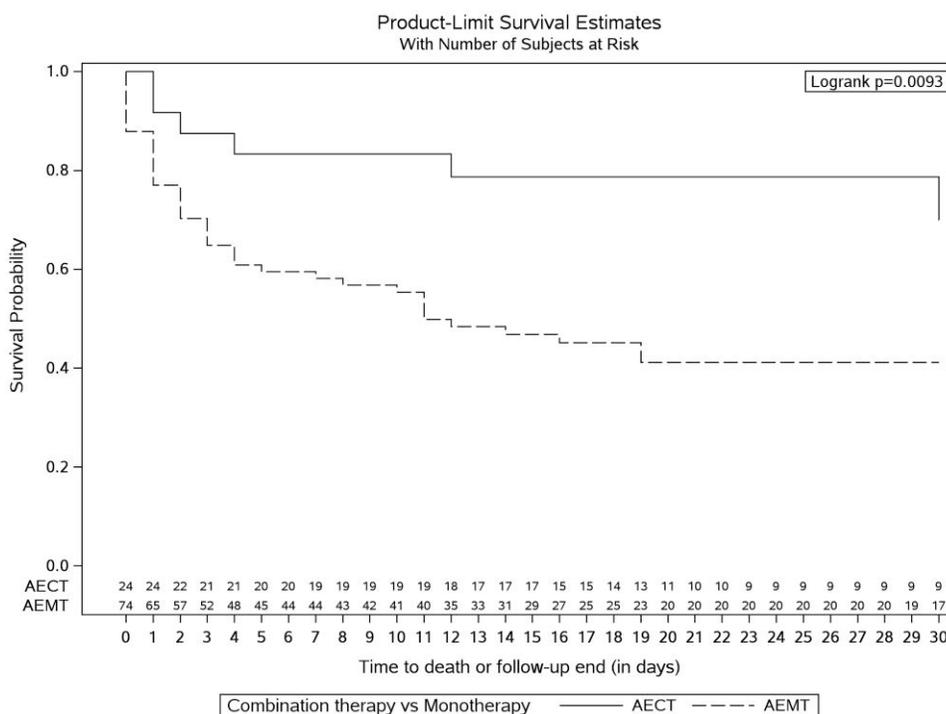
<sup>a</sup>Model A includes variables with a  $P < 0.1$  in the unadjusted model and characteristics associated with the type of empirical therapy. Model B includes variables selected by the backward procedure starting from Model A. Model C includes Model B plus centre as shared frailty. Variables corresponding to blank cells in Models B and C were eliminated by the backward procedure.

<sup>b</sup>Here we have not inserted the variable ‘CVC-associated BSI’ (unadjusted  $P < 0.1$ ) in Model A given the presence of the ‘High-risk BSI’ variable.

<sup>c</sup>Variable with a  $P < 0.1$  in the unadjusted model.

<sup>d</sup>Characteristic associated with the type of empirical therapy.

<sup>e</sup>Variable with a  $P < 0.1$  in the unadjusted model and associated with the type of empirical therapy.



**Figure 1.** Cumulative survival curve of patients receiving AECT compared with patients with AEMT.

therapy reported by us (~25%) and other colleagues (~15%–50%).<sup>13,15,17,18,28</sup>

Several studies have consistently reported a poor prognosis of septic shock due to *P. aeruginosa*, with an estimated attributable mortality rate ranging between 46% and 56%.<sup>17,25,29</sup> In our study, the 30-day all-cause mortality was 49% and this was independently predicted by two factors. One (i.e. the high-risk source of the infection) was related to the clinical status of the patient at infection onset, and this finding is consistent with previous

reports.<sup>15,18,30</sup> The second factor (and the only one that is potentially modifiable) was receiving an AECT. Regarding this aspect, current guidelines generally recommend administering an empiric combination therapy for patients with *P. aeruginosa* BSI to increase the likelihood of including at least one effective agent.<sup>5,6</sup> Yet, the benefits in terms of mortality of combining two *in vitro* active antibiotics remains a matter of debate.

