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A mathematical model to estimate the probability of blood cultures positive for pyogenic streptococci

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SUMMARY

Aims: The aim of this study was to assess the possible use of time to positivity (TTP) of blood cultures (BCs) collected at the Emergency Department (ED) to estimate the probability of pyogenic streptococci versus other Gram positive cocci in pairs and chains, such as *Streptococcus pneumoniae*, other viridans group streptococci or enterococci.
Methods: All patients 18 years of age or older evaluated at the ED from whom BCs were collected and were positive for Gram positive cocci in pairs and chains at the microscopic examination, were included in the study. The BCs included were collected by venipuncture, were mono-microbial and were the first bottles that flagged positive in each set. Complete blood count requested simultaneously with BCs along with medical history taken by the ED physician were also evaluated.
Results: In our case series, all BCs positive for Gram positive cocci in pairs or chains at microscopic examination with a TTP ≤6.3 hours were consistent with a pyogenic streptococcus (100% specificity; 95% CI: 92.7-100). Consequently, a TTP ≤6.3 hours has a 100% positive predictive value (95% CI: 30.9-100). Conversely, no pyogenic streptococci were recovered from positive BCs with a TTP >12.6 hours. Therefore, as screening test, it has 100% sensitivity (95% CI: 77-100) and 100% negative predictive value (95% CI: 83.4-100). The binomial logistic regression model showed how as TTP increases, in BCs positive for Gram positive cocci in pairs and chains at the microscopic examination, the probability of a positive result for pyogenic streptococci decreases (odds ratio: 0.548; 95% confidence interval: 0.387-0.775; P=0.001).
Conclusions: The results of this study are an adjunctive tool to clinical aspects and fast microbiology laboratory tests to help assessing the likelihood of a positive blood culture for pyogenic streptococci.

Keywords: Blood Cultures, Pyogenic streptococci, time to positivity, microbiology.

INTRODUCTION

Sepsis is a life-threatening condition associated with high mortality rate and the gold standard for etiologic diagnosis is blood culture (BC) [1, 2]. Apart for any other possible diagnostic technique, every positive BC is evaluated examining a Gram-stained smear of the broth followed by a report describing morphology and Gram stain reaction, that may lead to change the antibiotic empirical treatment [3]. Indeed, a patient with a BC positive for Gram negative rods will be treated with an antimicrobial therapy different from one positive for Gram positive cocci [4]. Unfortunately, pyogenic streptococci (*Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae* subsp. *equisimilis* and *Streptococcus dysgalactiae* subsp. *dysgalactiae*) cannot

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be reliably distinguished from viridans group streptococci (including *Streptococcus pneumoniae*) and enterococci, since no unique morphological feature exists [5, 6]. Nevertheless, from a clinical standpoint it would be of help to presumptively differentiate pyogenic streptococci from other Gram positive cocci in pairs and chains in a short time, first because bacteremia sustained by pyogenic streptococci is often fulminant, with mortality up to around 40% [7, 8]. Another reason is that while pyogenic streptococci are generally and universally expected to be susceptible to penicillin, viridans streptococci often show decreased susceptibility to penicillin and among enterococci, *Enterococcus faecium* resistance to vancomycin in Italy has been described by the 2023 report of European Centre for Disease Prevention and Control of invasive isolates as risen from 14.6% in 2017 to 28.2% in 2021 [9-11].

For many years now, continuous monitoring blood culture systems have been in use in clinical microbiology laboratories, checking for possible positive BCs every 10 to 15 minutes [12]. Among the many parameters provided by those systems, there is time to positivity (TTP), that is the interval from the start of incubation to the flagging positive by the device for possible growth of a microorganism [13]. It has been already described by several Authors how TTP is useful as predictor of mortality in patients suffering from bacteremia sustained by *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *S. pneumoniae* and in a recent systematic review and meta-analysis it has been reported how a shorter TTP for both Gram positive and Gram negative bacteria is associated to a higher risk of both mortality and septic shock [14-17]. The aim of this study was to use TTP to estimate the probability of recovery of pyogenic streptococci versus a *S. pneumoniae*, other viridans group streptococci or enterococci from a positive BC after a microscopic examination revealing Gram positive cocci in pairs and chains.

