Time to Blood Culture Positivity: An Independent Predictor of Mortality in *Streptococcus Pyogenes* Bacteremia

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Background. *Streptococcus pyogenes* bacteremia is a severe condition with high mortality. Time to blood culture positivity (TTP) is known to predict the outcome in bacteremia with other pathogens. This study aimed to determine the association between TTP and outcome in *S pyogenes* bacteremia.

Methods. This retrospective observational cohort study comprised adults with *S pyogenes* bacteremia, identified through the laboratory database between 2015 and 2018, in the Region of Skåne, Sweden. Correlations between TTP and outcomes were investigated. Primary outcome was death within 30 days, and secondary outcomes were presence of sepsis or disease deterioration within the first 48 hours.

Results. A total of 347 episodes of *S pyogenes* bacteremia were identified, of which 61 were excluded, resulting in 286 included episodes. Median TTP was 10.4 (interquartile range, 8.4–11.4) hours. Thirty-day mortality was 10%. Median TTP was shorter in patients who died within 30 days compared to survivors (8.6 vs 10.4 hours; $P < .001$). In a multivariable logistic regression, shorter TTP was associated with 30-day mortality when adjusting for age, Charlson Comorbidity Index, and focus of infection (odds ratio, 3.7 [95% confidence interval, 1.2–11.3]; $P = .02$). There was no statistically significant difference in TTP between patients with sepsis within 48 hours and those who did not have sepsis. Additionally, there was no statistically significant difference in TTP between patients with disease deterioration compared to those who did not deteriorate.

Conclusions. Knowledge on TTP might be a tool to determine the prognosis of a given patient with *S pyogenes* bacteremia.

Keywords. outcome; *Streptococcus pyogenes*; time to positivity.

Streptococcus pyogenes can cause mild infections such as tonsillitis, but also severe skin and soft tissue infections, necrotizing fasciitis, and septic shock. Underlying conditions such as diabetes mellitus, peripheral vascular disease, >60 years of age, and skin lesions have been associated to *S pyogenes* bacteremia [1]. However, in most cases with *S pyogenes* bacteremia, no focus of infection is established. Focus of infection to the lungs, high age, and leukopenia have been associated with fatal outcome [2], as has necrotizing fasciitis [3].

Time to positivity (TTP) in blood cultures indicates the time from the beginning of culture incubation to the detection of bacterial growth by the automated system. Shorter TTP may reflect a higher bacterial concentration in blood, which in turn may be associated with severe infection. TTP has been associated with higher risk for intravascular infections [4–6] and has been claimed as a predictive factor for poor outcome in infections caused by major pathogens such as *Staphylococcus aureus* and *Streptococcus pneumoniae* [4, 7, 8].

Streptococcus pyogenes expresses several potentially important virulence factors, such as the M protein. The cell surface M protein is encoded by the *emm* gene and there are >100 different *S pyogenes emm* types. The distribution of *emm* types varies with different geographical settings and time intervals [9]. Correlation with disease severity and certain *emm* types are not fully established, and both common and rare *emm* types have been linked to site of acquisition and higher risk of mortality [10, 11].

The objective of this study was to investigate the possible association between TTP and outcome, determined as mortality, sepsis, or disease deterioration, in patients with *S pyogenes* bacteremia.

MATERIALS AND METHODS

This is a retrospective cohort study comprising all cases of *S pyogenes* bacteremia occurring from 2015 to 2018 in

the Region of Skåne, Sweden, that were identified by the Department of Clinical Microbiology, Region Skåne, Lund, Sweden. The Region of Skåne has 1.4 million inhabitants and a single bacteriology laboratory. The region has 5 hospitals that are equipped with blood culture incubators where blood culture bottles are introduced around the clock. In addition, there are 5 smaller hospitals that transport blood culture bottles to a hospital with an incubator before incubation starts. The BACTEC FX blood culture system (Becton Dickinson, Franklin Lakes, New Jersey) is used throughout the region. Species determination of the isolates was performed using Microflex matrix-assisted laser desorption/ionization (MALDI)–time of flight mass spectrometry (Bruker, Bremen, Germany) with the direct transfer protocol and the software FlexControl and MALDI Biotyper (MBT) Compass 4.1 with reference database MBT Compass Library DB-7854 (Bruker). *Emm* typing based on the *emm* gene was performed according to the Centers for Disease Control and Prevention (https://www.cdc.gov/streplab/).

