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Time to positivity as a predictor of catheter-related bacteremia and mortality in adults with *Pseudomonas aeruginosa* bloodstream infection

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Abstract

Background Time to positivity (TTP) and differential TTP (DTP) emerge as diagnostic and prognostic tools for bloodstream infections (BSI) though specific cut-off values need to be determined for each pathogen. *Pseudomonas aeruginosa* BSI (PAE-BSI) is of critical concern, particularly in immunocompromised patients, due to high mortality rates. Catheter-related infections are a common cause, necessitating rapid and accurate diagnostic tools for effective management (source-control).

Methods Unicentric retrospective observational study analyzing the diagnostic utility and best cut-off values of time to positivity (TTP) and differential time to positivity (DTP) to identify catheter-related PAE-BSI and the association of TTP with 30-day mortality.

Results 1177 PAE-BSI cases TTP were included in the study. TTP was available in all episodes whereas DTP was available in 355 episodes. Breakthrough bacteremia disregarding the TTP, more than one positive blood culture or > 7 days with a catheter in place and both a TTP < 13h and a DTP > 2h were independently associated to catheter-related PAE-BSI. Secondly, lower TTP were significantly associated with higher 30-day mortality rates in both catheter-related and non-catheter-related PAE-BSI. For catheter-related infections, TTP < 14h exacerbated mortality among patients among patients in whom the catheter was not removed within 48h (OR 2.9[1.04–8]); whereas for other sources TTP < 16h increased mortality (OR 1.6[1.1–2.4]) particularly when the empiric antibiotic therapy was not active (OR 3.8[1.5–10]).

Conclusion These findings advocate for the routine use of TTP over DTP as a diagnostic tool to guide timely interventions such as catheter removal, thereby potentially improving patient outcomes in PAE-BSI. Moreover, lower TTP have also prognostic implications in both catheter-related and non-catheter-related infections.

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Keywords Time to blood culture positivity, Differential time to positivity, Bloodstream infection, *Pseudomonas aeruginosa*

Introduction

Pseudomonas aeruginosa (PAE) is considered one of the most relevant pathogens worldwide. It can present with a wide range of infections and often associated with bacteremia, which accounts for high morbidity and mortality rates, notably in the setting of fragile or immunocompromised patients, that frequently have received previous broad-spectrum antibiotics [1]. In addition, the capacity of PAE to develop resistance to nearly all antibiotics by spontaneous mutations in chromosomal genes or by the acquisition of transferable resistant determinants, represents a serious problem to clinicians and a high clinical burden globally [2, 3].

Among the potential sources of PAE bloodstream infection (PAE-BSI), catheter-related infections stand out for their high frequency [4]. More specifically, catheter-related PAE-BSI accounts for a 3–30% of PAE-BSI in published retrospective data [5, 6]. Rapid identification of the infection source is of utmost importance since PAE grows forming biofilms on the surface of the catheter [7] being necessary to remove the catheter as soon as possible [4, 8] to control the infection. Contrarily, if the catheter is not the origin of the infection, the exchange of intravenous line would be spared, reducing the associated morbidity [9] and promoting other diagnostic procedures for different sources [10].

Time to positivity (TTP) is defined as the time elapsed from the beginning of culture incubation to the detection of bacterial growth by an automated blood culture system. It depends on several factors such as species, bacterial load, active antibiotic treatment at the moment of obtaining the blood culture or host characteristics (splenectomy, neutropenia) [11]. TTP has emerged as a simple and inexpensive method to provide additional information with potential clinical impact to suggest the origin and the prognosis of the infection [12, 13]. Indeed, TTP has been identified as a predictor of resistance to antimicrobials, septic shock, or mortality in *S. aureus*, streptococci, gram-negative bacilli, and *Candida* spp bloodstream infections [14–18]. Differential time to positivity (DTP) has been used as a complementary tool to discern catheter-source bacteremia both in gram-positive and gram-negative bacteria [19, 20], but not specifically for PAE-BSI. Generally, a cut-off of 120 min or more between the positivity of a blood culture extracted from a catheter compared to the growth of a simultaneous blood culture obtained by venipuncture is considered diagnostic of catheter-related bacteremia [21, 22]. However, DTP has technical limitations (identification of blood cultures obtention or similar amount of blood in all flasks) that precludes its wide clinical implementation, and it is not clear whether 120 min its applicable to species with different TTP.

To date, only few studies have focused on TTP and DTP as diagnostic tools to predict source of BSI such as catheter-related infections, but no studies have specifically looked into PAE-BSI. The aim of our study was to analyze if TTP and DTP can be used to diagnose catheter-related bacteremia in PAE-BSI episodes. Additionally, we explored whether TTP can be used as a risk factor for 30-day mortality.

Methods

Setting

We conducted a retrospective study at an 800-bed university institution that offers care for 500,000 inhabitants in Barcelona, Spain. The hospital is a referral center for onco-hematological diseases and for solid organ and hematopoietic transplantation. We prospectively recorded data from all consecutive bloodstream infections from 1991 to 2019 using a routine purpose-designed surveillance database. From those, PAE-BSI episodes were selected and times to positivity (TTP and, when available, DTP) were tracked. Other variables collected were: age, sex, previous comorbidities, use of vascular and urinary catheters, presence of neutropenia, immunosuppressive treatments, source of bacteremia, septic shock, septic metastases and all-cause mortality at 30 days. Antibiotic treatment, antibiotic susceptibilities, previous use of antibiotics and appropriateness of empirical and targeted treatment were also recorded.

Inclusion and exclusion criteria

All episodes of PAE-BSI within the period of the study were tracked. In cases of persistent bacteremia in the same patient, the episode was considered to begin with the positivity of the first blood culture. Only the first time-to-positivity (TTP) or differential time-to-positivity (DTP) for each episode was recorded and included in the study. Episodes where blood cultures originated from extra-hospital facilities were excluded due to unknown incubation times.

Outcomes

The primary outcome was to determine whether TTP can be reliably used as a microbiological marker for

catheter-related bacteremia in PAE-BSI episodes. As secondary related outcomes, we aimed to assess the potential impact of concurrent antibiotic treatment at the time of blood culture extraction on TTP and to compare the overall diagnostic performance of TTP against DTP for the diagnosis of catheter-related PAE-BSI. The second primary outcome was to assess the prognostic value of shorter TTP in both catheter-related PAE-BSI and other sources of bacteremia. Patients were followed up for 30 days after the onset of bacteremia and the recorded variable was all-cause mortality at 30 days.

