Information delay of significant bloodstream isolates and patient mortality: A retrospective analysis of 6,225 adult patients with bloodstream infection

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Abstract

Objectives: The aim of this study was to evaluate the clinical and prognostic impact of communicating microbiological information in real time in adult patients with a bloodstream infection.

Methods. We have retrospectively reviewed 6,225 clinical episodes of bacteraemia in a 700-bed tertiary teaching hospital from January 2013 to December 2019. Bacteraemia-associated mortality was compared between periods where blood culture result was relayed to the infectious disease specialist [IDS] in real time and those periods where information was delayed to the following morning. An adjusted logistic regression analysis was used to evaluate the impact of information availability using mortality at 30 days as the main outcome of the study.

Results: The initial analysis (all microorganisms included) did not show an association of mortality and information delay to the IDS (OR 1.18; 95%CI: 0.99-1.42). However, information delay of BSI caused by fast-growing microorganisms (like *Enterobacteriaceae*) was associated with a significant increase in the odds of death at 30 days both in the univariate (OR 1.76; 95%CI: 1.30-2.38) and in the multivariate analysis (OR 2.22; 95%CI: 1.50-3.30). Similar results were found with mortality at 14 days and at 7 days in the univariate analysis (OR: 1.54; 95%CI:1.08-2.20 and OR.1.56; 95%CI: 1.03-2.37, respectively) and the multivariate analysis (OR: 2.05; 95%CI:1.27-3.32 and OR:1.92; 95%CI:1.09-3.40, respectively).

Conclusions: Information delivered in real time has prognostic relevance and it is likely to improve survival of patients with documented bloodstream infection. Future studies should address the prognostic impact of adequate resource allocation (microbiologist/IDS with 24/7 coverage) in bloodstream infections.

INTRODUCTION

Bloodstream infections (BSIs) remain a major clinical challenge with a high morbidity worldwide with estimated overall mortality rates ranging from 15% to 30% [1]. Rapid identification of BSI and prompt administration of effective treatment have a major impact in clinical outcome, particularly in those patients presenting with features of clinical severity [2]. In this context, a major emphasis has been placed on the development and implementation of rapid diagnostic tools [3], as subsequent development of sepsis has major prognostic implications [4]. The clinical impact of discordant empirical antibiotic therapy has been recently reported indicating an increased number of deaths in patients with BSI particularly for fast-growing bacteria like *Enterobacteriaceae* [5]. A less explored area in the management of BSIs is the time elapsed from blood culture positivity to patient re-assessment once actionable microbiological information becomes available to the infectious diseases specialist (IDS).

In this context, we have hypothesised that the mortality at 30 days of BSIs may be affected by the availability of resources to relay the information about a positive blood culture in real time to the IDS. In this study, we have analysed 6,225 cases of BSI prospectively collected from 2013 to 2019 and compared the clinical outcome when microbiological information is provided in real-time and when the information is delayed by 8 hours or more.

METHODS

Study design. This study was designed as an observational retrospective analysis of all episodes of bacteraemia diagnosed from January 2013 to December 2019 consecutively admitted at the Hospital Clínic in Barcelona (Spain), a 700-bed tertiary university hospital with a catchment area of 550,000 inhabitants. In this hospital, a dedicated team of infectious diseases physicians and clinical microbiologists operate in a 24/7 schedule to identify and prospectively follow up all patients with bacteraemia until discharge, death or 30 days after the diagnosis is made, whichever occurs first. For each patient, a comprehensive case-report form including demographic, clinical, biochemical, microbiological, and antimicrobial treatment variables was filled out and registered in a well-curated database.

For all blood cultures that became positive during daytime working hours (8:00 am to 1:59pm from 2013 to 2015 and 8:00 am to 7:59pm from 2016 to 2019), the microorganism was identified and reported to the IDS immediately, typically within one hour (time elapsed from positivity to MALDI-TOF MS identification). However, if the blood culture became positive during the night-time period (2:00 pm to 7:59 am from 2013 to 2015 and 8:00pm to 7:59am from 2016 to 2019), the identification and information was postponed until the next morning. This routine activity was followed from Monday to Sunday every day of the year. For this study, day-time positivity corresponds to real-time information (RTI) and night-time positivity to delayed information (DI).