The inclusion criterion was an episode with a clinical situation where a positive blood culture bottle with *S pyogenes* was obtained. When multiple separate blood culture bottles were obtained from the same patient, the shortest TTP was applied for further statistical analysis. Exclusion criteria were <18 years of age, lack of access to medical records, or blood cultures obtained from hospitals lacking blood culture incubators. Moreover, if recurrent episodes of bacteremia occurred, only the last episode was included. The rationale for this was that recurrence refuted death as a consequence of the first episode. Episodes with only polymicrobial growth in blood culture bottles were also excluded, since the contribution of each species to TTP could not be determined. Medical records of included patients with *S pyogenes* bacteremia were reviewed according to a prespecified protocol.

Mode of acquisition was recognized as community acquired, healthcare associated, or nosocomial (>48 hours of hospitalization after the start of blood culture). Healthcare-related infection was defined as a positive blood culture in the initial 48 hours of hospitalization, if the patient had been in contact with healthcare within 30 days prior to the episode, as an outpatient, or if the patient had been discharged from the hospital within 90 days prior to the episode [12]. Demographic factors such as age, gender, and antibiotic treatment were collected. Comorbidities were graded according to Charlson Comorbidity Index (CCI) [13].

Primary outcome was defined as 30-day mortality. Secondary outcomes were defined as presence of sepsis or of disease deterioration that comprised development from nonsepsis to sepsis/septic shock or sepsis to septic shock. Focus of infection was defined as fulfillment of at least 2 of the following criteria: (1) signs or symptoms of an infection, (2) isolation of *S pyogenes* at the site of the infection, and (3) imaging compatible with focal infection. Erysipelas was an exception where typical clinical findings were regarded sufficient to verify the focus. Data on onset of symptoms, length of stay, length of antibiotic treatment, intravenous immunoglobulin therapy, and surgery were collected.

The definition of sepsis and septic shock was according to the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) [14] and evaluated using the modified Sequential Organ Failure Assessment (SOFA) score [15]. Respiratory function was assured using the Severinghaus equation in patients with oxygen treatment [16]. The most deviating clinical vital parameters, irrespective of interventions, for every patient were collected at 2 different time intervals after admission or, for nosocomial infections, after blood culturing. The 2 time intervals were used to study possible disease deterioration within the first 48 hours after blood culturing. The early time interval (0–6 hours) was meant to correspond to an early phase where blood culture results were not known, and the later interval (6–48 hours) served as a comparator.

Statistical Analysis

For continuous variables, values are given as median with interquartile range (IQR). Simple logistic regression was applied for univariate analysis. Differences in quantitative variables were performed using Mann-Whitney *U* test. Multivariate analysis with logistic regression was undertaken. Correlations between ordinal variables were investigated utilizing Spearman rank correlation coefficient. A *P* value < 0.05 was regarded as statistically significant. Analyses were performed using R Statistical Software, version 3 (R Foundation for Statistical Computing; https://www.r-project.org/) and GraphPad Prism, version 9 software (GraphPad Software).

RESULTS

Description of the Study Cohort

A total of 347 episodes of *S pyogenes* bacteremia were reported in 2015–2018. Thirty-six episodes were excluded, due to age <18 years (n = 14), inaccessible medical records (n = 11), recurrent infection (n = 8), and polymicrobial growth in the same blood culture as *S pyogenes* (n = 3) (Figure 1). Additionally, episodes from hospitals lacking blood culture incubators (n = 25) were excluded as the time before the start of incubation was deemed likely to affect the TTP. The final cohort thus comprised 286 episodes of *S pyogenes* bacteremia.