Definitions

PAE bloodstream infection (PAE-BSI) was defined as ≥ 1 positive blood culture. The bacteremia source was determined based on clinical criteria and the isolation of the same strain from a clinical sample.

For the purpose of the study, only information regarding central venous catheters (both central lines and permanent devices) was collected. Catheter-related bacteremia was considered when the same species with the same antibiogram was isolated in the blood and in the catheter tip [23]. Bacteremia was considered to be hospital-acquired if it occurred ≥ 48 h after admission [24].

TTP was determined from the time interval between the start of incubation and the detection of microbial growth using an automated monitoring system (see microbiological procedures below). When multiple cultures were positive only the shortest TTP was selected for the analysis. DTP was the difference (in hours) of the TTP of blood culture obtained from a catheter and the TTP of simultaneous blood culture obtained by venipuncture.

Septic shock was defined when the patient required vasopressors due to persistent hypotension despite fluid resuscitation with a causal and temporal relationship with the PAE-BSI episode [8]. Persistent bacteremia was considered when a positive blood culture was documented despite ≥ 24h of active antibiotic treatment or when the first blood culture was positive under in vitro active antibiotic treatment (breakthrough bacteremia).

Empirical antibiotic therapy was considered appropriate when the patient received a proper antimicrobial agent within 24h after blood cultures were obtained and before antibiotic susceptibility results were reported.

Carbapenem resistance was defined if the isolate tested resistant to at least one of the carbapenem antibiotics. PAE strains were considered as multi-drug resistant when they were resistant to at least 1 antimicrobial agent within at least 3 antibiotic classes [25].

Immunocompromised patients were those receiving long-term (> 3 months) or high-dose (> 0.5 mg/kg/day) steroids or other immunosuppressant drugs, solid-organ or stem-cell transplant recipients, patients with solid tumor or hematological malignancy requiring chemotherapy or an absolute neutrophil count below 0.5×10^9/L [26, 27]. Patients with primary immune deficiency and AIDS were included as well.

Microbiological procedures

Samples for blood cultures were inoculated into aerobic and anaerobic vials and processed between 1991 and 1997 by BACTEC NR-730; between 1998 and 2013 by BACTEC 9240 System and since 2013 by BACTEC FX (Becton–Dickinson, Block Scientific Bellport NY 11713 United States). The incubation period was 5 days before being discarded as negative, and vials were loaded into the machine around the clock. Volumes between 8 to 10 mL of blood samples were inoculated into aerobic and anaerobic vials. The vials used were resin-containing BACTEC-Plus Aerobic/F and BACTEC-Plus/Anaerobic/F or non-resin-containing BACTEC-Standard 10/Aerobic/F and BACTEC-Lytic/10/Anaerobic/F. Blood cultures coming from outpatient clinics or hospital outpatient's departments (such as dialysis centers or hospital at home) were excluded from the study.

The identification of PAE from positive cultures was performed between 1991 and 2008 using Api-NE (Biomerieux®) and since 2009 by MALDI-ToF Antimicrobial susceptibility testing was performed using a microdilution system (Phoenix®, Becton Dickinson) or gradient diffusion strips. Susceptibility to antimicrobials was established according to the Clinical and Laboratory Standards Institute breakpoints until mid-2011 and to the current European Committee on Antimicrobial Susceptibility Testing criteria (EUCAST).

Statistical analysis

Categorical variables were presented as absolute numbers and percentage, and continuous variables were described as median and interquartile range (IQR) or mean and standard deviation (SD) according to their distribution. Categorical variables were compared using the χ^2 or Fischer test as appropriate. Continuous variables were compared using either the Student t-test or non-parametric tests depending on the homogeneity of the variable.

To evaluate the value of TTP and DTP for the diagnosis of PAE-BSI, only patients carrying at least one venous catheter were included in the analysis. ROC curves were used to choose the best TTP and DTP cut-offs for both analyses. Univariate and multivariate analyses were performed, considering only variables present during the first 24h from symptoms' onset, to identify characteristics independently associated with catheter-related bacteremia. Variables potentially associated with catheter-related bacteremia by univariate

analyses ($p < 0.1$) were included in the binary logistic regression model using a stepwise backwards procedure. Collinearity diagnostics package of SPSS (v.25) was used to test tolerance, variance inflation factors (VIF) and condition cndex for each variable included in the analysis.

The analysis of TTP as a risk factor for 30-day mortality was performed dividing the patients in 2 groups, those with a catheter-related bacteremia and those with other sources. The reason to divide the groups is because the TTP in catheter-related bacteremia is shorter than in any other source, but the mortality is the lowest probably because the line is removed immediately or within the first 24h in most cases. Univariate and multivariate analyses were performed to identify independent variables associated with 30-day mortality. Variables potentially associated with an increased mortality by univariate analyses ($p < 0.1$) were included in the binary logistic regression model using a stepwise backwards procedure.

Calculations were performed with the Statistical package for the Social Sciences, version 25 (IBM SPSS Inc., Chicago, USA).

Ethics statement

The study was approved by the Ethics Committee of Hospital Clinic of Barcelona, Spain (Register 2024/0934). Written informed consent was waived due to the non-interventional design. Patients remained anonymous.

