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Diagnosis of bacteraemia and growth times

Jose Manuel Ruiz-Giardín [a,*], Rosa M. Martin-Díaz [a], Jerónimo Jaqueti-Aroca [b], Isabel Garcia-Arata [b], Juan Víctor San Martín-López [a], Miguel Sáiz-Sánchez Buitrago [c]

[a] Internal Medicine Department, Fuenlabrada University Hospital, c/ Camino del Molino 2, Fuenlabrada, 28942 Madrid, Spain
[b] Microbiology Department, Fuenlabrada University Hospital, Fuenlabrada, Madrid, Spain
[c] 12 de Octubre University Hospital, Madrid, Spain

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SUMMARY

Objective: The objective of this study was to predict the diagnosis of bacteraemia as a function of the time at which the automated BacT/Alert system continuously detects microorganism growth.
Methods: A retrospective study of a database of 1334 patients with a positive blood culture between January 2011 and June 2013 was conducted. Together with the final blood culture results and the patient's history, growth was then analysed to assess whether it represented true bacteraemia or bacterial contamination. The earliest detection times of bacterial growth in each batch of blood cultures were analysed in a blinded fashion after classification.
Results: In total, 590 batches of blood cultures corresponded to true bacteraemia and 744 to bacterial contamination. In the bacteraemia group, the median growth time was 12.72 h (interquartile range (IQR) 10.08–17.58 h). In the contaminated blood culture group, the median growth time was 20.6 h (IQR 17.04–32.16 h) ($p < 0.001$). Analysis of the receiver operating characteristics (ROC) curve (area under the curve 0.80, 95% confidence interval 0.771–0.826) showed that 90% of the contaminants grew after 14.7 h (sensitivity 90.5%, specificity 63.4%, positive predictive value (PPV) 65.9%, negative predictive value (NPV) 90.7%). Forty-five percent of the bacteraemia organisms grew in under 12 h (sensitivity 45.3%, specificity 95%, PPV 87.8%, NPV 68.7%). Microorganisms such as *Candida sp* and *Bacteroides sp* presented median growth times significantly longer than those of the other microorganisms. The administration of antibiotics in the week prior to bacteraemia was found to delay the growth time of microorganisms ($p < 0.001$).
Conclusions: Knowing the time to detection of microorganism growth can help to distinguish between true bacteraemia and bacterial contamination, thus allowing more timely clinical decisions to be made, before definitive microorganism identification.

1. Introduction

The diagnosis of bacteraemia is one of the most critical functions of clinical microbiology laboratories. In general, conventional blood culture methods (manual systems such as biphasic blood culture, lysis filtration–centrifugation, manometer methods, and automatic systems, both radiometric and non-radiometric) provide results within 2 to 5 days, and incubation periods of over 5 days are not usually required with modern continuous automated monitoring methods.[1,2] The volume of blood extracted for each blood culture is the most important variable when harvesting bacteria and fungi from patients with bacteraemia.[1–3]

Contamination of blood culture is common, is very costly for the health system, and often confuses clinicians. To minimize the risk of blood culture contamination with the normal skin flora, meticulous attention should be paid when preparing the skin for venipuncture. In general, it is desirable to maintain the rate of contaminated blood culture at less than 3%. Rates of contamination any higher than this should be investigated and corrected with educational efforts.[4]

Clinicians should be notified every time there is a positive blood culture because the microorganism can often represent an infection that may lead to death. Furthermore, knowledge of the start times for adequate antibiotic therapy is critical for the

* Corresponding author. Tel.: +34 16006179.
E-mail address: josemanuel.ruiz@salud.madrid.org (J.M. Ruiz-Giardín).

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prognosis of patients with sepsis and bacteraemia. The association between mortality and the origin of bacteraemia appears to depend on the use and timing of treatment with adequate empirical antibiotics.[5–7]

The objective of this study was to predict the diagnosis of bacteraemia in the face of contaminants as a function of the time at which the automated BacT/Alert system continuously detects microorganism growth, and to identify whether this time to detection can help the clinician to distinguish true-positive growth from contaminated growth. This study also analysed whether taking antibiotics during the 7 days before bacteraemia influences culture growth times.

2. Methods

The study was conducted in a referral hospital serving the population of the southern part of the Community of Madrid. According to data from the National Institute of Statistics dating from January 1, 2012, this facility covers a health area of 224 549 inhabitants, of whom 171 164 are aged >14 years. The hospital is a 350-bed secondary hospital with general surgery, orthopaedics, urology, gynaecology and obstetrics, internal medicine, intensive care, cardiology, digestive system, pneumology, nephrology, oncology, haematology, and paediatric units.

The growth time in hours from the first vial of each blood culture batch in which microorganism growth was produced in a suspected case of bacteraemia was recorded retrospectively for cultures performed during the period January 2011 to June 2013. All subjects were non-paediatric patients aged >14 years. A retrospective study of this database was then performed.