Median age was 71 (IQR, 57–82) years, and 144 patients were male (50%). Most of the patients had sepsis within 48 hours of hospital stay (68%). Table 1 summarizes clinical characteristics of the episodes. The most common *emm* types were *emm* 1 (n = 104), *emm* 89 (n = 40), *emm* 28 (n = 30), and *emm* 3 (n = 21) (Table 2).
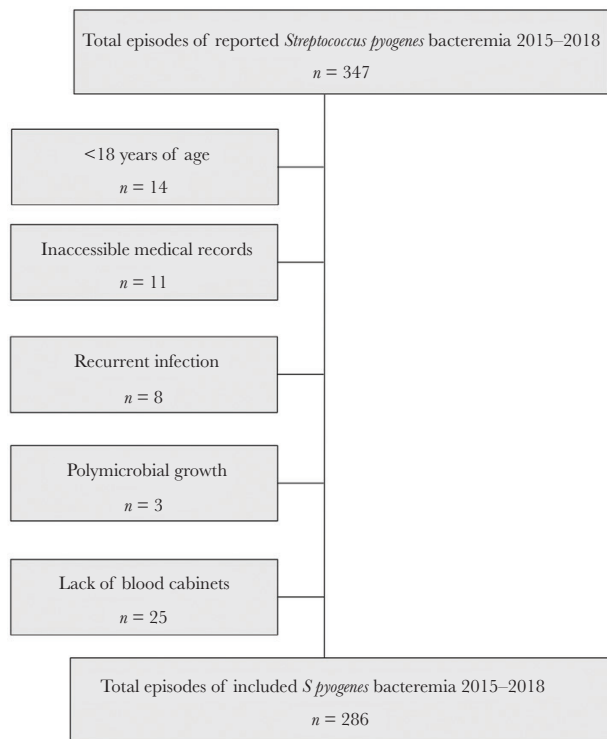
Figure 1. Flowchart of included and excluded cases of *Streptococcus pyogenes* bacteremia. Polymicrobial episodes had growth of either *Staphylococcus aureus* (*n* = 2) or *Bacillus* species (*n* = 1) in the same blood culture bottle as *S pyogenes*.

Table 1. Clinical Characteristics of Episodes of *Streptococcus pyogenes* Bacteremia (*N* = 286)

Characteristic	No. (%)
Age, y, median (IQR)	71 (57–82)
Sex, male	144 (50)
CCI, median (IQR)[a]	1 (0–2)
Site of acquisition	
Community acquired	148 (52)
Healthcare related	131 (46)
Nosocomial	7 (2)
Focus of infection	
Skin and soft tissue[b]	152 (53)
Skeletal and joint	8 (3)
Upper respiratory tract	12 (4)
Lower respiratory tract	33 (12)
Endometritis	12 (4)
Unknown	56 (20)
Other[c]	4 (1)
>1 focus	9 (3)
Onset of symptoms to hospitalization, d, median (IQR)	2 (1–3)
Antibiotic treatment[d]	
Length of treatment (intravenous), d, median (IQR)	7 (5–11)
Length of treatment (oral), d, median (IQR)	7 (3–10)
Length of treatment (total), d, median (IQR)[d]	14 (11–19)
Intravenous immunoglobulin therapy	23 (8)
Surgery	64 (22)
Length of stay, d, median (IQR) d	10 (6–17)
TTP, h, median (IQR)	10.4 (8.4–11.4)
Outcome	
Mortality, 30 d	28 (10)
Days to death, median (IQR)	4 (2–13)
Sepsis (0–48 h)	195 (68)
Septic shock (0–48 h)	59 (21)
Disease deterioration (0–6 to 6–48 h)	60 (21)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: CCI, Charlson Comorbidity Index; IQR, interquartile range; TTP, time to positivity.