Results

During the study period 1177 patients with PAE-BSI were included in the study. TTP was measured in all PAE isolations. Median (IQR) TTP was 15 (11.2–18) hours. DTP was obtained in 355 cases (30%) with a median (IQR) time of 1 (0.3–4.5) hour. Supplementary Table 1 shows the characteristics and outcomes of included cases grouped by catheter-related BSI and other sources. Catheter-related BSI was diagnosed in 33.3% of cases and was the most frequent source of bacteremia. These patients had significantly shorter TTP (median TTP 12.1h vs. 15.9h, $p < 0.001$) and longer DTP (median 2.6h vs. 0.7h, $p < 0.001$). They also had breakthrough bacteremia more frequently (23.3% vs. 6.5%, $p < 0.01$), and this characteristic was associated with a delayed catheter removal beyond 48h since the onset of bacteremia (37% vs. 10.9%, $p < 0.001$). Conversely, catheter-related BSI had

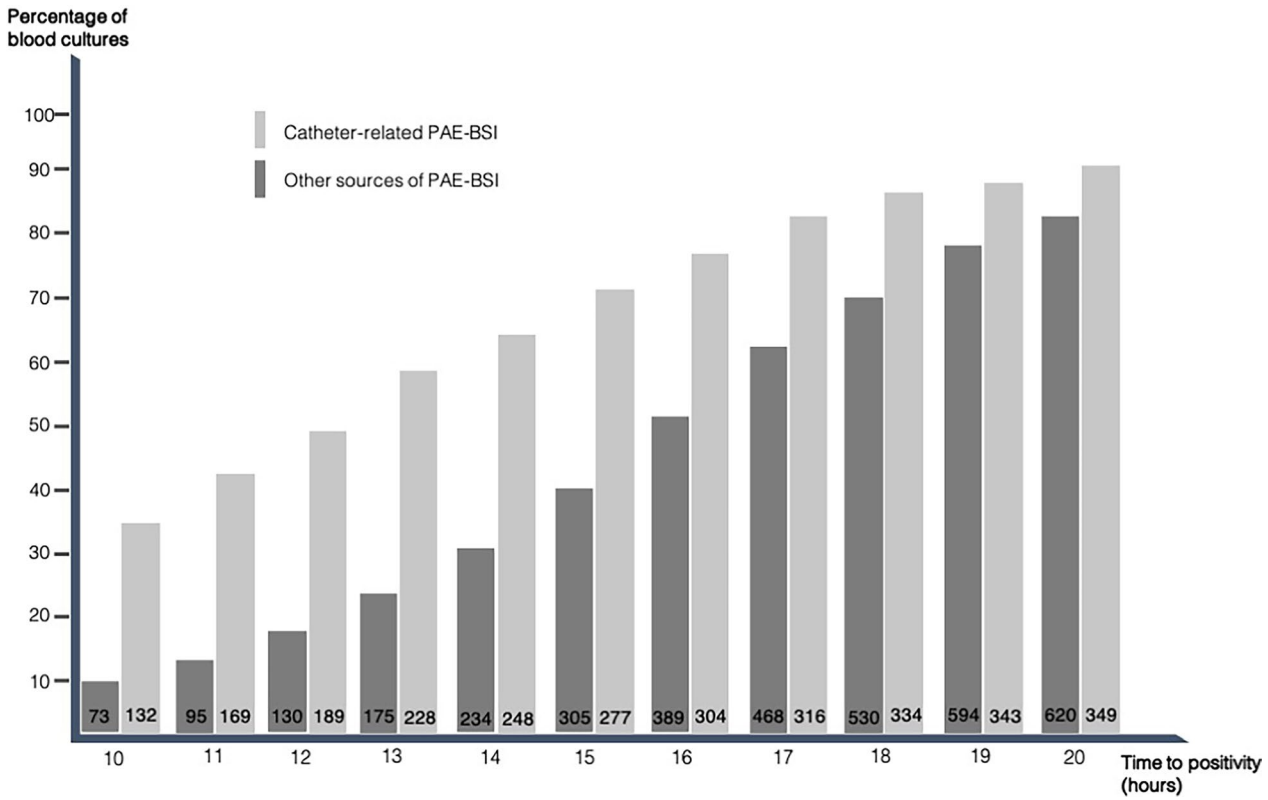

Fig. 1 Bar plot showing the percentage of positive blood cultures along hourly cut-offs between 10 and 20 h of incubation. Time to positivity (TTP) was shorter in catheter-related *Pseudomonas aeruginosa* blood stream infections (n = 393) compared to other sources of bacteremia (n = 784)

less septic shock (12.1% vs. 22.7%, $p<0.001$) and a lower 30-day mortality (7.7% vs. 26%, $p<0.001$). TTP distribution among catheter-related BSI and other sources are shown in Fig. 1.

Clinical value of TTP for the diagnosis of catheter-related PAE-BSI

From the whole cohort, 859 patients carried at least one venous catheter at the time of bacteremia and were eligible for the purpose of this analysis. The median (IQR) TTP was 14.5 (10.4–17.5) hours. Hourly TTP cut-off were tested using ROC analysis and showed that TTP < 13 h was the best cut-off for the diagnosis of catheter-related PAE-BSI (AUC (CI) 0.66 [0.62–0.7]). This cut-off showed a sensitivity, specificity, positive predictive value (PPV), and negative predictive value of 59.4%, 72.3%, 64.2% and 32%, respectively. However, lower cut-off (TTP < 10 h) incremented specificity and PPV to 86.7% and 70.55%, respectively (Supplementary Table 2). Table 1 shows the univariate and multivariate analysis for the rest of variables associated with catheter-related PAE-BSI. The binary logistic regression model included the following variables independently associated with catheter-related BSI: TTP < 13 h (OR 3.7, $p<0.001$), breakthrough bacteremia (OR 2.2, $p<0.001$), clinical diagnosis of phlebitis (OR 2.4, $p<0.001$), PAE isolation in two blood cultures (OR 1.8, $p=0.002$) and carrying a catheter for more than 7 days (OR 2.7, $p<0.001$), whereas septic shock (OR 0.59, $p=0.02$), and neutropenia (OR 0.31, $p<0.001$) were inversely related. AUC (CI) of the model was 0.8 (0.77–0.83).

