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The Association between Time to Positivity and Staphylococcus Aureus Bacteremia in a Geriatric Population

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Abstract

Background: Time to Positivity (TTP) of blood cultures is defined as the time elapsed between the start of incubation and the automated alert signal indicating growth in the culture bottle.

This study evaluates the TTP of blood cultures in patients with *Staphylococcus aureus* Bacteremia (SAB) and assesses the relationship between TTP and mortality.

Methods: We performed a retrospective study involving adults who had SAB between May 2007 and May 2010 in a tertiary hospital. TTP was defined as the time between onset of incubation and growth detection using an automated blood culture system.

Results: A total of 167 SAB were evaluated. Patient's median age was 72 years (range, 18-95 years). The median TTP was 13.6 h (range, 3.6-95.2 h). Attributable mortality rate (27.5%) was not related to the TTP ($P=0.558$) nor to the comorbidities. Age >60 years was the only independent predictor of attributable mortality ($P<0.001$). Univariate analysis revealed a significantly shorter TTP in persistent bacteremia, endovascular source of infection, catheter-related infection and in community-acquired SAB. A TTP >11.3 h had a negative predictive value of 96.4% for endocarditis. TTP was not related to methicillin susceptibility nor resistance of *Staphylococcus aureus* ($P=0.934$).

Conclusion: In our elderly population, shorter TTP was significantly associated with a central source of infection and a persistent SAB. In addition for the first time, community-acquired SAB was associated with a shorter TTP. TTP may contribute to a better management of SAB by facilitating clinical decisions, especially in endocarditis.

Keywords: *Staphylococcus aureus*; Bacteremia; Time to positivity; Endocarditis; Community-acquired

Introduction

Time to Positivity (TTP) of blood cultures is defined as the time elapsed between the start of incubation and the automated alert signal indicating growth in the culture bottle. TTP is related to the number of micro-organisms initially present in blood and their metabolism [1]. The higher the initial bacterial inoculum, the quicker the cut-off value for detection of positivity is reached [1,2]. TTP is an indirect marker of the bacterial load and is associated with a higher morbidity and mortality [3]. Differential TTP is used for the diagnosis of catheter-related bacteremia [2,4,5-7] and TTP is used for predicting the presence of *Staphylococcus* spp. bacteria in blood culture [8,9].

Staphylococcus aureus is a major cause of bloodstream infection and is associated with significant morbidity and mortality [10]. Only a few studies have described the relationship between TTP and clinical outcome in *S. aureus* Bacteremia (SAB) [3,11-13].

Our aim was to describe the TTP in adult patients with SAB and to assess its relationship with different variables such as mortality, severity of SAB, source of infection and methicillin resistance in order to improve the management of SAB based on TTP.

Materials and Methods

Study population

This retrospective study included all adult patients admitted to Brugmann University Hospital between 15th May 2007 and 15th May 2010 who presented at least one episode of SAB. The following data were collected: demographic characteristics; acquisition of SAB

(nosocomial or community-acquired); screening of nasal carriage for methicillin-resistant *S. aureus* (MRSA); sources of bacteremia (primary, catheter-related, secondary); predisposing conditions and Charlson weighted index of comorbidity (Charlson WIC); microbiological data (antimicrobial resistance and TTP); criteria of severity (complications of bacteremia, control blood cultures, intensive care admission, department of hospitalization and length of stay); outcome (cure, relapse, death).

The Brugmann University Hospital is an 854-bed hospital in Brussels with around 27 000 admissions per year. It has 32 intensive care unit beds, geriatric unit of 132 beds.

Microbiological data

A set of blood culture was performed by inoculating 7-10 mL of blood into BACTEC/F blood culture aerobic and anaerobic bottles. All the bottles were sent immediately at room temperature to the microbiology

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laboratory and were loaded into the BACTEC 9240 system (Becton Dickinson, Cockeysville, Md). Incubation was performed until positive and for a maximum of seven days. Bottles with positive results were examined by Gram staining. In case of characteristics colonies of Gram-positive cocci on direct examination, the standard coagulase reaction was performed with human plasma and their content was subcultured in a gelose. The gelose was incubated overnight at 37°C in aerobic atmosphere. If *S. aureus* was isolated, routine antibiotic susceptibility testing was performed including methicillin susceptibility determined by two methods: the disk diffusion method using an oxacillin disk and a cefoxitin one (Neo-Sensitabs, Rosco, Taastrup, Denmark) and a dilution technique on the automate Vitek-2 (bioMérieux, Marcy l'Etoile, France). In case of discordance between both techniques, the strain was sent to the Belgian reference laboratory for *Staphylococcus* spp. for molecular detection of the *mecA* gene.