[a]CCI was calculated, of which age did not give any point.

[b]Twenty-five cases were necrotizing fasciitis.

[c]Other focus of infection encompassed urinary tract infection, gastrointestinal infection, and pericarditis.

[d]Both survivors and nonsurvivors were included in length of stay and treatment. Data were missing in patients on length of antibiotic treatment and length of stay (n = 3).

Outcomes

Primary Outcome

Twenty-eight patients (10%) died within 30 days of admission to the hospital. Median TTP was significantly shorter in patients who died within 30 days compared to surviving patients (8.6 [5.3–10.6, IQR] hours vs 10.4 [8.6–11.5, IQR] hours; *P* = .0002; Figure 2). Thirty-day mortality was set as outcome and TTP was classified into 3 categories, as were age and CCI, in order to obtain groups of similar sizes. Univariate analysis identified short TTP (<9 hours), high age (>78 years), CCI, and focus of infection to the lungs as significantly associated with 30-day mortality. Short TTP was still correlated to 30-day mortality after adjustments for age, CCI, and focus of infection in a multivariate logistic regression analysis (odds ratio, 3.7 [95% confidence interval, 1.2–11.3]; *P* = .02) (Table 2). There were 14 patients with very low TTP (1.8–4.9 hours), and in this group the 30-day mortality was 43%.

Secondary Outcome.

Table 3 summarizes the secondary outcomes. There was no statistically significant difference in TTP between patients with sepsis compared to patients who never developed this condition (*P* = .06). Additionally, when comparing TTP between patients who deteriorated to sepsis or septic shock within 48 hours from admission and those who did not, there was no statistically significant difference (*P* = .8).

SOFA scores at 0–6 hours and 6–48 hours after admission were plotted against TTP. There was a negative correlation between TTP and SOFA scores at both time intervals, suggesting that short TTP correlated with increased SOFA score (Spearman coefficient –0.1), but this was not significant (*P* = .07 and *P* = .06, respectively; Supplementary Figure 1). No associations with the primary or secondary outcomes and *emm* types were observed (Supplementary Table 1).

DISCUSSION

This is to date the largest study on TTP and correlation to outcome in patients with *S pyogenes* bacteremia. We show that short TTP correlates with 30-day mortality in patients with *S*

Table 2. Thirty-Day Mortality and Correlations to Clinical Characteristics

Characteristic	30-Day Mortality, No. (n = 28)	Survivor, No. (n = 258)	OR (95% CI)	P Value	Adjusted OR (95% CI)	P Value
TTP, h						
11.0–29.1	5	96	Ref		Ref	
9.0–10.9	6	86	1.3 (.4–4.5)	.6	1.4 (.4–5.0)	.6
1.8–8.9	17	76	4.3 (1.5–12.2)	.006	3.7 (1.2–11.3)	.02
Gender						
Female	14	128	Ref		…	
Male	14	130	1.0 (.5–2.1)	1.0	…	
Age, y						
18–64	4	93	Ref		Ref	
65–78	5	90	1.3 (.3–5.0)	.7	0.7 (.2–3.2)	.7
79–98	19	75	5.9 (1.9–18.0)	.002	3.1 (.8–11.2)	.1
CCI						
0	5	137	Ref		Ref	
1–2	17	85	5.5 (1.9–15.4)	.001	3.1 (.9–10.2)	.06
≥3	6	36	4.6 (1.3–15.8)	.02	2.7 (.7–11.1)	.2
Focus of infection						
Skin and soft tissue	12	140	Ref		Ref	
Skeletal and joint	1	7	1.7 (.2–15.0)	.6	2.5 (.3–25.1)	.4
Upper respiratory tract	1	11	1.1 (.1–8.9)	1.0	1.9 (.2–18.8)	.6
Lower respiratory tract	7	26	3.1 (1.1–8.7)	.03	3.1 (1.1–9.5)	.05
Endometritis	0	12	2.8 (0–∞)	1.0	4.0 (0–∞)	1.0
Other	1	3	3.9 (.4–40.3)	.3	2.4 (.2–31.8)	.5
Unknown	6	50	1.4 (.5–3.9)	.5	1.4 (.5–4.3)	.6
>1 focus	0	9	2.8 (0–∞)	1.0	8.5 (0–∞)	1.0
emm type						
1	9	95	Ref		…	
89	3	37	0.9 (.2–3.3)	.8	…	
28	2	28	0.8 (.2–3.7)	.7	…	
3	2	19	1.1 (.2–5.6)	.3	…	
4	3	16	2.0 (.5–8.1)	.3	…	
12	1	12	0.9 (.1–7.6)	.9	…	
Other	8	51	1.7 (.6–4.6)	.3	…	