Clinical value of DTP for the diagnosis of catheter-related PAE-BSI

This analysis was done including the 355 patients with at least two positive vials and available information of DTP between a blood culture obtained from a catheter and the other from a peripheral vein. In this cohort, 135 (38.9%) were diagnosed as catheter-related PAE-BSI. The median (IQR) TTP was 14 (10.8–16.6)hours and the median DTP (IQR) was 1

Table 1 Univariate and multivariate analysis of variables associated with catheter-related PAE-BSI among patient carrying at least one venous catheter (n = 859)

		Univariate analysis			Multivariate analysis	
		Catheter-related PAE- BSI (n = 389)	Other sources (n = 470)	*p*-value	OR [95% CI]	*p*-value
Age > 64 years		157 (59.6)	241 (51.3)	0.001		
Sex (male)		240 (61.7)	318 (67.9)	0.043		
Comorbidities						
Diabetes mellitus		87 (22.4)	91 (19.4)	0.31		
Chronic pneumopathy		30 (7.7)	50 (10.7)	0.16		
CKD		40 (10.3)	19 (4)	0.001		
Chronic liver disease		26 (6.7)	25 (5.3)	0.47		
Immunocompromised status		242 (62.2)	345 (73.4)	< 0.001		
Hematologic malignancy		55 (14.1)	101 (21.5)	0.004		
Neutropenia		20 (5.2)	68 (14.5)	< 0.001	0.31 [0.17–0.55]	< 0.001
Solid neoplasm		93 (23.9)	109 (23.2)	0.87		
Solid organ transplantation		44 (11.3)	89 (18.9)	0.002		
Admission data						
Time since admission (days)		15 (IQR 1–30)	15 (IQR 6–28)	0.97		
Previous admission (< 1 month)		114 (29.3)	132 (28)	0.7		
Nosocomial bacteremia		382 (98.2)	446 (94.9)	0.05		
Phlebitis		48 (12.3)	7 (1.5)	< 0.001	2.4 [1.8–3.3]	< 0.001
Septic shock		46 (11.9)	95 (20.2)	0.001	0.59 [0.38–0.92]	0.02
Catheter > 7 days		312 (80.2)	267 (56.8)	< 0.001	2.7 [1.9–3.8]	< 0.001
Catheter > 14 days		215 (55.3)	166 (35.3)	< 0.001		
Microbiologic factors						
Active antibiotic during bacteremia		78 (20.1)	72 (15.3)	0.09	2.2 [1.4–3.3]	< 0.001
Median TTP		12 (IQR 8.8–15.5)	15.7 (IQR 12.6–18.3)	< 0.001		
	TTP < 13 h	231 (59.4)	129 (27.4)	< 0.001	3.7 [2.7–5.1]	< 0.001
PAE isolated in 2/2 vials		133 (34.2)	116 (24.7)	0.003	1.8 [1.2–2.5]	0.002

BSI, blood stream infection; CI, confidence interval; CKD, chronic kidney disease; OR Odds ratio; PAE, Pseudomonas aeruginosa; TTP, time to positivity

(0.3–4.5)hour. Breakthrough bacteremia was documented in 43 (12.1%) cases. The ROC analysis showed that a DTP > 2 h was the best cut-off point to predict catheter-related bacteremia. In this analysis, the following variables were found to be independently associated with catheter-related BSI in the binary logistic regression model: TTP < 13 h (OR 4.3, $p < 0.001$), DTP > 2 h (OR 2, $p = 0.02$), catheter in place for more than 7 days (OR 7.8, $p < 0.001$), whereas neutropenia (OR 0.28, $p = 0.01$) was inversely related. AUC (CI) of the model was 0.86 (0.82–0.9) (Table 2).

Impact of receiving active antibiotic treatment at the moment of blood culture obtention (breakthrough bacteremia) on TTP and DTP

Breakthrough bacteremia was more common in patients with catheter-related PAE-BSI than in other sources of PAE-BSI (20.4% vs. 9.7%, $p = 0.001$). The antibiotic had a lengthening effect on the median (IQR) TTP (15.9 [12.5–18.9] vs. 14.8 [11.4–17.7]h, $p = 0.04$) in the global cohort. However, the difference was more evident in catheter-related PAE-BSI (14.6 [11.5–19.5] vs. 11.4 [8.2–14.8]h, $p < 0.001$), than in the case of other sources of PAE-BSI (16.6 [13.8–18.9] vs. 15.9 [13.2–18.6]h, $p = 0.18$). Likewise, the median (IQR) DTP in cases with catheter-related PAE-BSI was significantly shorter among those with breakthrough bacteremia (2.2 [0.6–4.5] vs. 4.8 [1.7–6.6]h, $p = 0.02$).

Correlation between TTP and 30-day mortality

The global 30-day mortality was 19.8% for PAE-BSI cases. Among catheter-related PAE-BSI, 30-day mortality was 7.7%, whereas for other sources it was 26% ($p < 0.001$). Table 3 shows the univariate and multivariate analysis of risk factors for mortality in patients with catheter-related BSI. In this group, mortality did not increase at

Table 2 Univariate and multivariate analysis of variables associated with catheter-related PAE-BSI in the patients with at least two positive vials and available information about DTP (n = 355)

		Univariate analysis			Multivariate analysis	
		Catheter-related PAE- BSI (n = 135)	Other sources (n = 220)	*p*-value	OR [95% CI]	*p*-value
Age > 64 years		53 (39.3)	115 (52.3)	0.01		
Sex (male)		85 (63)	138 (62.7)	0.7		
Comorbidities						
Diabetes mellitus		25 (18.5)	38 (17.2)	0.31		
Chronic pneumopathy		16 (11.9)	25 (11.4)	1		
CKD		11 (8.1)	4 (1.8)	0.007		
Chronic liver disease		14 (10.4)	14 (6.5)	0.47		
Immunocompromised status		90 (66.7)	165 (75)	0.03		
Hematologic malignancy		22 (16.3)	72 (32.7)	< 0.001		
Neutropenia		10 (7.5)	57 (25.9)	< 0.001	0.28 [0.12–0.66]	0.01
Solid neoplasm		37 (27.4)	58 (26.4)	1		
Solid organ transplantation		15 (11.1)	31 (14.1)	0.42		
Admission data						
Time since admission (days)		15 (IQR 1–30)	3 (IQR 0–17)	< 0.001		
Previous admission (< 1 month)		42 (31.1)	85 (38.6)	0.03		
Nosocomial bacteremia		134 (99.3)	183 (86.7)	< 0.001		
Phlebitis		21 (15.6)	0 (0)	< 0.001		
Septic shock		18 (13.5)	66 (30)	< 0.001		
Catheter > 7 days		109 (80.7)	62 (28.2)	< 0.001	7.8 [4.4–14]	< 0.001
Catheter > 14 days		72 (53.3)	39 (17.7)	< 0.001		
Microbiologic factors						
Active antibiotic during bacteremia		20 (14.8)	23 (10.5)	0.31	2.2 [1.4–3.3]	< 0.001
Median TTP		11.2 (IQR 8.3–14.6)	15 (IQR 12.9–17.1)	< 0.001		
	TTP < 13 h	91 (67.4)	54 (24.5)	< 0.001	4.3 [2.5–7.7]	< 0.001
Median DTP		2.6 (IQR 0.7–6.5)	0.7 (IQR 0.3–2)	< 0.001		
	DTP > 2 h	72 (53.3)	52 (23.6)	< 0.001	2 [1.1–3.5]	0.024