Clinical data. The following data were obtained at the time of the diagnosis of the bloodstream infection for all patients included in the study and prospectively recorded in a purpose-built dataset: age, sex, previous admissions, days of admission, admission to intensive care unit (ICU), type of visit/admission (community or hospital/home hospitalization), catheter carrier,

dialysis catheter carrier, pre-existing comorbidities, source of infection and drainage of source (if appropriate), renal failure (RF), mechanic ventilation and presence of an indwelling urinary catheter. Data regarding the administration of immunosuppressive therapy (20 mg of daily prednisone or equivalent), surgery or other non-surgical invasive procedures and cardiac arrest were collected. Active empirical antibiotic therapy was defined as a treatment started within the first 24 h of the initial blood cultures, having *in vitro* activity against the bacteria isolated. The presence of the following clinical factors when the blood cultures were drawn was also documented: persistent bacteraemia, sodium (Na), potassium (K) and creatinine levels, C-reactive protein (CRP), drainage of the source of infection, neutropenia, disseminated intravascular coagulation (DIC), acute respiratory distress syndrome (ARDS), septic shock and presence of septic metastases. Persistent bacteraemia was defined as the presence of positive blood cultures after initiation of active antibiotic therapy. The main outcome variable was mortality at 30 days. Secondary analyses included mortality at 14 days and at 7 days.

Microbiological methods: Between 2013 and 2019, blood samples were processed using the Bactec FX system (Becton-Dickinson Microbiology System, NJ; USA) and typically incubated routinely for 5 days. Typically, for *Enterobacteriaceae* the time elapsed between the arrival of blood culture bottles to the laboratory and information reporting was less than 12 hours. All positive blood cultures were Gram-stained and immediately identified by matrix-assisted laser desorption– ionization time of flight (MALDI-TOF) mass spectrometry (Bruker, Bremen, Germany) using the bacterial pellet from a double centrifugation protocol[6,7]. Susceptibility testing was performed by BD Phoenix automated system (BD Diagnostic; Sparks, MD) and antibiotic susceptibility was determined according to the recommendations of EUCAST guidelines available at the time of diagnosis [8].

The time of sample arrival to the laboratory is registered by barcode scanning of clinical laboratory requests and logged into a laboratory information system (LIS). Similarly, the date and time of positivity and time from incubation to a positive/negative result is registered by the blood culture system and automatically exported to our LIS. The microorganism identified in culture, the antimicrobial susceptibility pattern, and the time at which the blood culture became positive (day or night) were subsequently added or calculated from the database (time of positivity) for the purpose of this study. Prior to 2016, positive blood cultures were not actively reported to the IDS from 2:00 pm until the morning after (8am).

Statistical analysis

Continuous data are described by the mean and the standard deviation (SD) or the median and corresponding interquartile range (IQR), as appropriate. Categorical data are expressed as numbers and percentages. We used t-test for comparison of quantitative normally distributed variables, and Mann-Whitney test for non-normally distributed variables. Comparison of categorical variables was conducted using $\chi 2$ test or Fisher's exact test.

The primary endpoint of the study was to 30-day mortality. A univariate logistic regression analysis was performed to explore factors associated with 30-day mortality. Multivariate logistic regression (MLR) was used to estimate the odds of the associations between information availability and death adjusted for potential confounders. MLR models were selected using a best subset regression approach. Variables were eliminated if exclusion of the variable: i) did not change the coefficient of information availability when modelling death (p of likelihood ratio test [LRT] < 0.01) and did not change the coefficients of other covariates when modelling information availability; ii) did not change the c-statistic (also known as Harrell's C) by more than 0.01 units; and iii) did not reduce the Akaike and Bayesian Information Criteria (AIC and BIC). The C-statistic corresponds to the area under the receiver

operating characteristic curve (AUC-ROC) of the predictions of the model and is a measure of model calibration[9–12]. Statistical analysis was performed using Stata, version 16 (Texas, USA).

Ethics approval

The study was approved by the Ethical Research Committee of the Hospital Clínic of Barcelona (HCB/2022/0597), Spain.