Definitions

A set of blood culture was considered positive if at least one of both bottles was positive for *S. aureus* [14]. An episode of SAB was defined as ≥ one positive blood culture. The time of the SAB episode was the time of inoculation of the first positive blood culture [14]. Time to positivity of the blood culture was defined as the time between the start of incubation and the time that the automated alert signal indicating growth in the culture bottle sounded [11,12]. In case of multiple positive blood cultures inoculated within maximum two hours, the shortest TTP was taken into account [1,3]

SAB was considered as community-acquired if it occurred within 48 h after admission and as nosocomial thereafter [14].

Source of bacteremia was determined according to the definitions of the National Surveillance Program for Hospital Infections (NSIH). SAB was considered as primary, secondary or primary related to catheter [14]. We pooled the following sources into one group named as "central source": primary, primary related to catheter and secondary endovascular (endocarditis, arterio-venous fistula, vascular graft) [10]. Infective endocarditis was defined according to the modified Duke criteria [15]. Severity of underlying diseases present before the episode of SAB was assessed according to the Charlson WIC [16].

SAB was qualified as complicated if multiple clinical sources were identified simultaneously during the bacteremia or if there was metastatic infection [14]. Persistent SAB was defined if blood culture remained positive beyond 48 h of appropriate antibiotic treatment. A prolonged hospitalization was defined as a length of stay ≥ 15 days, minimum time necessary to consider an uncomplicated SAB as optimally treated [17].

If an episode was pre-treated with an appropriate antibiotic (*in-vitro* activity against the isolated *S. aureus* strain) 72 h before inoculation, it was excluded from the analysis [18].

Cure was defined as a negative blood culture and/or absence of septic signs during seven days following the initiation of antibiotics [14]. SAB occurring more than 8 days after the end of one episode was considered as a new episode [14]. The attributable mortality was defined as death occurring with persistent bacteremia, with persistent signs of sepsis or occurring before the end of the episode of bacteremia without any other obvious cause [14].

Statistical analysis

Non-normally distributed quantitative variables were reported as median values with their range and their differences were evaluated

with the Mann-Whitney test. Qualitative variables were assessed by Chi-square test or Fisher's exact test where applicable. Logistic regression was used for multivariate analysis. Receiver Operating Characteristics (ROC) curve was used to determine the cut-off values of TTP when univariate analysis (Mann-Whitney) was significant. The positive predictive value and negative predictive value were calculated according to the prevalence of that parameter in our cohort. A P<0.05 was considered to be statistically significant.

Results

A total of 205 episodes of SAB were identified. Among these, 18 were excluded from the study because of incomplete or missing data and 20 episodes were excluded because they had received previous antibiotic treatment. A total of 167 episodes in 154 patients were reviewed for TTP analysis. Among ten patients with multiple episodes, one patient had four episodes, one presented three episodes and eight had two episodes.

Characteristics of the study population

The median age was 72 years (18-95 years) and 100 episodes (59.9%) occurred in men. Among the 167 episodes of SAB, 112 (67.1%)

	N	(%)		N	(%)
Patient groups			Cardiac echography	98	(58.7)
Geriatric ≥ 75 years	76	(45.5)			
Non Geriatric	91	(54.5)	Endocarditis	21	(12.6)
Emergency	22	(13.2)	Native	18	(10.8)
Intensive care unit	22	(13.2)	Biological	2	(1.2)
Internal medicine	21	(12.8)	Mechanical	1	(0.6)
Surgery	14	(8.4)			
Dialysis	12	(7.2)	Primary Source	22	(13.2)
Charlson score			Catheter-related Source	36	(21.6)
0-5	56	(33.5)	Short term central venous catheter	18	(10.8)
> 5-10	83	(49.7)	Long term central venous catheter	16	(9.6)
> 10-15	27	(16.2)	Others	2	(1.2)
> 15	1	(0.6)			
			Secondary Source	109	(65.3)
Comorbidities			Respiratory	26	(15.6)
Cardiac insufficiency	92	(55.1)	Endovascular	25	(15.0)
Diabetes	50	(29.9)	Endocarditis	18	(10.8)
COPB	50	(29.9)	Cutaneous	24	(14.4)
Cirrosis	6	(3.6)	Osteoarticular	13	(7.8)
Dialysis	26	(15.6)	Urinary	12	(7.2)
Neoplasia	40	(24.0)	Others	9	(5.4)
Immunodeficiency	30	(18.0)			
Prothesis	43	(25.7)	Outcome		
Obesity	20	(12.0)	Cure	91	(54.5)
Long term catheter	20	(12.0)	Attributable mortality	46	(27.5)
Renal insufficiency	26	(15.6)	Non-attributable mortality	13	(7.8)
Ethylism	26	(15.6)	Relapse	13	(7.8)
Drug user	8	(4.8)	Unknown	4	(2.4)
Peripheral arterial disease	18	(10.8)			
Stroke	67	(40.1)			
Others	94	(56.3)			

Table 1: Characteristics among 167 episodes of *S. aureus* bacteremia.

