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Short Communication

Mortality impact of further delays in active targeted antibiotic therapy in bacteraemic patients that did not receive initial active empiric treatment: Results from the prospective, multicentre cohort PROBAC

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ABSTRACT

Objectives: The early initiation of the empirical antibiotic treatment and its impact on mortality in patients with bacteraemia has been extensively studied. However, information on the impact of precocity of the targeted antibiotic treatment is scarce. We aimed to study the impact of further delay in active antibiotic therapy on 30-day mortality among patients with bloodstream infection who had not received appropriate empirical therapy.

Design: We worked with PROBAC cohort (prospective and compound by patients from 26 different Spanish hospitals). We selected a total of 1703 patients, who survived to day 2 without having received any active antibiotic therapy against the causative pathogen.

Results: The 30-day mortality was 14% (238 patients). The adjusted odds of mortality increased for every day of delay, from 1.53 (95% confidence interval (CI) 1.13-2.08) for day 3 or after to 11.38 (95% CI 7.95-16.38) for day 6 or after.

Conclusion: We concluded that among patients who had not received active treatment within the first 2 days of blood culture collection, additional delays in active targeted therapy were associated with increased mortality. These results emphasize the importance of active interventions in the management of patients with bloodstream infections.

Introduction

Bloodstream infections (BSIs) are an important cause of morbidity and mortality worldwide [1]. Early initiation of active drugs in patients with BSI, typically as empirical therapy, has been associated with better outcomes [2–5]. Further delay in administering active therapy even once the susceptibility results are available is not infrequent in absence of specific specialized interventions [6,7]. However, the impact of delay in administering active target therapy has not received much attention despite being potentially important for intervention purposes. The objective of this analysis was to assess whether further delay in providing active targeted therapy is associated with increased mortality in patients with BSI previously receiving inappropriate empirical therapy.

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Methods

The PROBAC study (NCT03148769) is a prospective, multicentre cohort study investigating the epidemiology, clinical and prognostic features of BSI. Consecutive adult patients with clinically significant bacteraemia diagnosed in the participating sites (26 Spanish hospitals) from October 2016 to March 2017 were included. Details of the study methodology were previously published [8].

Patients from the PROBAC cohort were included in this analysis if the following criteria were fulfilled: (1) they had survived at least 2 days since blood cultures were obtained (day 0), so they had the opportunity to receive targeted therapy; and (2) they had not received any antimicrobial agent with *in vitro* activity against the bacteria causing the BSI before day 2. Patients who were alive at day 7 and had not received any active drug were excluded, as BSI in these patients was probably self-limited or not clinically relevant. We also excluded patients in whom time until the start of active therapy was missing.

The primary endpoint was 30-day all-cause mortality. The main exposure variable was the delay in receiving appropriate targeted treatment, measured as the number of days from day 0 to administration of an *in vitro* active drug. Other variables collected are included in Table 1, and were previously defined [8]. Antimicrobial therapy was considered appropriate if at least one drug active *in vitro* against the causative pathogen(s) was administered at recommended dosing. Remote monitoring for data quality was performed.

The PROBAC project was approved by the ethic board of Hospital Universitario Virgen Macarena (reference code: FIS-AMO-2016-01) and by ethic boards of the participant centres as needed. The need to obtained written informed consent was waived because of the observational nature of the study. We followed the STROBE recommendations for reporting of observational studies [9] (Supplementary Table S1).

The bivariate association of the different variables with mortality was analysed by chi-squared test for categorical variables, and by Mann-Whitney U test for continuous variables. Aetiologies and source of bacteraemia were classified into low- and high-risk groups according to their association with mortality. Also, continuous variables were dichotomized according to strata association with mortality. We first identified the mortality predictors without considering antimicrobial treatment by logistic regression; those variables were used to provide adjusted estimations of the association of the delay of active drug administration with 30-day mortality using logistic regression for each day of delay. The landmark method was used to avoid immortal time bias for each day. The software used for the statistical analysis was SPSS programme version 25 Software (IBM Statistics for Windows, version 25.0; IBM Corp, Armonk, NY, USA).

Results

Overall, 6313 patients were included in the PROBAC cohort; of these, 4140 (65.6%) had received appropriate treatment before day 2, 272 (4.3%) died during the first 2 days, and 198 (3.1%) were excluded because time to active therapy was not available. Therefore, 1703 episodes were included in this analysis.

The features of the patients are shown in Table 1. Overall, 1052 (61.8%) patients were men; the median age was 72 years (interquartile range (IQR) 60-81), and 1028 (60.4%) had an age-adjusted Charlson index >3. The most frequent comorbidities were solid cancer (414 patients, 24.3%) and diabetes mellitus (341 patients, 20 %). The most frequent sources of BSI were the urinary tract (388; 22.8%), vascular-catheter (306; 18%) and biliary tract (210; 12.3%), and the most common aetiologies were *Escherichia coli* (497; 29.2%) and *Staphylococcus aureus* (201; 11.8%). Overall,

Table 1
Demographic, epidemiological, baseline characteristics, and clinical presentation of patients with bloodstream infections who had not received active therapy in the first 48 hours.