RESULTS

Study population

A total of 6,225 bacteraemia episodes were included in the study. The main characteristics of the study population and the risk factors associated with mortality at 30 days are detailed in Table 1. Of 6,225 patients, 625 (10%) died at 30 days. Of the 6,225 BSI analysed, 2,130(34.2%) became positive during daytime working hours and 4,095 (65.8%) during night-time working hours (not reported to the IDS in real time) (see supplementary sTable1). Blood cultures that become positive overnight were reported to the IDS the following morning. There were not statistically significant differences between the two groups of patients compared, namely those with daytime (real-time information) and that night-time (delayed information) blood culture positivity. Only mild differences were observed in the following clinical variables: sex, prior hospital admissions, catheter carrier, administration of immunosuppressive therapy, persistent bacteremia presence of respiratory disease. These differences were unlikely to indicate a population bias in subsequent comparisons of the two groups.

Delayed information and prognosis of BSI

Of the 625 deaths documented at 30 days, 193 (30.8%) corresponded to blood cultures that became positive during daytime working hours (8:00am-7:59pm) and 432(69.2%) during night-time hours (*P* value >0.05). Empirical antibiotic treatment was appropriate in 4,661 out of 6,015 patients (77.4%). The initial analysis showed a modest effect of delayed information on 30-day mortality (OR:1.18; 95%CI: 0.99-1.42) but this association was not significant (P=0.06). However, we reasoned that the impact on clinical outcome of fast-growing microorganisms (e.g, *Enterobacteriaceae*) was likely to be more noticeable than that for slower-growing bacteria (see supplementary sFigure 1 and sTable2). Indeed, when the same analysis was stratified by fast-growing microorganisms (*Enterobacteriaceae* in general) delayed information was associated with death (See Table 2).

Expectedly, other clinical features, which could have confounded the association, were also associated with a poor outcome of the bacteraemia episode (see Table 3). However, in the multivariate analysis, delayed response remained significantly associated with death (OR: 2.22; 95%CI: 1.50-3.30) after adjusting for potential confounders (see Table 4) in a highly informative model (c-statistic: 0.84, see supplementary sFigure2)

The same analysis was repeated using mortality at 14 days and at 7 days as the dependent variable. This analysis showed the same significant trends in the univariate (OR: 1.54; 95%CI:1.08-2.20 and OR.1.56; 95%CI: 1.03-2.37 respectively) and the multivariate analysis (OR: 2.05; 95%CI:1.27-3.32 and OR:1.92; 95%CI:1.08-3.40 respectively) when the analysis was performed for BSI caused by *Enterobacteriaceae* (see supplementary sTable 3 and sTable4).

Of note, the overall mortality decreased from 2016 onwards. We reasoned that decreased mortality could have been attributed to changes in management over time; however, the

differences between the two groups (real-time/delayed) over time did not disappear (see supplementary sTable 5).

In addition, other pre-analytical variables that could have incurred substantial diagnostic delays were considered. The time elapsed between blood culture practice and when the time when the blood cultures cultures arrive to the microbiology laboratory was also analysed. These data were available for 6,221 records and the median (IQR) time elapsed was 1.63 (0.88-2.98) hours. We did not find any association between this parameter and 30-day mortality in BSI (OR:0.99; 95%CI: 0.98-1.00, P=0.10) or in BSI associated with *Enterobacteriaceae* (OR:0.99; 95%CI: 0.98-1.00, P=0.45).

DISCUSSION

Early identification of significant bacterial isolates is of paramount importance to effectively manage patients with BSI [13,14]. This study suggests that relaying clinically relevant microbiological information of blood culture isolates in real time, particularly in rapidly growing bacteria (eg., *Enterobacteriaceae*), may impact clinical outcome.

Several clinical studies have consistently identified rapid reporting of microbiological findings as key parameter for patient management[15,16]. The advent and implementation of novel and faster molecular methods for microorganism identification and/or susceptibility testing, from high-throughput mass spectrometry identification [17] to low-throughput lateral flow assays [18] have revolutionised clinical microbiology markedly reducing turn-around times from days to hours [13,19,20].

However, rapid turn-around times do not necessarily imply that the information produced by the microbiology laboratory is readily available to the clinician, or even when available, it is not warranted that appropriate action is taken by the clinician. Despite of this parameter being of critical importance [21,22] for resource allocation, namely 24/7 microbiology or IDS coverage, information relay has been rarely explored (if at all) as a prognostic factor.

