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Time to positivity of blood cultures in patients with bloodstream infections: A useful prognostic tool

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ABSTRACT

Objective: The time to positivity (TTP) of blood cultures in patients with bloodstream infections (BSIs) has been considered to be a possible prognostic tool for some bacterial species. However, notable differences have been found between sampling designs and statistical methods in published studies to date, which makes it difficult to compare results or to derive reliable conclusions. Our objective was to evaluate the clinical and microbiological implications of TTP among patients with BSI caused by the most common pathogens.
Methods: A total of 361 episodes of BSI were reported for 332 patients. The survival of the entire cohort was measured from the time of blood culture sampling. In order to compare our results with those of previous studies, TTP was divided in three different groups based on log rank (short TTP <12 h; medium TTP ≥12 h to ≤27 h, and long TTP >27 h). Cox proportional hazard models were used to calculate crude and adjusted hazard ratios (HR).
Results: The Cox proportional hazard model revealed that TTP is an independent predictor of mortality (HR = 1.00, $p = 0.031$) in patients with BSIs. A higher mortality was found in the group of patients with the shortest TTP (<12 h) (HR = 2.100, $p = 0.047$), as well as those with longest TTP (>27 h) (HR = 3.277, $p = 0.031$).
Conclusions: It seems that TTP may provide a useful prognostic tool associated with a higher risk of mortality, not only in patients with shorter TTP, but also in those with longer TTP.

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El tiempo de positividad de los hemocultivos: una herramienta pronóstica útil en pacientes con bacteriemia

Palabras clave:
Bacteriemia
Tiempo de positividad
Hemocultivo
Mortalidad

RESUMEN

Objetivo: El tiempo de positividad (TP) de los hemocultivos en pacientes con bacteriemia ha sido considerado como una posible herramienta pronóstica. Sin embargo, en los estudios publicados hasta la fecha, hemos observado importantes diferencias tanto en el diseño experimental como en la metodología utilizada. Esto dificulta el poder comparar los resultados obtenidos u obtener conclusiones consistentes. El objetivo de este estudio ha sido evaluar las implicaciones clínicas y microbiológicas del TP en pacientes con bacteriemia causada por los microorganismos más frecuentes, revisando la metodología utilizada en estudios anteriores.
Métodos: Se estudiaron un total de 361 episodios de bacteriemia de 332 pacientes. La supervivencia de nuestra cohorte se midió desde que se tomó la muestra de hemocultivo. El TP fue dividido en

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tres grupos en base al log rank (TP cortos <12 h; TP medios ≥12 h y ≤27 h; TP largos >27 h), con el objetivo de comparar nuestros resultados con los obtenidos en estudios previos. Se utilizó el modelo de riesgos proporcionales (Cox) para calcular los hazard ratios (HR) tanto crudos como ajustados.
Resultados: El modelo Cox mostró que el TP es un factor independiente relacionado con la mortalidad en pacientes con bacteriemia (HR = 1,00, p = 0,031). Concretamente, encontramos una mayor mortalidad en aquellos pacientes con TP cortos (<12 horas) (HR = 2.100, p = 0,047), así como en pacientes con TP largos (>27 h) (HR = 3.277, p = 0,031).
Conclusiones: En el presente estudio demostramos que el TP puede ser utilizado como una herramienta pronóstica útil de mortalidad no solo en pacientes con TP cortos, sino también en aquellos con TP largos.
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Introduction

Bloodstream infections (BSIs) are a significant cause of morbidity and mortality in the general population. Over 1.2–1.4 million episodes of BSI are estimated to occur annually in Europe, leading to nearly 157,000 deaths.[1] The delay on appropriate antimicrobial therapy in patients with BSI is considered a bad prognostic factor. Moreover, inappropriate use of antibiotics during BSIs is currently a global problem, increasing morbidity and mortality, provoking longer stays, higher costs and favouring development of antibiotic resistance.[2] For these reasons, prompt and accurate identification of the causative pathogen is critical for guiding rapid initiation of appropriate antimicrobial therapy, diminishing mortality especially in patients with septic shock.[1,2]