MATERIALS AND METHODS

Design of the study

This was a retrospective observational study conducted from January 2022 to December 2023. Inclusion criteria: all patients 18 years of age or older evaluated at the Emergency Department (ED) of our Hospital, with the suspect of sepsis, from whom BCs were collected and were positive for Gram positive cocci in pairs or chains at the microscopic examination, were included in the study. All the BCs included in this study were collected by venipuncture, were mono-microbial and were the first bottles that flagged positive in each set. All BCs included were positive within 24 hours of incubation. Complete blood count requested simultaneously with BCs along with medical history taken by the ED physician were also evaluated. The choice of evaluating only the subset of patients from ED was driven by the need to minimize the effect of possible confounding variables such as: processing time (that is time between sampling and incubation, not significant in this study due to the availability of a satellite BC incubator in ED) and variables due to hospitalization, such as subsequent antimicrobial therapy and central line placement or other invasive procedures. Most of the variables considered for modeling are those already found as associate to TTP by other Authors, such as neutropenia, corticosteroid therapy, antibiotic pre-treatment, shock and cirrhosis of the liver [18, 19].

Blood cultures

Blood cultures processing at our laboratory has been described elsewhere [20]. Briefly, for each patient at least two sets of BCs were collected and subsequently incubated. The BCs flagged positive underwent microscopic examination and subculturing. If the microscopic examination was consistent with Gram positive cocci in pairs or chains, TTP of the first bottle in that set was evaluated. Microorganisms were divided into two groups:

1) pyogenic streptococci, such as *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae*;
2) *Streptococcus pneumoniae, v*iridans group streptococci (other than *S. pneumoniae*) and Enterococci such as *Enterococcus faecalis / Enterococcus faecium.*

Identification and antimicrobial susceptibility testing

Identification of isolates was performed by Vitek 2® system (bioMérieux, Marcy l'Etoile, France) or by matrix-assisted laser desorption ionization–time of flight mass spectrometry Vitek® MS (bioMérieux, Marcy l'Etoile, France).

Data extraction

The data were extracted by the Laboratory Information System Concerto (Dedalus Healthcare Systems Group SpA, Firenze, Italy).

Statistical methods

Continuous variables were expressed as median and interquartile range (IQR). Categorical variables were expressed as absolute numbers and percentage. Comparison of median values was performed by Mann-Whitney U test. The Fisher's exact test was used for testing relationships on categorical variables. A Receiver Operator Characteristic (ROC) curve analysis was performed to look for possible thresholds of classifiers resulting significantly different by comparison of median values. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) with 95% confidence intervals (95% CI) were calculated as described by Eusebi P [21]. A binomial logistic regression analysis was performed to assess possible independent predictors of pyogenic streptococci over *S. pneumoniae*, other viridans group streptococci or enterococci. Microsoft Excel 2010 (Microsoft Corporation. Microsoft Excel. Available from: https://office.microsoft.com/excel) and IBM SPSS Statistics for Windows, Version 25.0 (Released 2017. IBM Corp., Armonk, New York) were used for the analysis. The significance level was set at $P \leq 0.05$.

RESULTS

Demographic, clinical and laboratory data

A total of 79 patients were included in the study. Median age was 78.8 years (IQR: 69.8-85.2) and 50/79 (63.3%) were males. The data collected at admission to Hospital are described in Table 1. The median values of neutrophil count in the whole sample was 11.27 cells*10^3/mm^3 (IQR: 7.28 -15.75).

Blood cultures

The microorganisms recovered from BCs are reported in Table 2. It can be seen how pyogenic streptococci accounted for more than 20% of the total. In Figure 1 pictures taken from some of the BCs evaluated in this study are shown. It is clear how no unique morphological features can be found. The median value of TTP in the whole sample was 11.2 hours (IQR: 9.2-13.2). Within the group of pyogenic streptococci, we had four isolates of *S. pyogenes*, with a TTP median value of 9.8 hours (IQR: 8.4-11.3), whereas for the 8 strains of *S. agalactiae* the TTP median value was of 8.3 hours (IQR: 6.7-10.3) and for *S. dysgalactiae* was of 8.1 hours (IQR: 7.1-9.7).

Table 1 - Clinical data considered in the model (n=79).