Univariate test of significance was performed with simple logistic regression. Multivariable testing was performed using a binary multivariable logistic regression with 30-day mortality as outcome, with the following variables: TTP, age, CCI, and focus of infection.

Abbreviations: CCI, Charlson Comorbidity Index; CI, confidence interval; OR, odds ratio; TTP, time to positivity.

pyogenes bacteremia. Similar findings have been observed with TTP and other Gram-positive bacteria, suggesting that TTP may be an important prognostic factor in patients with bacteremia. However, in a recent study published by Hamilton et al, TTP correlated with mortality rate only for *Candida* and β-hemolytic streptococci and not for other major pathogens [17]. In that study, β-hemolytic streptococci were divided into groups based on the Lancefield group antigen, which does not always correlate with the species. In future studies it would be interesting to investigate TTP and outcome in cases of bacteremia with other β-hemolytic streptococci such as *Streptococcus dysgalactiae* and *Streptococcus agalactiae*.

Information on TTP, in addition to positive findings of β-hemolytic streptococci from blood cultures, may be an important tool when it comes to prediction of prognosis. Our study confirms this, even when adjustments have been made to age, comorbidities, and focus of infection. However, the cohort

was too small to make any other adjustments for other factors. Furthermore, we did not detect any significant correlation of TTP and disease deterioration. For disease deterioration, we only measured parameters according to Sepsis-3 criteria at 2 different time intervals (0–6 hours and 6–48 hours within hospital stay). Patients who developed a more severe disease after this time interval may therefore have been missed.

Emm types have been thought to be important prognostic factors in *S pyogenes* bacteremia; however, we did not detect such correlations to either mortality, sepsis, or disease deterioration. Focus of infection to the lower respiratory tract has previously been associated with fatal outcomes in patients with *S pyogenes* bacteremia. In our study there were 33 patients (12%) with focus to the lungs, of whom 7 died within 30 days of admission. In the univariate analysis, focus of infection to the lungs was associated with 30-day mortality, and there was a borderline significant trend in the multivariable analysis. This is
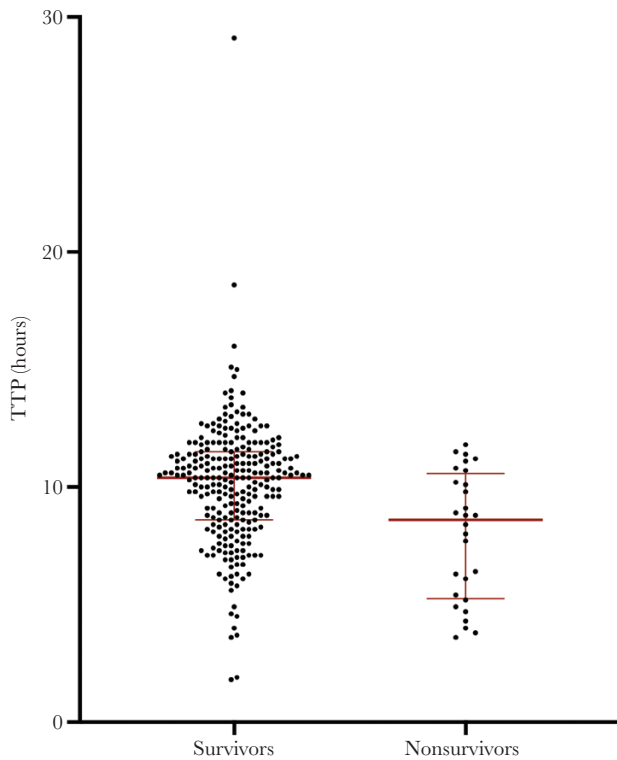
Figure 2. Comparison of time to positivity (TTP) between patients who died within 30 days and survivors. Median TTP was statistically significantly lower in patients who died within 30 days compared to survivors (8.6 [5.3–10.6, IQR] hours and 10.4 [8.6–11.5, IQR] hours, respectively; *P* = .0002, Mann-Whitney *U* test).