Our study provides a novel insight into this topic. Indeed, although the global analysis for bacteraemia and real-time information showed a non-statistically significant association with 30-day mortality, the stratified analysis for *Enterobacteriaceae* revealed significant prognostic differences both in the unadjusted and adjusted models. However, this study was not designed to understand the prognostic factors of BSI caused by *Enterobacteriaceae*. Indeed, most of the prognostic features identified are clinically plausible and have been reported previously[23–25]. The aim of this research was to ascertain that the differences between information delay and death was not explained by known confounders.

Due to observational nature of the study, our results do not provide a mechanistic insight that explains how real-time information leads to improved clinical management and hence, reduced mortality. A priori, most confounders for this association are accounted for, namely appropriate empirical antibiotic, drainage of source of infection, infection of catheter. Two major factors support the hypothesis that real-time may affect outcome. Firstly, the fact that the association of delayed information with death in the adjusted model increases as the endpoint gets closer to the admission date (i.e. mortality at 30, 14 and 7 days). Secondly, the association is found only for bacteria with rapid growth, like *Enterobacteriaceae*.

This study has limitations. This was a single-centre study conducted at a 700-bed teaching hospital that primarily manages complex patients. It is therefore expected that the demographics may not readily translate to all hospitals. Secondly, our hospital during the study period had a microbiologist and ID specialist 24h a day 7 days a week, which based on the results obtained may underestimate the clinical impact as many health services in our country have no ID or microbiology coverage during weekends. Moreover, the time taken for samples to arrive to the microbiology laboratory and to the automated culture system has been shown to be of importance [26], but we could not find this association when we formally examined the time elapsed.

The descriptive nature of the study cannot conclusively attribute mortality to the delay in communication of clinically relevant results. However, we would cautiously speculate that lack of specialist coverage may affect the prognosis of BSI. Indeed, if future studies conducted in comparable clinical settings (but with lower specialist coverage) corroborate this association, the need for a 24/7 hospital coverage for a clinical microbiologist and/or an ID specialist should be revisited in view of the important prognostic implications.

REFERENCES

[1] Hattori H, Maeda M, Nagatomo Y, Takuma T, Niki Y, Naito Y, et al. Epidemiology and risk factors for mortality in bloodstream infections: A single-center retrospective study in Japan. Am J Infect Control 2018;46:e75–9. https://doi.org/10.1016/j.ajic.2018.06.019.

[2] Leibovici L, Shraga I, Drucker M, Konigsberger H, Samra Z, Pitlik SD. The benefit of appropriate empirical antibiotic treatment in patients with bloodstream infection. J Intern Med 1998;244:379–86. https://doi.org/10.1046/J.1365-2796.1998.00379.X.

[3] Lamy B, Sundqvist M, Idelevich EA. Narrative review Bloodstream infections e Standard and progress in pathogen diagnostics. Clinical Microbiology and Infection 2020;26:142–50. https://doi.org/10.1016/j.cmi.2019.11.017.

[4] Singer M, Deutschman CS, Seymour C, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315:801. https://doi.org/10.1001/JAMA.2016.0287.

[5] Kadri SS, Lai YL, Warner S, Strich JR, Babiker A, Ricotta EE, et al. Inappropriate empirical antibiotic therapy for bloodstream infections based on discordant in-vitro susceptibilities: a retrospective cohort analysis of prevalence, predictors, and mortality risk in US hospitals. Lancet Infect Dis 2021;21:241–51. https://doi.org/10.1016/S1473-3099(20)30477-1.

[6] Bassi MA, Lopez MA, Confalone L, Gaudio RM, Lombardo L, Lauritano D. Enhanced Reader.pdf. Nature 2020;388:539–47.

[7] Zengin Canalp H, Bayraktar B. Direct Rapid Identification from Positive Blood Cultures by MALDI-TOF MS: Specific Focus on Turnaround Times. Microbiol Spectr 2021;9. https://doi.org/10.1128/spectrum.01103-21.

[8] EUCAST clinical MIC breakpoints n.d. https://www.eucast.org/clinical_breakpoints/.