Variable	All patients N = 1703
Age in years, median (IQR)	72 (60-81)
Age ≥65 years	1128 (66.2)
Male sex	1052 (61.8)
Age-adjusted Charlson index >3	1028 (60.4)
Underlying conditions	
Diabetes mellitus	341 (20)
Chronic pulmonary disease	170 (10)
Chronic heart insufficiency	172 (10.1)
Chronic renal insufficiency	232 (13.6)
Liver cirrhosis	153 (9)
Solid cancer	414 (24.3)
Haematologic cancer	102 (24.3)
Immunosuppressive drugs	141 (8.3)
Neutropenia	40 (2.3)
Type of infection acquisition	
Community-acquired	600 (35.2)
Healthcare-associated	383 (22.5)
Nosocomial	720 (42.3)
Type of ward of admission	
Emergency room	593 (34.8)
Medical ward	673 (39.5)
Surgical ward	246 (14.4)
Intensive care unit	191 (11.2)
Severity of infection at presentation	
Pitt score >3	131 (7.7)
SOFA score ≥2	414 (24.3)
Invasive procedures	
Central venous catheter[a]	16 (0.9)
Urinary catheter[a]	326 (19.1)
Mechanical ventilation[a]	91 (5.3)
Major surgery[b]	241 (14.2)
Previous antibiotic therapy[b]	575 (33.8)
Source of bacteraemia	
Urinary tract	388 (22.8)
Vascular catheter	306 (18.0)
Biliary tract	210 (12.3)
Intra-abdominal, non-biliary tract	136 (8.0)
Respiratory tract	136 (7.9)
Skin and skin structures	118 (6.9)
Endocarditis	48 (2.8)
Osteoarticular	42 (2.5)
Central nervous system	16 (0.9)
Others	23 (1.4)
Unknown	280 (16.4)
High-risk sources[c]	600 (35.2)
Aetiology	
Escherichia coli	497 (29.2)
Staphylococcus aureus	201 (11.8)
Staphylococcus epidermidis	165 (9.7)
Klebsiella pneumoniae	109 (6.4)
Enterococcus faecalis	76 (4.5)
Pseudomonas aeruginosa	73 (4.3)
Enterococcus faecium	71 (4.2)
Streptococcus pneumoniae	41 (2.4)
Others	470 (18.2)
Polymicrobial bacteraemia	138 (8.1)
High-risk aetiology[d]	367 (21.55)
30-day mortality	238 (14)
Treatment started on day 2	75/681 (11.0)
Treatment started on days 2-3	114/1130 (10.1)
Treatment started on days 2-4	133/1411 (9.4)
Treatment started on days 2-5	132/1517 (8.7)

SOFA: Sequential Organ Failure Assessmentl, QR: interquartile range.
[a] Previous week.
[b] Previous month.
[c] High-risk sources: Infectious endocarditis, abdominal not biliary tract, unknown, respiratory.
[d] High-risk aetiology: *S. aureus, P. aeruginosa, Candida* spp.

Table 2
Crude and adjusted estimates of the association of delay in administering active therapy with mortality.

Delay in active therapy	Died (n = 238)	Alive (n = 1465)	OR (95% CI)	*P* value	Adjusted OR (95% CI)[a]	*P* value
Day 4 or after	124 (52.1)	449 (30.6)	2.50 (1.88-3.33)	<0.001	2.26 (1.69-3.02)	<0.001
Day 5 of after	105 (44.1)	187 (12.7)	5.38 (3.99-7.26)	<0.001	4.33 (3.45-6.49)	<0.001
Day 6 or after	104 (43.6)	82 (5.5)	13.05 (9.30-18.38)	<0.001	11.38 (7.95-16.38)	0.006

CI: confidence interval, OR: odds ratio.
[a] Adjusted for age-adjusted Charlson index, type of acquisition, Pitt score, aetiology, and source.

681 patients (40.0%) received active treatment at day 2, 534 (31.3%) at day 3, 281 (16.5%) at day 4, 106 (6.2%) at day 5, and 101 (5.9%) at days 6 or 7.

Mortality at day 30 was 14.0% (238 patients). The mortality rates according to delay in active therapy were 15.9% after day 2, 21.6% after day 3, 36% after day 4 and 57% after day 5 (Supplementary Table S2). Mortality predictors by multivariate analysis were age-adjusted Charlson index, type of acquisition, Pitt score, aetiology, and source of bacteraemia (Supplementary Table S3). These variables were used to provide adjusted estimate of the effect of the delay in administering active therapy (Table 2); the odds of mortality increased per day of delay, from 1.53 (95% CI 1.13-2.08) for administering active therapy at day 3 or after to 11.38 (95% CI 7.95-16.38) for day 6 or after. No significant interaction between delay of treatment and other variables were found.

Discussion

In this study, we found that further delay in receiving active therapy in patients with bacteraemia who had received inappropriate empirical therapy was associated with higher risk of death.