Table 3. Secondary Outcomes

Outcome	TTP, h, Median (IQR)	*P* Value
Sepsis[a]		.06
Yes (n = 195)	10.1 (8.0–11.4)	
No (n = 91)	10.6 (9.6–11.3)	
Disease deterioration[b] (0–6 to 6–48 h)		.8
Yes (n = 60)	10.5 (8.2–11.5)	
No (n = 226)	10.3 (8.6–11.4)	

Abbreviations: IQR, interquartile range; TTP, time to positivity.

[a]Sepsis was defined as sepsis or septic shock any time within 48 hours from admission.

[b]Disease deterioration between the 2 time intervals included transition from no sepsis to sepsis and from sepsis to septic shock.

in line with previous observation that lung focus may be associated with worse prognosis in *S pyogenes* bacteremia [18].

Invasive infections with *S pyogenes* have a substantial mortality ranging from 8% to 23% within 30 days of infection [17, 19]. In our cohort, the mortality was only 10%, although most of the patients developed sepsis during hospital stay. We do not know the reason for this, but a contributing factor may be, in our setting, that blood cultures are commonly taken also for relatively benign conditions such as erysipelas. This could possibly result in a higher number of patients diagnosed with bacteremia despite having a nonfatal infection.

This study has several limitations, mainly due to its retrospective design. Information on time between blood collection and start of incubation of blood culture bottle in culture incubator was not available, and the volume of blood cultured was unknown. Delay of loading a bottle can be a major confounder since it can reduce TTP as *S pyogenes* starts to divide at room temperature. We tried to minimize this problem by excluding cases with *S pyogenes* bacteremia from hospitals lacking blood culture incubators. TTP was much shorter in the excluded blood cultures obtained from hospitals lacking blood culture incubators (Supplementary Figure 2). Still, we cannot adjust for exact time points when the cultures were taken and the bottles were put into the incubators. The results from this study were from

a single-region cohort study with a single laboratory, making extrapolations difficult. For example, Hamilton et al [17] found a median TTP of 17.1 hours in bacteremia with β-hemolytic streptococci compared to the 10.4 hours in our study. The reason for this difference is unknown but could be due to different blood culture systems, different TTP of different groups or species of β-hemolytic streptococci, or logistics. We did not detect any cases of infective endocarditis (IE) due to *S pyogenes* in our cohort, whereas a recent publication by Chamat-Hedemand et al reported a prevalence of 1.9% of IE in cases of *S pyogenes* bacteremia [20]. However, as a large proportion of patients did not undergo echocardiography, we cannot exclude that some cases of IE may have been missed. One major strength, though, is the fact that the study is based on a large population-based cohort.

In summary, TTP is an independent prognostic factor for mortality in patients with *S pyogenes* bacteremia. Knowledge on TTP might provide the clinician with an additional tool to determine the prognosis of a given patient with *S pyogenes* bacteremia.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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