[9] Altman DG, Bland JM. Education and debate: Statistics Notes: Interaction revisited : the difference between two estimates. Bmj 2003;326:219.

[10] Hosmer D LS. Assessing the Fit of the Model. In: Applied Logistic Regression. John Wiley & Sons, Ltd; 2005.

[11] Rowe AK, Kleinbaum DG, Koplan JP. Practical methods for public health practitioners. Am J Prev Med 2004;26:252–3. https://doi.org/10.1016/j.amepre.2003.12.002.

[12] Harrell F. RegressionModeling Strategies: With Applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis. 2nd ed. Springer International Publishing; 2015. https://doi.org/DOI:10.1007/978-3-319-19425-7.

[13] Giacobbe DR, Giani T, Bassetti M, Marchese A, Viscoli C, Rossolini GM. Rapid microbiological tests for bloodstream infections due to multidrug resistant Gram-negative bacteria: therapeutic implications. Clinical Microbiology and Infection 2020;26:713–22. https://doi.org/10.1016/j.cmi.2019.09.023.

[14] Surviving Sepsis Campaign International Guidelines for Management of Sepsis and Septic Shock 2016 Enhanced Reader.pdf n.d.
[15] Lamy B, Sundqvist M, Idelevich EA. Bloodstream infections – Standard and progress in pathogen diagnostics. Clinical Microbiology and Infection 2020;26:142–50. https://doi.org/10.1016/j.cmi.2019.11.017.
[16] Ehren K, Meißner A, Jazmati N, Wille J, Jung N, Vehreschild JJ, et al. Clinical Impact of Rapid Species Identification From Positive Blood Cultures With Same-day Phenotypic Antimicrobial Susceptibility Testing on the Management and Outcome of Bloodstream Infections. Clin Infect Dis 2020;70:1285–93. https://doi.org/10.1093/CID/CIZ406.
[17] Idelevich EA, Schüle I, Grünastel B, Wüllenweber J, Peters G, Becker K. Rapid identification of microorganisms from positive blood cultures by MALDI-TOF mass spectrometry subsequent to very short-term incubation on solid medium. Clinical Microbiology and Infection 2014;20:1001–6. https://doi.org/10.1111/1469-0691.12640.
[18] Aguirre-Quiñonero A, Martínez-Martínez L. Non-molecular detection of carbapenemases in Enterobacteriaceae clinical isolates. Journal of Infection and Chemotherapy 2017;23:1–11. https://doi.org/10.1016/j.jiac.2016.09.008.
[19] Banerjee R, Komarow L, Virk A, Rajapakse N, Schuetz AN, Dylla B, et al. Randomized Trial Evaluating Clinical Impact of RAPid IDentification and Susceptibility Testing for Gram-negative Bacteremia: RAPIDS-GN. Clinical Infectious Diseases 2021;73:E39–46. https://doi.org/10.1093/cid/ciaa528.
[20] Barenfanger J, Drake C, Kacich G. Clinical and financial benefits of rapid bacterial identification and antimicrobial susceptibility testing. J Clin Microbiol 1999;37:1415–8. https://doi.org/10.1128/jcm.37.5.1415-1418.1999.
[21] Yamada K, Kuwabara G, Imoto W, Yamairi K, Shibata W, Oshima K, et al. Blood culture reports by infectious disease physicians can improve prognosis of bacteremia, including weekend-onset cases. International Journal of Infectious Diseases 2020;100:174–9. https://doi.org/10.1016/j.ijid.2020.08.013.
[22] Byl B, Clevenbergh P, Jacobs F, Struelens MJ, Zech F, Kentos A, et al. Impact of Infectious Diseases Specialists and Microbiological Data on the Appropriateness of Antimicrobial Therapy for Bacteremia. Clinical Infectious Diseases 1999;29:60–6.
[23] F Deulofeu, B Cervelló, S Capell, C Martí VM. Predictors of mortality in patients with bacteremia: the importance of functional status. J Am Geriatr Soc n.d.;46. https://doi.org/10.1111/j.1532-5415.1998.tb01007.x.
[24] Uzun Ö, Erdal Akalin H, Hayran M, Ünal S. Factors influencing prognosis in bacteremia due to gram-negative organisms: Evaluation of 448 episodes in a turkish university hospital. Clinical Infectious Diseases 1992;15:866–73. https://doi.org/10.1093/clind/15.5.866.
[25] Wang F der, Chen YY, Chen TL, Liu CY. Risk factors and mortality in patients with nosocomial Staphylococcus aureus bacteremia. Am J Infect Control 2008;36:118–22. https://doi.org/10.1016/j.ajic.2007.02.005.
[26] Péan de Ponfilly G, Benmansour H, Manda V, Lecorche E, Mougari F, Munier AL, et al. Impact of 24/7 loading of blood culture bottles in a new automated incubator on the diagnosis of bloodstream infections.