Research on this topic has produced inconclusive and fragmented results, primarily attributed to the diverse range

of Gram-negative infections included and the substantial number of patients receiving monotherapy with a single aminoglycoside.<sup>14,21,28,31</sup> Many studies, which included few septic shock patients, have agreed that AECT does not reduce the risk of death compared to monotherapy.<sup>13–16,20,26</sup> However, our research, which evaluated unselected patients with septic shock due to *P. aeruginosa* BSI, indicates that the decision between AECT and monotherapy might affect patient outcomes. This observation is consistent with earlier retrospective cohort studies in which empirical combination antibiotic therapy was shown to influence 30-day mortality,<sup>12,17–19</sup> notably in a specific sub-group of 61 individuals with septic shock caused by *P. aeruginosa*.<sup>18</sup>

Several factors may explain the differences between our study's results and previous findings including discrepancies in patient demographics, the prevalence of MDR strains<sup>13,15</sup> and variations in definitions of septic shock. Additionally, our research followed the susceptibility breakpoints recently recommended by EUCAST,<sup>26</sup> which are stricter than those used in earlier studies.<sup>15</sup> Consequently, it is plausible that some patients presently categorized under the AEMT group might have been classified under the AECT group in previous studies.

From a clinical point of view, translating our findings into everyday clinical practice may be challenging. However, our results suggest that to mitigate mortality associated with septic shock due to *P. aeruginosa* BSI, it may be reasonable to administer an empirical antibiotic combination therapy consisting of at least two antimicrobial agents *in vitro* active against this pathogen. The selection of this therapeutic strategy should consider individual patient risks, previous history of colonization and the local epidemiology. We postulate that novel antibiotics, such as ceftazidime-avibactam, ceftolozane-tazobactam, imipenem-cilastatin-relebactam and cefiderocol, when combined with aminoglycosides or fosfomycin, may offer a promising approach. Nevertheless, additional investigations are warranted.<sup>25,32–34</sup>

We acknowledge that our study has several limitations. First, because of its retrospective design, it is possible that confounding factors associated with treatment decision and the clinical outcomes were not included in our multivariate analysis. Second, antibiotic therapy was prescribed by physicians in charge of the patients. Accordingly, we included various empirical combination therapies, which may have had different effects on mortality and that prevent us from drawing definitive conclusions about synergy. In fact, since synergistic interactions can be drug dependent,<sup>35</sup> evaluating synergy would require examining the role of specific synergistic antibiotic combinations, both at the antibiotic class level and considering specific antibiotics. Third, we did not collect information on other core elements of general supportive care that can vary between hospitals and are crucial for adequate septic shock management (i.e. the need for mechanical ventilation, use of intravenous fluids and oxygen therapy). Fourth, we did not monitor the development of resistance and adverse events, which are positive and negative factors associated with empirical combination therapy; however, our study was not designed to address this issue. Fifth, based on inclusion criteria, only patients who received adequate empirical antibiotic therapy within the first 24 hours from BSI onset were included. Therefore, an immortal time bias could not be excluded. However, this bias would have occurred in the two study groups. Finally, because of our sample size was relatively small for some comparison we

cannot rule out a type II error. Larger studies might reveal more about the benefits of AECT.

In conclusion, our study supports the hypothesis that AECT can decrease 30-day all-cause mortality in patients with septic shock caused by *P. aeruginosa* BSI. Our study underlines the urgent need for well-designed randomized controlled trials to confirm the clinical benefit of AECT in septic shock patients with *P. aeruginosa* BSI.

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## Transparency declaration

Outside the submitted work, A.V. reports research grants and/or personal fees for advisor/consultant and/or speaker/chairman from Gilead, Menarini, MSD, Pfizer, Astella and Shionogi. Outside the submitted work, M.B. reports research grants and/or personal fees for advisor/consultant and/or speaker/chairman from BioMérieux, Cidara, Gilead, Menarini, MSD, Pfizer and Shionogi. Outside the submitted work, D.R.G. reports investigator-initiated grants from Pfizer Inc., Shionogi, BioMérieux and Gilead Italia, and personal fees for advisor/speaker from Pfizer Inc., Menarini and Tillotts Pharma. The other authors have nothing to declare.

## Supplementary data

Tables S1 and S2 and Figure S1 are available as [Supplementary data](#) at JAC Online.

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