BSI, blood stream infection; CI, confidence interval; CKD, chronic kidney disease; OR Odds ratio; PAE, Pseudomonas aeruginosa; TTP, time to positivity

Table 3 Univariate and multivariate analysis of risk factors for mortality at 30 day of patients with catheter-related PAE-BSI (n = 393)

			Univariate analysis			Multivariate analysis	
			Deceased (n = 30)	Survivors (n = 363)	*p*-value	OR [95% CI]	*p*-value
Age > 64 years			16 (53.3)	140 (38.6)	0.1		
Sex (male)			240 (61.7)	318 (67.9)	0.043		
Comorbidities							
	Diabetes mellitus		9 (30)	77 (21.2)	0.26		
	Chronic pneumopathy		3 (10)	28 (7.7)	0.72		
	CKD		2 (6.7)	67 (18.5)	0.13		
	Chronic liver disease		3 (10)	31 (8.5)	0.73		
	Immunocompromised status		19 (63.3)	226 (62.3)	1		
	Hematologic malignancy		9 (30)	46 (12.7)	0.02		
	Neutropenia		3 (10)	17 (4.7)	0.19	4 [1.4–11]	0.01
	Solid neoplasm		6 (20)	88 (24.2)	0.66		
	Solid organ transplantation		3 (10)	63 (17.4)	0.45		
Admission data							
	Time since admission (days)		22 (IQR 11.5–54)	14 (IQR 1–29)	0.16		
	Previous admission (< 1 month)		114 (29.3)	132 (28)	0.7		
	Nosocomial bacteremia		29 (96.7)	353 (97.2)	0.43		
	Phlebitis		48 (12.3)	7 (1.5)	< 0.001		
	Septic shock		46 (11.9)	95 (20.2)	0.001		
	Catheter > 7 days		312 (80.2)	267 (56.8)	< 0.001		
	Catheter > 14 days		215 (55.3)	166 (35.3)	< 0.001		
	Mechanical ventilation		8 (26.7)	35 (9.6)	0.01	4.7 [1.5–14.7]	0.008
Microbiologic factors							
	Active antibiotic during bacteremia		10 (33.3)	89 (24.5)	0.19		
	Incorrect empiric antibiotic		18 (60)	134 (36.9)	0.01	2.9 [1.2–7.3]	0.02
	Carbapenem resistant strain		19 (63.3)	72 (19.8)	< 0.01	6.6 [2.6–16.4]	< 0.001
	Median TTP		13 (IQR 8–17.5)	12.1 (IQR 8.8–15.5)	0.33		
	TTP < 13 h		15 (50)	213 (58.3)	0.3		
	PAE isolated in 2/2 vials		21 (70)	222 (61.2)	0.43		
Severity							
	Septic shock		5 (16.7)	41 (11.3)	0.38		
	Persistent bacteremia		9 (30)	80 (22)	0.36		
Source							
	Catheter removal > 48 h		19 (63.3)	165 (45.5)	0.08	2.7 [1.1–6.7]	0.04
		Catheter removal > 48 h by TTP < 14 h	11 (36.7)	96 (26.4)	0.04		

CI, confidence interval; CKD, chronic kidney disease; IQR, inter-quartile range; OR Odds ratio; PAE, Pseudomonas aeruginosa; TTP time to positivity

lower TTP (Fig. 2). A significant increase in mortality was observed among patients in whom the catheter was not removed within 48h since the onset of bacteremia (OR 2.7 [1.1–6.7], $p = 0.04$). This surplus in mortality was more pronounced every hour of TTP shortening below TTP < 14h (OR 2.9 [1.04–8], $p = 0.04$) (Fig. 2). The rest of risk factors that were also independently associated with increased 30-day mortality in the multivariate model were: hematological malignancies (OR 4 [1.4–11], $p = 0.01$), carbapenem-resistant strains (OR 6.6 [2.6–16.4], $p < 0.001$), incorrect empiric antibiotic treatment (OR 2.9 [1.2–7.3], $p = 0.02$) and the need for mechanical ventilation (OR 4.7 (1.5–14.7), $p = 0.008$). AUC (CI) of the model was 0.84 (0.77–0.92).

For the analysis of non-catheter PAE-BSI, patients with unknown source of BSI, with a TTP < 13h and