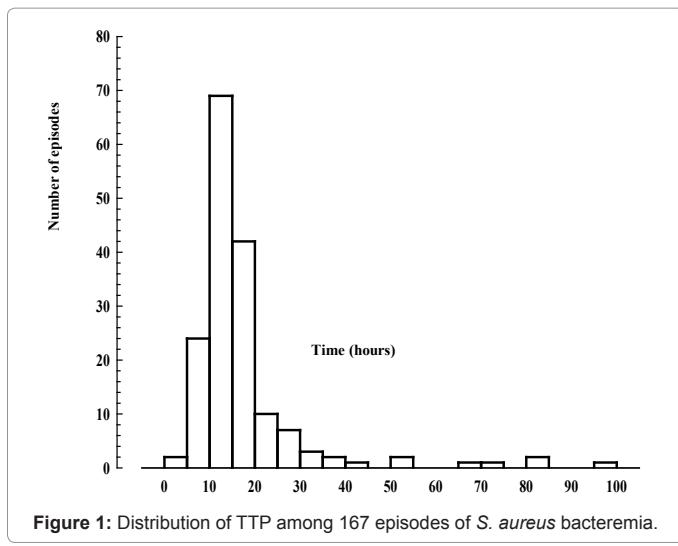


Figure 1: Distribution of TTP among 167 episodes of *S. aureus* bacteremia.

were caused by methicillin-sensible *S. aureus* (MSSA) and 72 (43.1%) were classified as community-acquired. Screening of nasal carriage for MRSA was performed in 148 (88.6%) episodes and in 46 (31.1%) it was positive. Control blood cultures were performed in 34 (17.9%) of the episodes 24 h after the beginning of an adequate antibiotic and in another 32 (10.2%) after 48 h of adequate treatment. The overall median length of hospitalization was 30 days (0-237 days). The attributable mortality rate was 27.5% with a median age of 82 years at the time of death (31-94 years). Characteristics of the 154 patients with SAB are listed in table 1.

Time to positivity: Univariate analysis and predictive values

The median TTP was 13.6 h (3.6 to 95.2 h). Distribution of TTP is represented in figure 1.

There was no significant relationship between TTP and attributable mortality ($P=0.558$). Age >60 years did not influence the TTP ($P=0.256$) but influenced the attributable mortality independently (OR: 8.93; 95% CI: 2.62-30.3; $P<0.001$). The logistic regression represented in table 2 showed that age was the only independent factor that influenced the attributable mortality ($P<0.001$). Attributable mortality was not related to any of the comorbidities studied.

Univariate analysis represented in table 3 revealed an association between a TTP ≤ 13.9 h and community-acquired SAB ($P=0.032$), a TTP ≤ 12.4 h and persistent bacteremia ($P=0.010$), a TTP ≤ 12.7 h and an endovascular source of infection ($P=0.037$) and a TTP ≤ 13.3 h and an intravascular catheter-related infection ($P=0.019$). TTP >11.3 h had a negative predictive value of 96.4% for endocarditis. The cut-off values of TTP are listed in table 4. Influence of different comorbidities on TTP was evaluated. Chronic Obstructive Pulmonary Disease (COPD), drug user and stroke significantly increased the TTP.

There was no relation between TTP and methicillin resistance: the median TTP was 13.55 h in MRSA bacteremias compared to 13.45 h in MSSA bacteremias ($P=0.934$).

Discussion

In 1998, Blot et al. described that TTP of blood culture was related to the number of micro-organisms initially present in blood and their metabolism. They concluded that the higher the initial bacterial inoculum, the quicker the cut-off value for detection of positivity

was reached [1]. Hence differential TTP was used in the diagnosis of catheter-related bacteremia [2,7].