Clinical data	*N*	*%*
Shock at presentation	3	3.8
Hematologic Malignancy	10	12.7
Immunosuppression	6	7.6
Chronic kidney disease	2	2.5
Cirrhosis of the liver	1	1.3
Systemic corticosteroid therapy	7	8.9
Clinical suspicion of infective endocarditis	13	16.5
Already on antibiotic therapy	1	1.3

Bivariate analysis between demographic/clinical/laboratory data and the two groups of microorganisms and receiver operating characteristic analysis

The association between demographic/clinical/laboratory data and the two groups of microorganisms is shown in Table 3. The ROC curve of TTP as classifier of a positive result from blood cultures for pyogenic streptococci compared to the other group of pathogens, is displayed in Figure 2.

Table 2 - Microorganisms recovered from blood cultures (N=79).

Microorganism	*N*	*%*
Pyogenic streptococci		
Streptococcus agalactiae	8	10.1
Streptococcus dysgalactiae	5	6.3
Streptococcus pyogenes	4	5.1
Streptococcus pneumoniae	20	25.3
Enterococci		
Enterococcus faecalis	17	21.5
Enterococcus faecium	4	5.1
Viridans group streptococci		
Streptococcus gallolyticus subsp. *gallolyticus*	6	7.6
Streptococcus anginosus	6	7.6
Streptococcus mitis	3	3.8
Streptococcus infantarius ssp coli	2	2.4
Streptococcus mitis/oralis	1	1.3
Streptococcus parasanguinis	1	1.3
Streptococcus gordonii	1	1.3
Streptococcus intermedius	1	1.3
Total	79	100

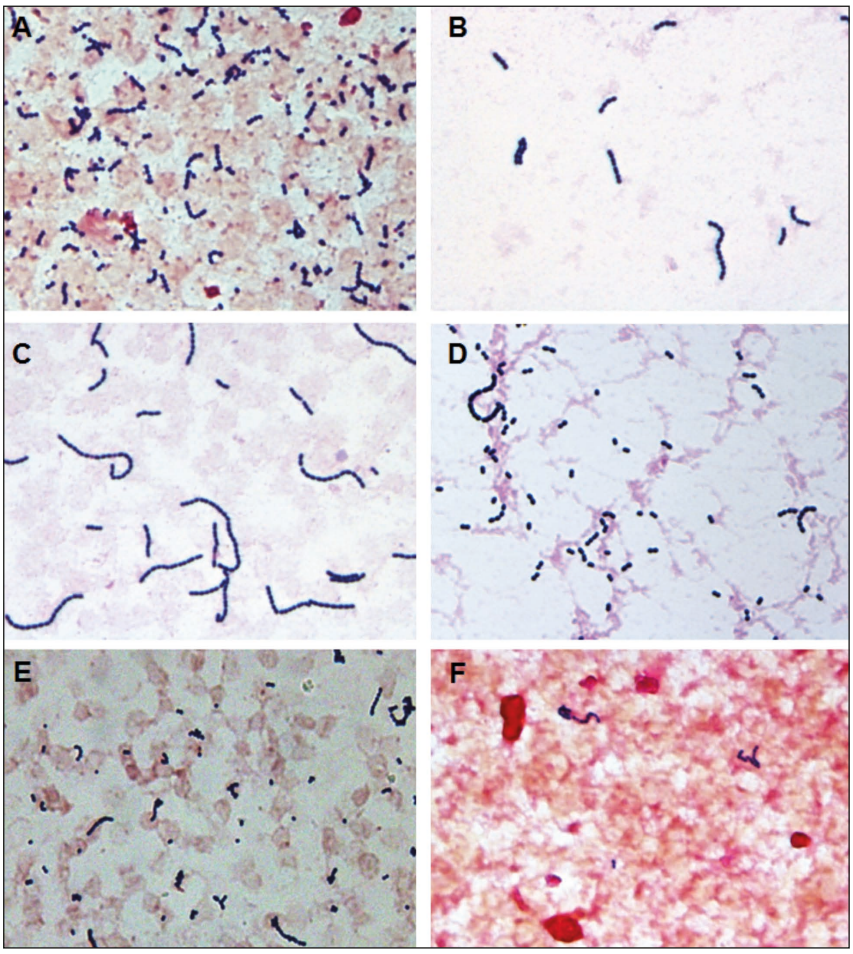

Figure 1
Microscopy images of Gram positive cocci in pairs and chains from some of the positive blood cultures included in this study taken at the Microbiology Laboratory of our Institution.
A) *Streptococcus pyogenes*;
B) *Streptococcus dysgalactiae* subsp. *equisimilis*;
C) *Streptococcus pneumoniae*;
D) *Enterococcus faecium*;
E) *Streptococcus gallolyticus* subsp. *gallolyticus*;
F) *Streptococcus gordonii*.