Automated blood culture systems are the gold standard method for diagnosis of BSI in hospitals.[3] These systems allow continuous monitoring of bacterial growth, which ensures faster reports to the physicians. Time to positivity (TTP) is defined as the span of time from the beginning of culture incubation to the detection of bacterial growth by an automated system. Several studies have shown that shorter TTPs are associated with a significantly higher mortality risk in patients with bacteraemia caused by several bacterial species, like *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*.[4–7] This fact is correlated with the blood bacterial load, and therefore, shorter TTPs reflect greater disease severity.[8] A majority of studies have reported significant associations between shorter TTP and risk of mortality. However, the methodology used by the different authors is dissimilar, which would decrease the reliability of the predictive models. Furthermore, the use of different statistical methods can lead to different interpretations, and could induce biased conclusions.[9] The purpose of our study was to evaluate the association between TTP and mortality risk inpatients with BSIs in our hospital, examining the statistical methods carried out in previous studies in order to optimize the use of the TTP as a useful prognostic tool.

Methods

Setting and patients

A prospective study of 361 cases of BSI was carried out at the tertiary-care University Hospital Virgen del Rocío, in Seville, Spain, from January–December 2012. This study was part of an institutionally supported and educational stewardship programme for antimicrobial usage optimization, which included all clinical departments, and that has been developed in our centre in order to improve the use of antimicrobial therapy.[10] This programme was launched in our hospital in the year 2011 and continues its successful development, with the first results published after one year of its implementation.[11]

One of the main objectives of this stewardship programme was to evaluate some indicators of its clinical impact, such as the evolution of mortality after its implementation. We performed a retrospective study of patients with microbiologically documented BSI. Since the time of diagnosis of bacteraemia due to the following organisms: *E. coli*, *S. aureus*, *K. pneumoniae*, *Streptococcus pneumoniae*, *P. aeruginosa* and *Acinetobacter baumannii*, the in-hospital mortality and the period of time until death in these patients were analyzed. In all BSI episodes that we studied, the following variables with a prognostic value were recorded: TTP (hours), sex, age, site of acquisition (nosocomial, community or health care related), source of infection, aetiology, clinical presentation (sepsis, severe sepsis, septic shock), underlying conditions (Charlson comorbidity Index) empirical antimicrobial therapy, and clinical outcome (length of stay, crude mortality and days until death). Patients under 14 years of age were excluded of this study.

Selection of articles

All potentially relevant articles, in which TTP and mortality are related, in English and Spanish languages from January 1974 to April 2014 were identified by computerized searches of PubMed using the following Medical Subject Headings (MeSH) and keyword terms: time to positivity, bloodstream infection, sepsis, bacteraemia, blood culture and mortality. Relevant articles, judged on the basis of the title and abstract, were retrieved for more detailed evaluation.

Variable definitions

Bacteremia infection was defined as ≥1 positive blood culture result with systemic manifestations of infection.[12] Sepsis was defined according to the definition of the Surviving Sepsis Campaign Guidelines for Management of Severe Sepsis and Septic Shock.[13] Nosocomial infection was considered when the first positive blood culture was obtained >48 h after hospital admission, or when the infection occurred <48 h but the patient had been hospitalized in the 3 previous weeks. Community-onset infections were considered when the first positive blood culture was obtained ≤48 h after admission without previous hospitalization.[14]

The sources of infection were defined according to the Centres for Disease Control and Prevention (CDC) criteria.[15] The diagnosis of the infection source was based on clinical, bacteriological and radiological criteria. Empirical antimicrobial therapy was defined as adequate in terms of in vitro susceptibility of an organism isolated, and if antibiotic treatment was started within 24 h after drawing blood cultures. The severity of the underlying conditions was classified according to the Charlson's weighted comorbidity index.[16]

Microbiological methods

Approximately 20 mL of blood from patients were aseptically obtained via peripheral venepuncture and distributed equally

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