Further, studies showed that a TTP ≤ 14 h was correlated to attributable mortality in bacteremia varying from 11.9% to 18% [3,11,12]. In our study, attributable mortality (27.5%) was higher than those reported in the literature but there was no significant association between TTP and attributable mortality. Two hypotheses could explain these results. First, our elderly population presented an important rate of comorbidities (Charlson score ≥ 5 in 74% patients) that could have influenced mortality in SAB. However, we did not find a relation between attributable mortality and comorbidities as described in the literature [11,13,16]. The second hypothesis is the higher median age (72 years) in our cohort and the even higher age (82 years) among the deceased patients. In other studies, the population considered was heterogeneous including pediatric patients with a median age inferior to 62 years [3,11,12]. In fact, the only independent factor in our population that influenced the attributable mortality was age. Age has been described as correlated to attributable mortality in elderly patients with SAB [19,20]. It is possible that the mortality rate in our cohort was not only attributable to SAB but rather to age which might have annihilated the influence of TTP on mortality.

To our knowledge, our study is the first one to describe that a community-acquired bacteremia influences TTP with a cut-off TTP ≤ 13.9 h. It has been reported that community-acquired SAB is more severe and complicated because the diagnosis is delayed due to the absence of major symptoms [21-23]. We hypothesize that community-dwelling patient, presenting to the emergency unit after a delay of three to four days of fever, when the bacteremia is already established with a large inoculum explaining a shorter TTP. In contrast, nosocomial bacteremia is often secondary or related to catheter infection and therefore more easily recognized [21]. Hospitalized patients are managed more promptly and this implies a smaller inoculum and hence a longer TTP.

Some comorbidities increased TTP (COPD, drug user and stroke). The reasons are not clear and warrant additional studies addressing specifically that question.

We observed also a relationship between TTP and one criteria of severity. In our study, 9% of the patients had persistent bacteremia, which was correlated to a TTP ≤ 12.4 h. These results are similar to those reported by Khatib et al. [3], but their rate of persistent bacteremia was higher (32.1%), probably because they used a different definition of persistent bacteremia.

As reported in the literature, we also found a relation between TTP and different sources of bacteremia such as endocarditis, endovascular, central and catheter-related infection [9,12]. Our cut-off values of TTP were in majority similar to those previously reported [3,11]. In our hospital, the knowledge of the negative predictive value in endocarditis and catheter-related bacteremia has a clinical impact on the medical approach of these situations.

Finally, TTP tended to be shorter, but not significantly in MSSA bacteremia when compared to MRSA bacteremia. Martinez et al. [9] described that median TTP in a MSSA bacteremia was significantly shorter than in MRSA bacteremia. In contrast, Ruimy et al. [8] reported a median TTP in MSSA longer than in MRSA bacteremia but it was not significant and without excluding pre-treated bacteremia. With these conflicting reports, one would think that TTP in MSSA and MRSA bacteremia is influenced by other factors than micro-organisms themselves such as the origin of bacteremia and prior antibiotic therapy

Variable	Unadjusted					Adjusted					
	Total		OR	(95% CI)		p	Total		OR	(95% CI)	
	N	(%)					N	(%)			
Age > 60 years	48	(29.4)	8.93	(2.62-30.3)		<0.001	115	(70.6)	9.09	(2.53-33.3)	<0.001
Male	66	(40.5)	1.34	(0.67-2.68)		0.400	97	(59.5)	0.91	(0.43-1.95)	0.810
Charlson score ≥ 5	44	(27.0)	1.48	(0.66-3.30)		0.343	119	(73.0)	0.94	(0.38-2.35)	0.893
MRSA	109	(66.9)	1.45	(0.71-3.78)		0.307	54	(33.1)	1.095	(0.52-2.32)	0.813
Community-acquired	94	(57.7)	1.06	(0.53-2.12)		0.868	69	(42.3)	0.84	(0.397-1.78)	0.649

Table 2: Characteristics among 167 episodes of *S. aureus* bacteraemia.