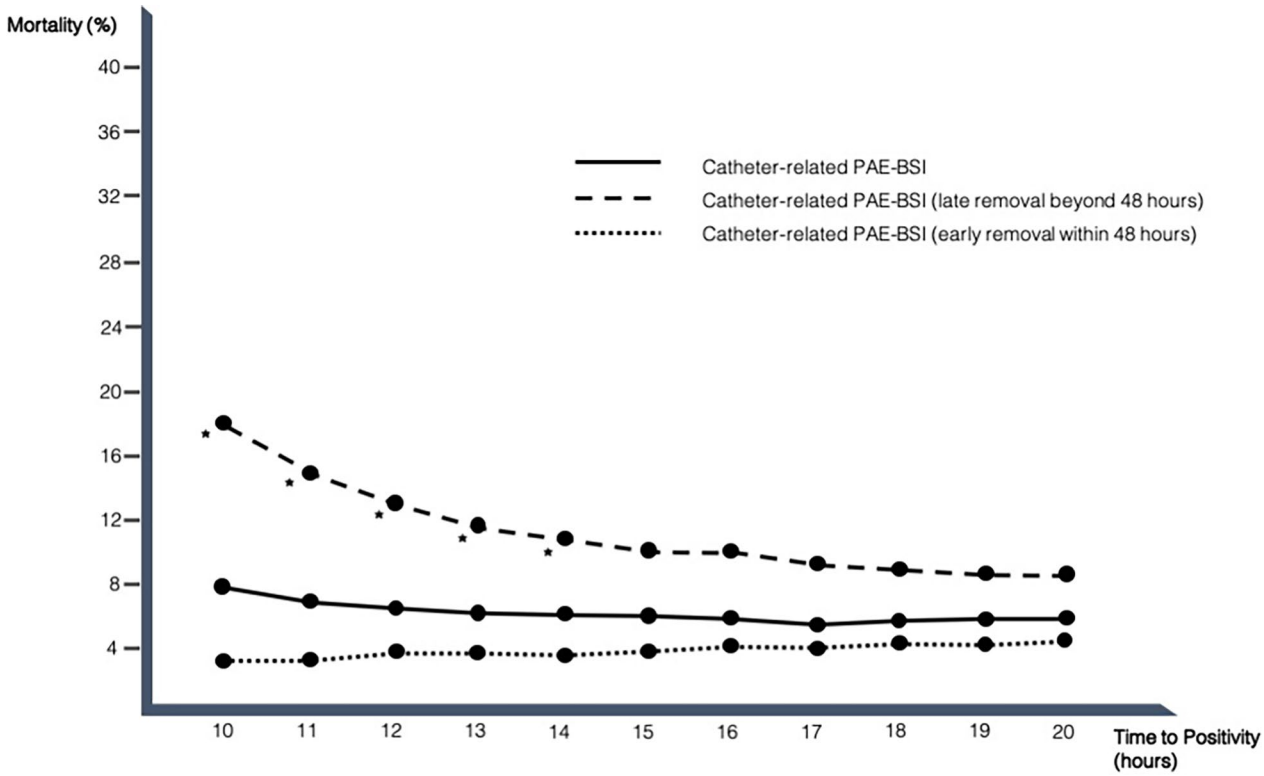

Fig. 2 Line graph showing the percentage of deceased patients at 30-day follow-up in accordance *Pseudomonas aeruginosa* blood stream infection (PAE-BSI) source. Among catheter-related PAE-BSI in which catheter removal was delayed beyond 48 h (dashed line), mortality increased at lower TTP. Conversely, when catheter was early removed within 48 h, lower time to positivity (TTP) did not have an impact in mortality rates (dotted line). Asterisks denote statistically significant differences ($p < 0.05$) in mortality rates between early and delayed catheter removal subgroups

non-neutropenic, were removed from the analysis since we considered that, according to our results, the most likely source of these episodes was the catheter. An association was found between TTP and mortality among patients with a source of infection different from catheter. Hourly TTP was tested resulting in a TTP < 16 h (the median value) as the best cut-off for predicting 30-day mortality. Moreover, we identified a significant interaction between TTP and receiving correct empirical treatment. The statistical interaction indicates that the impact of a TTP < 13h on mortality was more pronounced in those patients receiving incorrect empiric antibiotic therapy (OR 3.8 [1.8–10], $p = 0.006$) (Fig. 3). Table 4 shows the rest of risk factors for 30-day mortality included in the univariate and multivariate analyses for patients with non-catheter-related bacteremia. In the final binary logistic regression model, septic shock (OR 4.8 [3.1–7.4], $p < 0.001$), mechanical ventilation (OR 2.3 [1.2–4.5], $p = 0.01$), respiratory source (OR 2.6 [1.6–4], $p < 0.001$), chronic liver disease (OR 2.7 [1.3–5.7], $p = 0.01$), hematologic malignancy (OR 1.8 [1.2–2.8], $p = 0.013$), TTP < 16h (OR 1.6 [1.1–2.4], $p = 0.03$), and carbapenem resistant strains (OR 1.5 [1–2.3], $p = 0.05$) were independent predictors of mortality. AUC (CI) of the model was 0.8 (0.76–0.84).

No collinearity issues were detected for the following combinations: incorrect antibiotic and carbapenem resistant strain, incorrect antibiotic and TTP < 13h, carbapenem resistant strain and TTP < 16h and respiratory source and mechanical ventilation.

Discussion

In a cohort of patients with PAE-BSI we found that shorter TTP can be used as predictor of catheter-related bacteremia. Likewise, a DTP > 2h is associated with catheter-related BSI in PAE-BSI. Additionally, we found an association of shorter TTP with higher 30-day overall mortality for sources other than catheter-related PAE-BSI and for catheter-related PAE-BSI when the catheter removal is delayed > 48h.

Patients at risk of infection by PAE often need long-lasting catheters or present difficulties for catheter replacement. Therefore, non-invasive tools are needed for better selection of patients that would benefit of early catheter removal. Our results demonstrate that both a