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Table 1: Characteristics of patients in the study population

	All patients		Real-time information		Delayed information		P-value
		N		N		N	
Age, median (Q1, Q3)	67 (55, 77)	6225	66 (55, 77)	2130	67 (55, 77)	4095	0.58
Sex, N (%), female	2428 (39.00)	6225	792 (37.18)	2130	1636 (39.95)	4095	0.03
Prior hospital admissions (previous month), N (%)	1966 (31.84)	6175	707 (33.47)	2112	1259 (30.73)	4096	0.05
Hospital-acquired bacteraemia*, N (%)	4039 (64.88)	6225	1363 (64)	2130	2676 (65.3)	4095	0.36
Days of admission, median (Q1, Q3)	1 (0, 12)	5954	1 (0, 11)	2036	1 (0, 12)	3918	0.26
Intubation / mechanical ventilation, N (%)	290 (4.68)	6203	92 (4.33)	2120	198 (4.84)	4083	0.37
Urinary catheter, N (%)	1380 (22.50)	6132	471 (22.41)	2101	909 (22.55)	4031	0.91
Fever, N (%)	5433 (88.40)	6143	1868 (88.78)	2104	3565(88.26)	4039	0.55
DIC, N (%)	102 (1.68)	6054	32 (1.55)	2065	70 (1.75)	3989	0.56
ARDS, N (%)	174 (2.82)	6164	61 (2.90)	2102	113 (2.78)	4062	0.79
Catheter, N (%)	3080 (49.72)	6195	1014 (47.9)	2117	2066 (50.66)	4078	0.04
Neutropenia, N (%)	511 (8.33)	6136	186 (8.89)	2094	325 (8.04)	4042	0.26
Corticosteroids, N (%)	1385 (22.45)	6165	437 (20.73)	2108	948 (23.36)	4057	0.02
Chronic renal failure, N (%)	1558 (25.95)	6005	525 (25.51)	2058	1033 (26.17)	3947	0.58
ICU, N (%)	708 (12.57)	5632	247 (12.97)	1904	461 (12.36)	3728	0.52
Persistent bacteraemia, N (%)	536 (8.83)	6070	161 (7.75)	2076	375 (9.39)	3994	0.03
C-Reactive Protein, median (Q1, Q3)	13.53 (6.99,22.15)	5728	12.91 (6.8, 21.9)	1954	13.93 (7.07, 22.32)	3774	0.06
Serum Sodium, median (Q1, Q3)	138 (135, 140)	6068	138 (135, 140)	2073	138 (135, 140)	3995	0.12
Serum Potassium, median (Q1, Q3)	3.9 (3.6, 4.4)	5959	3.9 (3.6, 4.4)	2046	3.9 (3.6, 4.4)	3913	0.72
Creatinine, median (Q1, Q3)	1.07 (0.76, 1.71)	6071	1.05 (0.75, 1.67)	3997	1.08 (0.77, 1.73)	2074	0.22
Shock, N (%)	1006 (16.27)	6182	334 (15.81)	2112	672 (16.51)	4070	0.48
Drainage of source, N (%)	1576 (26.74)	5893	564 (27.93)	2019	1012 (26.12)	3874	0.14
Metastasis, N (%)	187 (3.14)	5950	62 (3.08)	2015	125 (3.18)	3935	0.84
Surgery, N (%)	1118 (18.31)	6107	375 (17.97)	2087	743 (18.48)	4020	0.62
Medical manipulation, N (%)	1148 (18.85)	6088	402 (19.33)	2080	746 (18.61)	4008	0.50
Appropriate empirical antibiotic treatment, N (%)	4661 (77.49)	6015	1591 (77.57)	2051	3070 (77.44)	3964	0.91
Source of infection							0.14
Unknown	1264 (20.31)	6225	448 (21.03)	2130	816 (19.93)	4095	
Abdominal	1239 (19.86)	6225	446 (20.94)	2130	793 (19.36)	4095	
Catheter	1156 (18.57)	6225	362 (17)	2130	794 (19.38)	4095	
Gynaecological	49 (0.79)	6225	13 (0.75)	2130	36 (0.87)	4095	
Urinary tract	1486 (23.87)	6225	503 (23.62)	2130	983 (24)	4095	