Variable	Yes				No				P	
	Total		Median TTP		Total		Median TTP			
	N	(%)	Hours	(range)	N	(%)	Hours	(range)		
Characteristics										
Age > 60 years	117	(71.3)	13.3	(3.6-95.2)	50	(29.9)	14.5	(7.3-65.1)	0.256	
Male	100	(59.9)	14.1	(3.6-95.2)	67	(40.1)	12.6	(4.4-69.9)	0.074	
Charlson score ≥5	123	(73.7)	13.6	(3.6-95.2)	44	(26.3)	13.2	(7.9-52.6)	0.740	
MRSA	55	(32.9)	13.5	(7.9-81.5)	112	(67.1)	13.5	(3.6-95.2)	0.934	
Community-acquired	72	(43.1)	12.4	(7.2-69.9)	95	(56.9)	12.4	(7.2-69.9)	0.032	
Attributable mortality	46	(27.5)	13.2	(3.6-82.0)	117	(70.1)	13.6	(4.4-95.2)	0.558	
Comorbidities										
Cardiac insufficiency	92	(55.1)	13.2	(3.6-74.8)	75	(44.9)	14.4	(7.2-95.2)	0.053	
Peripheral arterial disease	18	(10.8)	13.2	(4.4-28.0)	149	(89.2)	13.6	(3.6-95.2)	0.541	
Diabetes	50	(29.9)	12.4	(7.9-65.2)	117	(70.1)	13.8	(3.6-95.2)	0.156	
COPD	50	(29.9)	14.1	(3.6-95.2)	117	(70.1)	12.8	(4.4-81.5)	0.040	
Prothesis	43	(25.7)	15.4	(3.6-81.9)	124	(74.3)	13.2	(7.0-95.2)	0.222	
Stroke	67	(40.1)	15.4	(8.2-81.9)	100	(59.9)	12.9	(3.6-95.2)	0.016	
Drug user	8	(4.9)	21.7	(10.2-38.4)	159	(95.2)	13.3	(3.6-95.2)	0.018	
Criteria of severity										
Complicated bacteraemia	32	(19.2)	12.4	(7.2-38.4)	135	(80.8)	13.8	(3.6-95.2)	0.088	
Persistent bacteraemia	15	(9.0)	11.6	(4.4-18.5)	152	(91.0)	13.8	(3.6-95.2)	0.010	
Intensive care unit stay	51	(30.5)	13.0	(3.6-52.6)	116	(69.5)	13.6	(7.0-95.2)	0.074	
Prolonged hospitalization	103	(61.7)	14.0	(3.6-95.2)	64	(38.3)	12.7	(7.2-69.9)	0.478	
Source of bacteraemia										
Primary (a)	22	(13.2)	13.0	(4.4-23.2)	145	(86.8)	13.7	(4.4-23.2)	0.435	
Primary related to catheter (b)	36	(21.6)	11.6	(3.6-95.2)	131	(78.4)	13.9	(4.4-81.9)	0.019	
Secondary endovascular (c)	25	(15.0)	12.4	(7.2-32.7)	142	(85.0)	13.8	(3.6-95.2)	0.037	
Endocarditis	18	(10.8)	11.0	(7.2-32.7)	149	(89.2)	13.8	(3.6-95.2)	0.006	
Central (a+b+c)	83	(49.7)	12.2	(3.6-95.2)	84	(50.3)	15.5	(7.0-81.9)	<0.001	

Table 3: Univariate analysis of different variables and TTP among 167 episodes of *S. aureus* bacteraemia.

Variable	TTP cut-off (hours)	AUC (95%CI)		Sensibility (%)	Specificity (%)	PPV (%)	NPV (%)
Community-acquired bacteraemia	13.9	0.60	(± 0.04)	66.7	56.8	38.4	80.9
Persistent bacteraemia	12.4	0.70	(± 0.07)	66.7	61.8	10.0	96.7
Primary source related to catheter	13.3	0.63	(± 0.05)	66.7	58.3	21.1	91.3
Secondary endovascular source	12.7	0.63	(± 0.06)	60.0	57.7	12.1	93.5
Endocarditis	11.3	0.70	(± 0.06)	61.1	73.8	14.2	96.4
Central source	15.4	0.68	(± 0.04)	53.6	73.5	47.6	77.9

Table 4: Sensibility, Specificity and Predictives Values of TTP.

[23]. On the other side, the genetic diversity of MRSA between countries with dominant MRSA spa types forming distinctive geographical clusters could explain the fact that in our study, methicillin resistance was not associated with a short TTP. MRSA strains in Belgium may be less virulent as compared to other clusters in the literature [24,25].

Our study had several limitations. Firstly it was limited by the retrospective nature of our analysis, the small size of our cohort and the lack of complete clinical data during the SAB except admission into intensive care unit; secondly, the volume of blood drawn in the bottles

remained uncontrolled and may have influenced the TTP. Finally, all patients had not systematic blood culture control after introduction of adequate antibiotic therapy and therefore the number of persistent bacteraemia might have been under-estimated.

In conclusion, this study suggests that attention should be paid to a short TTP because it is associated with a persistent bacteraemia, an endovascular source of infection, a catheter-related infection and very interestingly with a community-acquired SAB. Another important information concerns the negative predictive value of 96.4% for a TTP

>11.3 h in endocarditis. In our population, the high age of the patients and their comorbidities influence the TTP and modify its classically reported relation with attributable mortality. TTP, already useful for catheter-related bloodstream infection diagnosis is a relatively simple and fairly reliable method that can optimize the management and treatment of SAB.

Conflicts of Interest Statement

The authors disclose any financial and personal relationships with other people or organizations that could inappropriately influence their work.

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