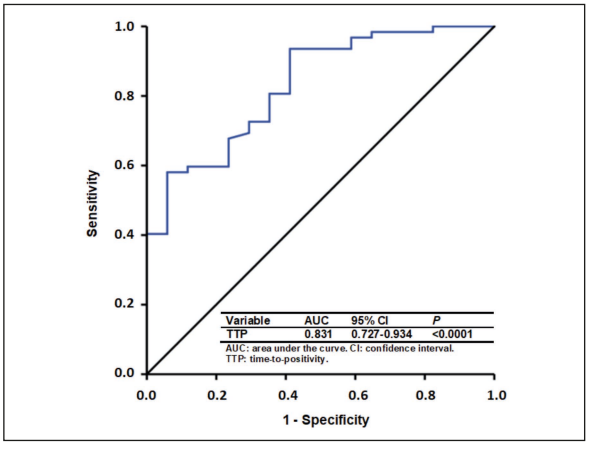

Figure 2 - Receiver operating characteristic analysis of time to positivity as classifier of a positive result from blood cultures for pyogenic streptococci versus *S. pneumoniae*, other viridans streptococci and enterococci.

In our case series, all BCs positive for Gram positive cocci in pairs or chains at microscopic examination with a TTP ≤6.3 hours were consistent with a pyogenic streptococcus (100% specificity; 95% CI: 92.7-100). Consequently, a TTP ≤6.3 hours has a 100% PPV (95% CI: 30.9-100). Conversely, no pyogenic streptococci were recovered from positive BCs with a TTP >12.6 hours. Therefore, as screening test, it has 100% sensitivity (95% CI: 77-100) and 100% NPV (95% CI: 83.4-100).

Binomial logistic regression

The binomial logistic regression is reported in Table 4 and Figure 3. In the analysis, TTP (X) and the first positivity of an anaerobic bottle (Y_1) or aerobic bottle (Y_2) as predictors of a BC positive for pyogenic streptococci compared to *S. pneumoniae*, other viridans group streptococci, *E. fae-*

Table 3 - Bivariate analysis between demographic/clinical/laboratory data and the two groups of microorganisms (n=79).

Variable	*Pyogenic streptococci (N=17)*	*Other Gram positive cocci in pairs and chains (N=62)*	*P*
Males	12 (70.6)	38 (61.3)	0.577
Shock at presentation	0 (0)	3 (4.8)	1.000
Hematologic Malignancy	2 (11.8)	8 (12.9)	1.000
Immunosuppression	2 (11.8)	4 (6.5)	0.604
Chronic kidney disease	0 (0)	2 (3.2)	1.000
Cirrhosis of the liver	0 (0)	1 (1.6)	1.000
Systemic corticosteroid therapy	2 (11.8)	5 (8.1)	0.639
Clinical suspicion of infective endocarditis	2 (11.8)	11 (17.7)	0.723
Already on antibiotic therapy	0 (0)	1 (1.6)	1.000
Anaerobic bottle positive first	14 (82.4)	31 (50)	0.026
Age (years)	74.5 (71.3-77.8)	79.8 (69.8-85.5)	0.152
Neutrophils (cells*10^3/mm^3)	11.3 (8.1-12.9)	11.2 (6.7-15.9)	0.877
Time to positivity (hours)	8.3 (7.3-10.4)	12.1 (9.6-14.4)	<0.0001

Categorical variables are expressed as absolute numbers (column percentage). Continuous variables are expressed as median (interquartile range).
Pyogenic streptococci: *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae*.
Other Gram positive cocci in pairs and chains: *Streptococcus pneumoniae*, *Streptococcus gallolyticus* subsp. *gallolyticus*, *Streptococcus anginosus*, *Streptococcus mitis*, *Streptococcus infantarius* subsp. *coli*, *Streptococcus mitis/oralis*, *Streptococcus parasanguinis*, *Streptococcus gordonii*, *Streptococcus intermedius*, *Enterococcus faecalis*, *Enterococcus faecium*.

Table 4 - Binary logistic regression analysis to evaluate the performance of the variables significantly associated with the bivariate analysis as independent predictors of a blood culture positive for pyogenic streptococci versus other Gram positive cocci in pairs and chains at microscopic examination.