Iatrogenic	86 (1.38)	6225	26 (1.22)	2130	60 (1.46)	4095	
Cutaneous	223 (3.58)	6225	73 (3.43)	2130	150 (3.66)	4095	
Pulmonary	389 (6.24)	6225	149 (6.99)	2130	240 (5.86)	4095	
Others	326 (5.24)	6225	110 (5.16)	2130	223 (5.44)	4095	
Comorbidities							
HIV	174 (2.80)	6225	55 (2.58)	2130	119 (2.91)	4095	0.46
Cardiovascular disease	2549 (40.95)	6225	826 (38.8)	2130	1723 (42.10)	4095	0.01
Abdominal disease	1111 (17.85)	6225	398 (18.7)	2130	713 (17.4)	4095	0.21
Gastrointestinal disease	293 (4.71)	6225	98 (4.60)	2130	195 (4.76)	4095	0.78
Cutaneous disease	39 (0.63)	6225	11 (5.16)	2130	28 (6.84)	4095	0.43
Genitourinary disease	1184 (19.02)	6225	386 (18.12)	2130	798 (19.5)	4095	0.20
Diabetes	1361 (21.86)	6225	449 (21.1)	2130	912 (22.3)	4095	0.28
Respiratory disease	561 (9.01)	6225	220 (10.33)	2130	341 (8.33)	4095	*0.09*
Haematological malignancy	2750 (44.21)	6225	980 (46)	2130	1770 (43.22)	4095	0.04
Solid organ transplant	865 (13.89)	6225	298 (14)	2130	567 (13.8)	4095	0.88
Autoimmune disease	115 (1.85)	6225	39 (1.83)	2130	76 (1.85)	4095	0.95
Osteoarticular disease	296 (4.76)	6225	108 (5.1)	2130	188 (4.59)	4095	0.40
Other conditions	554 (8.90)	6225	204 (9.6)	2130	350 (8.55)	4095	

DIC: Disseminated intravascular coagulation**;** ARDS**:** acute respiratory distress syndrome**.** Persistent bacteraemia was defined as the presence of positive blood cultures after initiation of active antibiotic therapy. ***** Includes hospital-acquired infection and day-hospital.

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Table 2: Univariate analysis between information availability of blood culture positivity and 30-day mortality

Bacteraemia aetiology	Dead/Alive	Real-time information Dead/Alive	Delayed Information Dead/Alive	OR	(95% CI)	P-value
All	625/5600	193/1937	432/3663	1.18	(0.99, 1.42)	0.06
Enterobacteriaceae	262/2867	58/957	204/1910	1.76	(1.30, 2.38)	0.00
Pseudomonas aeruginosa	65/466	21/156	44/310	1.05	(0.61, 1.83)	0.85
Staphylococcus aureus	72/430	21/137	51/293	1.14	(0.66, 1.96)	0.65
Enterococcus (E.faecalis* and *E.faecium)	94/625	32/231	62/394	1.14	(0.72, 1.79)	0.58

Table 3: Univariate analysis between characteristics of patients with bloodstream infections by *Enterobacteriaceae* and 30-day mortality