Overall, about one quarter of patients in the PROBAC cohort survived >48 hours despite not having received appropriate empirical drugs; although these patients might represent a lower-risk group within the BSI population, their crude mortality was not negligible. Other variables associated with mortality in this population were similar to that described in all patients with BSI [2], including age, chronic comorbidities, acute severity of disease, and certain sources and aetiologies of BSI. Even when the effects of these predictors were considered, the odds of mortality increased per day of delay in providing active therapy.

Some studies have addressed the impact of delayed therapy in BSI beyond the typical time point in which susceptibility results are typically available using standard microbiological techniques (day 2). Lodise et al. [10] found that a delay of ≥5 days in receipt of appropriate antibiotic therapy was associated with lower probability of being discharged home in a large US database with 40,549 patients with BSI due to gram negative bacteria. Van Heuverswyn et al. [4] found an increased risk of death with delayed active therapy >12 hours which continued to increase at 72 hours (last time lag they studied) in a retrospective cohort including 10,628 patients with BSI in Sweden. These data and that in our study reinforce the importance of active interventions including unsolicited real-time specialized advice for the management of patients with BSI (so-called bacteraemia programmes), which allow earlier adjustment of antimicrobial therapy and may improve outcomes of patients with BSI [6,7].

Our study has limitations that must be considered when interpreting the results, including lack of assessment of non-antibiotic measures such as early source control and exclusion of patients with missing data on time until active treatment, and potential. Some strengths include the prospective inclusion of patients, the multicentre nature of the study and the quality monitoring of data.

We conclude that delayed administration of active targeted antibiotic treatment in patients is associated with a deleterious impact in the prognosis of patients; these results reinforce the importance of rapid reporting of blood culture results and of specialized advice in the management of BSI.

Declarations of competing interest

L.E.L.-C. has been scientific advisor for Angelini, speaker for Angelini, ViiV, Gilead, Menarini and Correvio, and has served as trainer for ViiV. J.R.-B. has received honoraria from Merck for accredited educational activities. The other authors report no conflicts of interest relevant to this article.

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Author contributions

All these authors contributed to the collection of data from the cohort cases.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2024.107072.

References

[1] Goto M, Al-Hasan MN. Overall burden of bloodstream infection and nosocomial bloodstream infection in North America and Europe. *Clin Microbiol Infect* 2013;**19**:501–9. doi:10.1111/1469-0691.12195.
[2] Retamar P, Portillo MM, López-Prieto MD, Rodríguez-López F, de Cueto M, García MV, et al. Impact of inadequate empirical therapy on the mortality of patients with bloodstream infections: a propensity score-based analysis. *Antimicrob Agents Chemother* 2012;**56**:472–8. doi:10.1128/AAC.00462-5.11.
[3] Ohnuma T, Chihara S, Costin B, Treggiari MM, Bartz RR, Raghunathan K, et al. Association of appropriate empirical antimicrobial therapy with in-hospital mortality in patients with bloodstream infections in the US. *JAMA Netw Open* 2023;**6**:e2249353. doi:10.1001/jamanetworkopen.
[4] Van Heuverswyn J, Valik JK, Desirée van der Werff S, Hedberg P, Giske C, Nauclér P. Association between time to appropriate antimicrobial treatment and 30-day mortality in patients with bloodstream infections: a retrospective cohort study. *Clin Infect Dis* 2023;**76**:469–78. doi:10.1093/cid/ciac727.
[5] Fidalgo B, Morata L, Cardozo C, Del Río A, Morales J, Fernández-Pittol M, et al. Information delay of significant bloodstream isolates and patient mortality: a retrospective analysis of 6,225 adult patients with bloodstream infection. *Clin Infect Dis* 2023;**77**(5):680–6. doi:10.1093/cid/ciad243.
[6] Minton J, Clayton J, Sandoe J, Mc Gann H, Wilcox M. Improving early management of bloodstream infection: a quality improvement project. *BMJ* 2008;**336**:440–3. doi:10.1136/bmj.39454.634502.80.
[7] Jiménez-Aguilar P, Romero-Palacios A, De-la-Calle IJ, Martínez-Rubio MC, Girón-González JA, Rodríguez-Baño J. Unsolicited consultation by Infectious diseases specialist improves outcomes in patients with bloodstream infection: a prospective cohort study. *J Infect* 2018;**77**:503–8. doi:10.1016/j.jinf.2018.08.014.
[8] Pérez-Crespo PMM, Lanz-García JF, Bravo-Ferrer J, Cantón-Bulnes ML, Sousa Domínguez A, Goikoetxea Aguirre J, et al. Revisiting the epidemiology of bloodstream infections and healthcare-associated episodes: results from a multicentre prospective cohort in Spain (PRO-BAC Study). *Int J Antimicrob Agents* 2021;**58**:106352. doi:10.1016/j.ijantimicag.2021.106352.
[9] von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol* 2008;**61**:344–9. doi:10.1016/j.jclinepi.2007.11.008.
[10] Lodise TP, Kanakamedala H, Hsu WC, Cai B. Impact of incremental delays in appropriate therapy on the outcomes of hospitalized adult patients with gram-negative bloodstream infections: “every day matters.”. *Pharmacotherapy* 2020;**40**:889–901. doi:10.1002/phar.2446.