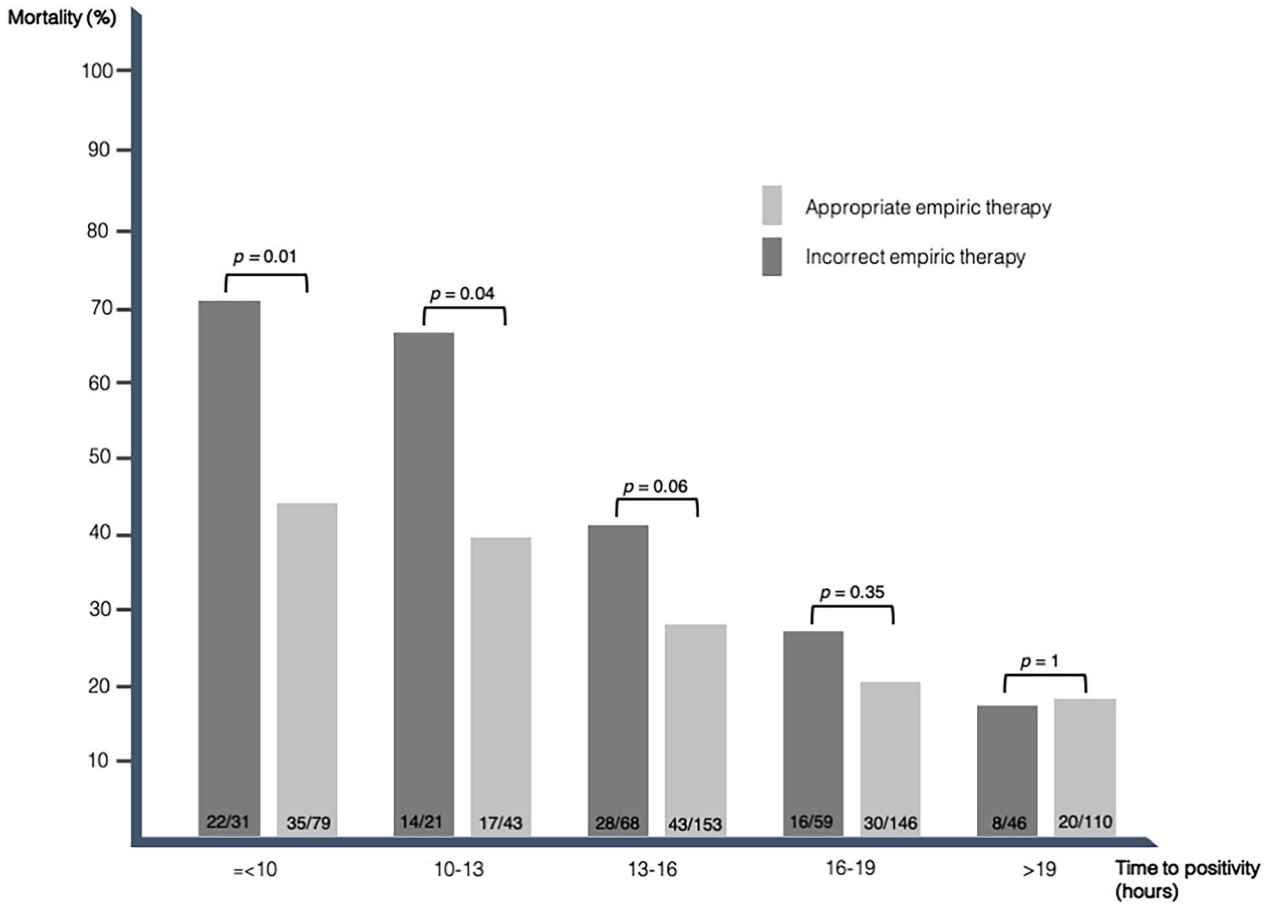

Fig. 3 Bar plot showing mortality distribution among non-catheter related episodes of PAE-BSI according to different TTP ranges and appropriateness of empiric antibiotic therapy. Square brackets and *p*-values indicate statistically significant difference based on appropriateness of empirical antibiotic therapy for the different TTP ranges

TTP < 13h and a DTP > 2h are significantly associated with catheter-related PAE-BSI. Several studies have demonstrated an association between TTP and endovascular infection (including catheter BSI) due to gram-positive cocci [18]. In contrast, Willmann et al [28] in a cohort of 74 PAE-BSI with a similar median TTP (14.5h) to ours, failed to find an association between TTP and the source of bacteremia. Of note, in 40% of the cases the source was unknown, and they only included 7 patients with a catheter-related BSI that limits the validity of this study to determine the potential value of TTP as a surrogate marker of catheter-related BSI. In our study, with 859 episodes in patients wearing a catheter and a 33% of documented catheter-related BSI, we show that a TTP < 13 h was almost 4 times more frequent among patients with a catheter-related bacteremia (OR 3.7, $p < 0.001$). We also assessed the usefulness of DTP as a predictor of catheter-related PAE-BSI. The original description stablishing the diagnostic value of a DTP > 2h included only 5 episodes of PAE-BSI out of 93 [21]. In the present article we confirm that a DTP > 2h has the highest accuracy for predicting catheter-related PAE-BSI and it was an independent predictor of this source (OR 2, $p = 0.02$). However, DTP requires a blood culture from a catheter and a peripheral vein, and adequate identification of all flasks, explaining why this variable was only available in one-third of the cases. In contrast, TTP is easy to obtain and the median TTP in 3 studies from different countries using a similar processing system (BACTEC), showed the same median TTP (15h) [28–30]. This supports the reproducibility of this parameter and its clinical value.

Our study reflects that active antibiotic treatment during bacteraemia (breakthrough bacteremia) significantly influences the interpretation of both TTP and DTP. Indeed, this treatment is the main confounding factor when these parameters are evaluated. For this reason, previous studies focusing on TTP have excluded patients receiving an active antibiotic treatment at the time of blood culture extraction [28, 29, 31]. However, breakthrough bacteremia is a common situation in catheter-related PAE-BSI, being necessary to

Table 4 Univariate and multivariate analysis of risk factors for mortality at 30 day of patients with non-catheter-related PAE-BSI (n = 683)

			Univariate analysis			Multivariate analysis	
			Deceased (n = 192)	**Survivors (n = 491)**	***p*-value**	**OR [95% CI]**	***p*-value**
Age > 64 years			119 (62)	277 (56.4)	0.2		
Sex (male)			72 (37.5)	134 (27.3)	0.012		
Comorbidities							
	Diabetes mellitus		36 (18.8)	107 (21.8)	0.4		
	Chronic pneumopathy		29 (15.1)	59 (12)	0.31		
	CKD		25 (13)	65 (13.2)	1		
	Chronic liver disease		21 (10.9)	24 (4.9)	0.006	2.7 [1.3–5.7]	0.01
	Immunocompromised status		150 (78.1)	370 (73.3)	0.21		
	Hematologic malignancy		64 (33.3)	98 (20)	< 0.001	1.8 [1.2–2.8]	0.013
	Neutropenia		52 (27.1)	91 (18.5)	0.01		
	Solid neoplasm		53 (27.6)	128 (26.1)	0.7		
	Solid organ transplantation		17 (8.9)	97 (19.8)	< 0.001		
Admission data							
	Time since admission (days)		6 (IQR 0–22)	7 (0–19)	0.57		
	Previous admission (< 1 month)		64 (33.3)	174 (35.4)	0.42		
	Nosocomial bacteremia		157 (81.8)	399 (81.3)	0.5		
	Mechanical ventilation		33 (17.2)	27 (5.5)	< 0.001	2.3 [1.2–4.5]	0.01
Microbiologic factors							
	Active antibiotic during bacteremia		21 (10.9)	46 (9.4)	0.57		
	Incorrect empiric antibiotic		69 (35.9)	143 (29.1)	0.1		
		Incorrect empiric antibiotic by TTP < 13 h	20 (28.9)	10 (7)	< 0.001	3.8 [1.5–10]	0.006
	Carbapenem resistant strain		65 (33.9)	125 (25.5)	0.028	1.5 [1–2.3]	0.05
	Median TTP		15.1 (IQR 13.1–17.5)	16.7 (14.5–19.2)	< 0.001		
	TTP < 16 h		118 (61.5)	204 (41.5)	< 0.001	1.6 [1.1–2.4]	0.03
	PAE isolated in 2/2 vials		71 (37)	119 (24.2)	0.001		
Severity							
	Septic shock		96 (50)	63 (12.8)	< 0.001	4.8 [3.1–7.4]	< 0.001
	Persistent bacteremia		13 (7)	30 (3.2)	0.73		
Source							
	Respiratory		82 (42.7)	77 (15.7)	< 0.001	2.4 [1.5–3.8]	< 0.001
	Primary bacteremia		43 (22.4)	139 (28.3)	0.12		
	Abdominal		20 (10.4)	76 (15.4)	0.03		
	Urinary tract		27 (14.1)	146 (29.7)	< 0.001		
	Other		20 (10.4)	53 (10.8)	1		