Variable	β	*SE*	*OR*	*(95% CI)*	*P*
Time to positivity	-0.602	0.177	0.548	0.387-0.775	0.001
Anaerobic bottle positive first	1.759	0.773	5.806	1.275-26.436	0.023
Intercept	3.768	1.755	43.308		0.032

SE: standard error; OR: odds ratio; CI: confidence interval.
Pyogenic streptococci: *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae*.
Other Gram positive cocci in pairs and chains: *Streptococcus pneumoniae*, *Streptococcus gallolyticus* subsp. *gallolyticus*, *Streptococcus anginosus*, *Streptococcus mitis*, *Streptococcus infantarius* subsp. *coli*, *Streptococcus mitis/oralis*, *Streptococcus parasanguinis*, *Streptococcus gordonii*, *Streptococcus intermedius*, *Enterococcus faecalis*, *Enterococcus faecium*.

calis and E. faecium, were evaluated. The model proposed had a chi-square of 27.73 (P<0.0001), a Nagelkerke R square of 0.457 and correctly predicted 83.5% of the overall results. The regression equations and graphs for estimating the conditional probability of a BC positive for pyogenic streptococci according to our series are displayed in Figure 3.

For example, an anaerobic bottle positive for Gram positive cocci in pairs or chains with a TTP of 7 hours has an estimated probability of being positive for a pyogenic streptococcus of ≈80%:

$$\mathbf{Y}_1 = e^{(3.77 + 1.76 - 0.6 * 7)} \div [1 + e^{(3.77 + 1.76 - 0.6 * 7)}] = 3.78 \div 4.78 = 0.79$$

Conversely, an aerobic bottle positive for Gram positive cocci in pairs or chains with a TTP of 7 hours has an estimated probability of being positive for a pyogenic streptococcus of ≈40%:

$$\mathbf{Y}_2 = e^{(3.77 - 0.6 * 7)} \div [1 + e^{(3.77 - 0.6 * 7)}] = 0.65 \div 1.65 = 0.39$$

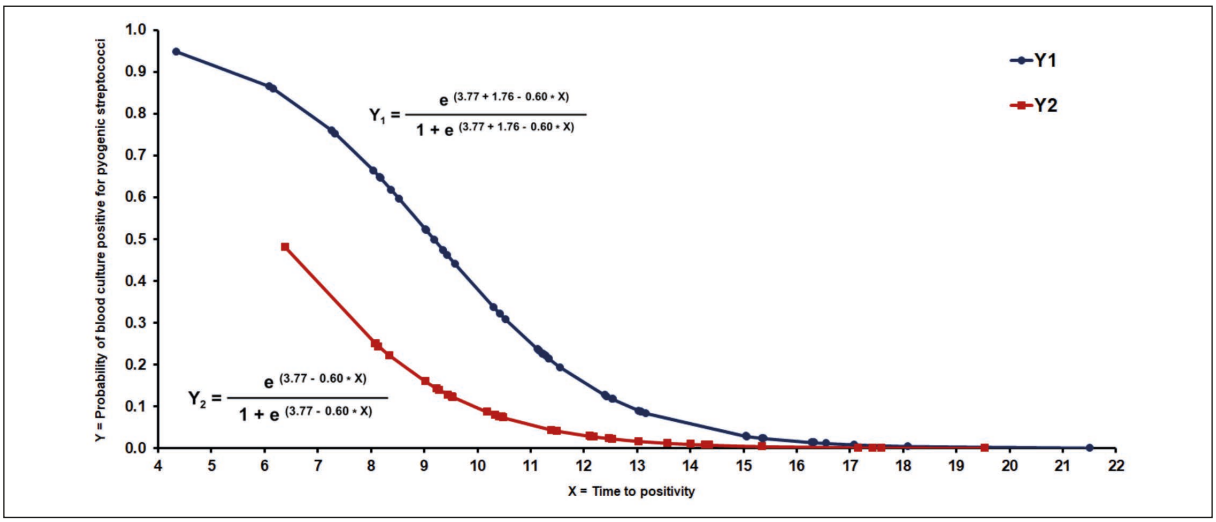

Figure 3 - Regression equations and graph illustrating the time to positivity and anaerobic bottle positive first as independent predictors of a positive result for pyogenic streptococci versus *S. pneumoniae*, other viridans streptococci and enterococci from blood cultures collected at the Emergency Department. In our case series, as time to positivity (X) increases, in the subset of anaerobic (Y_1) and aerobic (Y_2) blood cultures bottles positive first for Gram positive cocci in pairs and chains at the microscopic examination, the probability of a positive result for a pyogenic streptococcus decreases.