Together with the final blood culture results and the patient's history (146 different clinical, analytical, and epidemiological variables were recovered), the growth and treatment received were analysed in a blinded fashion by four different clinicians to assess whether the growth represented true bacteraemia or bacterial contamination. The data were analysed using SPSS statistical software (version 15.0). The distribution of these times was studied to decide whether to work with the mean and standard deviation or with the median and interquartile range. Non-parametric tests of the median were conducted to calculate any significant differences between medians. A receiver operating characteristics (ROC) curve was also produced to determine the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for the different growth times. The unpaired Student's *t*-test or Mann–Whitney *U*-test was used for the analysis of quantitative data.

During the study period, the BacT/Alert blood culture system was employed. Two pairs of blood culture vials were used for each patient, with a total recommended extracted volume of blood of 20–40 ml. These four vials, two for aerobic and two for anaerobic culture, were termed a 'blood culture batch'. Blood cultures were performed depending on medical criteria in patients with suspected sepsis; there is no predictive model able to identify which patients should have blood cultures done.

A blood culture was considered to be a true positive (bacteraemia) when at least one of the following microorganisms was isolated in at least one blood culture vial: Gram-negative bacilli, fungi, and Gram-positive cocci different from coagulase-negative Staphylococcus. A blood culture was also considered to be a true positive when coagulase-negative Staphylococcus was isolated in at least one vial of each pair and the patient presented a compatible clinical workup of bacteraemia. The blood culture was considered contaminated when coagulase-negative Staphylococcus, *Bacillus sp*, *Propionibacterium acnes*, or *Corynebacterium sp* was isolated in a single vial without any clinical indication. When coagulase-negative Staphylococcus isolated from a single vial was associated with intravascular catheter colonization (over 15 colony-forming units) caused by the same microorganism, the blood culture was considered positive if the patient's doctor initiated treatment based on this result. The growth time in hours was defined as the time elapsed between incubation and the detection of growth utilizing the automated blood culture system.

The same episode was considered bacteraemia if a new extraction with growth of the same microorganism was produced in the 5 days following the first extraction.

Patients were considered to have received prior antibiotic therapy if they received at least one dose of antibiotics in the 7 days prior to the blood culture. This information was analysed only in bacteraemic patients.

3. Results

During the study period from January 2011 to June 2013, 6816 blood culture batches were collected from patients older than 14 years of age. From this total, 1350 positive blood culture batches were associated with 1334 episodes of suspected bacteraemia; 590 of these corresponded to true bacteraemia and 744 were classified as contaminated blood culture batches.

3.1. Microorganisms

Of the 1334 blood culture batches with growth in the blood culture vials, true-positive bacteraemia ($n = 590$) was produced by enterobacteria (46.8%), coagulase-negative Staphylococcus (15.2%), *Staphylococcus aureus* (8.3%), polymicrobial infections (5.4%), *Enterococcus sp* (5.3%), non-fermenting Gram-negative bacilli (4.2%), *Streptococcus pneumoniae* (2.5%), *Candida sp* (2%), and *Streptococcus agalactiae* (1%).

Of the contaminated blood cultures ($n = 744$), coagulase-negative Staphylococcus made up 70.2%, *Propionibacterium sp* 9.5%, polymicrobial microorganisms 8.2%, and *Corynebacterium sp* 4.6%.

3.2. Growth times of contaminated and true-positive blood cultures

The growth time of the contaminated blood cultures ($n = 744$) was a median 20.6 h (IQR 17.04–32.16 h). Regarding the true-positive blood culture bacteraemia ($n = 590$), the growth time was a median 12.72 h (IQR 10.08–17.58 h). The difference between the two growth times was statistically significant ($p < 0.001$).

A ROC curve (Figure 1) was produced to determine the sensitivity, specificity, PPV, and NPV of the growth time as a determinant of contaminated growth. The area under the curve was 0.80, with a 95% confidence interval of 0.771–0.826.

In true bacteraemia, if the first vial detecting microorganism growth did so in less than 12 h, a specificity of over 95% and sensitivity of 45.3 % was found (PPV 87.8%, NPV 68.7%). In total, 90% of the contaminants grew beyond 14.7 h (sensitivity 90.5%, specificity 63.4%, PPV 65.9%, NPV 90.7%) and 95% of the contaminants grew beyond 12 h (sensitivity 95%, specificity 43.6%, PPV 57.8%, NPV 92.1%).

Comparing the growth times between distinct microorganisms producing true bacteraemia, there were microorganisms with significantly slower growth than others, as was the case with *Bacteroides sp* and *Candida sp* (Table 1) (Figures 2 and 3).

Comparing the growth times of coagulase-negative staphylococci in bacteraemia cases (90 cases; median 16.32 h, IQR 12.84–19.92 h) to the growth times of coagulase-negative staphylococci considered to be a contaminant (538 cases; median 19.20 h, IQR 16.80–24.72 h), the difference in growth times was found to be statistically significant with $p < 0.001$ (Figures 2 and 3).

Analyses of the growth times of true bacteraemia according to whether the patient received antibiotic therapy in the week prior