CI, confidence interval; CKD, chronic kidney disease; IQR, inter-quartile range; OR Odds ratio; PAE, Pseudomonas aeruginosa; TTP time to positivity

incorporate it in the analysis. Although both intra- and extra-luminal catheter surfaces are colonized, the main source of bacteria in catheter-related bacteremia is the intraluminal population [32, 33]. Passing an active antibiotic through the catheter lumen exposes intra-luminal bacteria to a high antibiotic concentration, leaving the extra-luminal ones as the only source of bacteremia. Indeed, in our cohort, TTP was lengthened when the patient was receiving an active antibiotic treatment and these lengthening was more pronounced in cases with catheter-related PAE-BSI (14.6h vs. 11.4h, $p < 0.001$), and consequently this was also associated with a shortened DTP. Accordingly, the interpretation of both TTP and DTP in the setting of PAE-BSI should be made considering the concomitant active antibiotic treatment at the time of blood culture extraction. By itself breakthrough bacteremia, particularly when 2 blood cultures are positive, obligates to discard the catheter as a source of the bacteremia even when TTP is long.

A recent meta-analysis including 24 studies revealed that shorter TTP were a significant predictor of mortality in Gram-positive and Gram-negative bloodstream infections [14]. Since catheter-related BSI has a significantly lower mortality compared to other sources and it implies shorter TTP, we aimed to analyze both groups differently. In catheter-related PAE-BSI, shorter TTP was not associated with an increased mortality rate as long as catheter were promptly removed within the first 48h. Inversely, a delay of more than 48h in the catheter removal was associated with a threefold increase in mortality, and this increase was more pronounced among those with TTP < 14h (Fig. 2).

In non-catheter-related PAE-BSI, there was a significantly higher mortality when the TTP was < 16h in line with previous studies [29, 30]. As expected, we highlight that the impact of incorrect empirical antibiotic administration is more evident when the TTP is short (Fig. 3). Therefore, when the bacterial load in blood is high, every hour of delay in active antibiotic administration is critical for the patient and it should be considered when the impact of empirical therapy is evaluated.

These findings, correlating the TTP as a surrogate marker of bacterial load in blood, are applicable to all microorganisms but it is necessary to know the specific TTP of each pathogen. Also, considering that TTP below the median are highly suggestive of endovascular infection and a higher risk of mortality, a tight collaboration with microbiology laboratory is needed and continuous 24 h microbiology and infectious diseases attention to patients with bacteremia is a worthy investment.

The major drawback of our study is the retrospective nature of the design; however, this data was prospectively collected by experts on infectious diseases. Secondly, the unicentric nature of the study and the large time span for data collection (28 years) may be another source of bias linked to changes in clinical practice or changes in microbiological definitions, limiting the extrapolation of our results. Thirdly, the volume of blood cultures and the time span between drawing the blood sample and its placement into the incubator were not available, however, the TTP was consistent with the ones reported by previous authors. Furthermore, culture vials were processed with only one commercial brand, which could potentially hamper the extrapolation of TTP and DTP cut-offs to other processing systems. This study relied on catheter tip cultures for the diagnosis of catheter-related PAE-BSI, which may have introduced a bias because catheter is not always cultured or even removed in case of catheter-related bacteremia. However, we have a dedicated team to attend all episodes of bacteremia that promotes catheter removal and tip culturing. This explains the high documented rate of catheter source in our cohort (33%). Even though we assume that some catheter-related PAE-BSI episodes were not captured, and they were included in unknown (primary) bacteremia group. For the analysis of mortality and considering that catheter-related bacteremia has both characteristics, short TTP and lower mortality than other sources, we decided to remove non-neutropenic patients with unknown source of the bacteremia and a TTP < 13 h (potential catheter source) for the analysis of TTP and mortality. We acknowledge that this introduces a potential bias.

In conclusion, our study underscores the diagnostic value of TTP and its superiority in comparison to DTP in managing catheter-related PAE-BSI. Breakthrough bacteremia disregarding the TTP, or > 7 days of catheter in place, more than one positive blood culture and a TTP < 13h, are characteristics highly suggestive of catheter-related BSI. Moreover, lower TTP predict a higher mortality, especially among patients with a catheter-related PAE-BSI in whom the catheter is not removed within the first 48h and among those with other sources of the BSI, particularly when the empiric antibiotic therapy is not active.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13054-025-05292-z.

Additional file1 (DOCX 125 KB)

Author contribution

All authors have made substantial contributions. DM, SH, JMe and AS were responsible for the conception or design of the work; the acquisition, analysis, and interpretation of data; and have drafted the work and substantively revised it MB, SA were responsible for the acquisition, analysis, and interpretation of data CP, PP, PM, MB, LM, MH, CC, FG, AR, JMa, AS, IG, CG, MC, GC, MV, TA, ME, and CCas were responsible for the acquisition of data, have revised the manuscript All authors have approved the submitted version.

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Availability of data

"Data is provided within the manuscript or supplementary information files".

Declarations

Competing interest

The authors declare no conflict of interest for the purpose of the present manuscript.

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