DISCUSSION

The sample evaluated was mainly composed by male elderly patients (more than 80% were ≥65 years of age). As shown in Table 1, only few patients suffered from conditions possibly influencing TTP. Indeed, even though the sample was limited to 79 patients, the bivariate correlation analysis (Table 3) showed it was substantially homogeneous. No association was found between any categorical variable and any group of pathogens.

With respect to neutropenia, we included in the model the absolute neutrophil count because continuous data are more informative and because in our population only two patients had a count $<2.5*10^3$ cell/mm^3 (one suffered from leukemia and the second had a lobar pneumonia caused by *S. pneumoniae*).

Regarding TTP, we found how pyogenic streptococci had median values significantly shorter than all the other Gram positive cocci in pairs and chains visualized at microscopic examination. The differences in TTP among the Gram positive cocci found in this study match with the findings of Martínez et al. that in a study including 1872 episodes of significant monomicrobial bacteraemia, among Gram positive bacteria, beta-haemolytic streptococci flagged positive faster than any other streptococcus, while no difference was found between *Enterococcus* spp. and viridans group streptococci other than *S. pneumoniae*. In agreement with Martínez et al., a possible explanation could be the different generation time of bacteria and a higher bacterial load at the time of collection [19].

Concerning *S. pyogenes*, the median TTP values found in the present study are perfectly in line with the findings of Bläckberg et al., that in 286 *S. pyogenes* bacteremia, reported a median TTP of 10.4 hours (interquartile range, 8.4–11.4). As regards to *S. dysgalactiae*, the median TTP value observed in this study substantially matches that of Bläckberg et al, on 287 episodes of *S. dysgalactiae* bacteraemia [22, 23]. Also in the study of Krisanapan P and Chaiwarith R on 181 patients, the TTP median values found for pyogenic streptococci are in line with those found in the present study [24].

The finding of an independent association between the first positivity of an anaerobic bottle with a pyogenic streptococcus can be explained by the findings of Ransom EM and Burnham CD that in a total of 158,710 bottles reported TTP of *S. pneumoniae* as significantly shorter in aerobic bottles. In

our series *S. pneumoniae* represents more than 25% of the non-pyogenic cocci [25].
The ROC analysis in Figure 2 shows how TTP is a good classifier to discriminate pyogenic streptococci from other Gram positive cocci in pairs and chains. This is confirmed also by the binomial logistic regression model proposed (Table 4). Indeed, looking at Figure 3, as time to positivity (X) increases, in both anaerobic (Y_1) and aerobic (Y_2) BC bottle positive first for Gram positive cocci in pairs and chains at the microscopic examination, the probability of a positive result for a pyogenic streptococcus decreases. Obviously, the estimated probability is reliable only by interpolation, therefore within the range of the TTP of pyogenic streptococci defined by ROC analysis.
As reported by Lamy B, although limited by some variables often not considered such as previous antibiotic therapy, time to bottle load and blood volume, TTP provides important information for better patient management, nevertheless. Time to positivity has been indeed proposed for both a revision of antimicrobial therapy and a possible antimicrobial de-escalation within 24 hours [26]. Although affordable cut-offs and algorithms have yet to be defined for use in clinical practice, in the present study the information given by the Gram staining along with the probability calculated by means of TTP could be considered to discontinue or add glycopeptides to therapy.
This study has limitations. The retrospective observational design of the study frames it as a hypothesis generator and the sample size is limited, in relation to the need of minimizing all possible confounding variables. Other variables possibly associated with the outcomes considered, such as volume of blood collected, were not available.

CONCLUSIONS

We proposed this model as an adjunctive tool to clinical aspects and fast microbiology laboratory tests to help assessing the likelihood of a positive blood culture for pyogenic streptococci collected at the Emergency Department of our institution.

Conflict of interest
The authors declare that this research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Ethical considerations
Ethical approval was not needed because this is a secondary analysis of data collected as part of standard care and those included in the database were deidentified before access. No personal information was stored in the study database. No patient intervention occurred with the obtained results.

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