	N	(Alive/death)	OR	(95% CI)	P-value
Delayed information	3,129	(2867/262)	1.76	(1.30, 2.38)	0.00
Age (years) q5	3,129	(2867/262)	1.23	(1.13, 1.40)	0.00
Sex (female)	3,129	(2867/262)	0.93	(0.72, 1.21)	0.61
Prior hospital admissions (previous month)	3,114	(2853/261)	1.28	(0.98, 1.66)	0.07
Hospital-acquired bacteraemia	3,129	(2867/262)	1.72	(1.31, 2.26)	0.00
Days of admission	2,996	(2741/255)	0.97	(0.95, 0.98)	0.00
Intubation or mechanical ventilation	3,124	(2862/262)	1.78	(0.96, 3.33)	0.07
Urinary catheter	3,090	(2831/259)	0.95	(0.69, 1.31)	0.77
Fever	3,096	(2837/259)	0.26	(0.19, 0.35)	0.00
Catheter	3,114	(2854/260)	1.06	(0.81, 1.36)	0.69
Neutropenia	3,087	(2828/259)	2.92	(1.96, 4.32)	0.00
Corticosteroids	3,103	(2842/261)	1.60	(1.20, 2.13)	0.00
Chronic renal failure	3,030	(2780/250)	3.23	(2.49, 4.21)	0.00
UCI	2,829	(2595/234)	1.58	(1.07, 2.34)	0.02
Persistent bacteraemia	3,053	(2803/250)	2.40	(1.46, 3.95)	0.00
PCR	2,922	(2681/241)	1.02	(1.01, 1.04)	0.00
Serum sodium	3,058	(2808/250)	0.98	(0.96, 1.01)	0.27
Serum potassium	3,006	(2764/242)	1.43	(1.19, 1.72)	0.00
Creatinine	3,057	(2806/251)	1.23	(1.13, 1.33)	0.00
Shock	3,113	(2855/258)	6.01	(4.61, 7.83)	0.00
Bilirrubin	2,398	(2182/216	1.07	(1.04, 1.09)	0.00
DIC	3,044	(2787/257)	8.60	(4.88, 15.15)	0.00
ARDS	3,103	(2843/260)	11.73	(7.20, 19.11)	0.00
Drainage of source	2,971	(2728/243)	0.38	(0.26, 0.57)	0.00
Metastasis	2,982	(2739/243)	2.03	(0.78, 5.32)	0.00
Surgery	3,068	(2811/257)	0.37	(0.23, 0.60)	0.00
Medical manipulation	3,058	(2801/257)	0.64	(0.44, 0.93)	0.02
Appropriate empirical antibiotic treatment	3,030	(2809/221)	0.84	(0.58, 1.21)	0.35
Source of infection					
Urinary tract (reference)	1,270	(1211/59)			
Abdominal	847	(780/67)	2.35	(1.67, 3.31)	0.00
Catheter	314	(297/17)	1.17	(0.67, 2.04)	0.57
Gynecological	17	(17/0)	1		
Unknown	468	(402/66)	3.37	(2.33, 4.87)	0.00
Iatrogenic	54	(54/0)	1		
Cutaneous	61	(53/8)	3.10	(1.41, 6.81)	0.01
Pulmonary	77	(53/24)	9.29	(5.37, 16.09)	0.00

Others	21	(20/1)	1.03	(0.14, 7.78)	0.98
Comorbidities					
HIV	3,129	(2867/262)	1.08	(0.49, 2.37)	0.85
Cardiovascular disease	3,129	(2867/262)	0.74	(0.57, 0.97)	0.03
Abdominal disease	3,129	(2867/262)	1.75	(1.31, 2.33)	0.00
Gastrointestinal disease	3,129	(2867/262)	0.78	(0.39, 1.54)	0.47
Cutaneous disease	3,129	(2867/262)	1		
Genitourinary disease	3,129	(2867/262)	0.89	(0.65, 1.23)	0.48
Diabetes	3,129	(2867/262)	0.85	(0.62, 1.16)	0.31
Respiratory disease	3,129	(2867/262)	1.30	(0.86, 1.96)	0.22
Haematological malignancy	3,129	(2867/262)	2.50	(1.92, 3.26)	0.00
Transplanted	3,129	(2867/262)	0.50	(0.31, 0.82)	0.01
Autoimmune disease	3,129	(2867/262)	0.22	(0.03, 1.57)	0.13
Neurological disease	3,129	(2867/262)	1.70	(1.08, 2.66)	0.02
Osteoarticular disease	3,129	(2867/262)	0.33	(0.12, 0.91)	0.03
Other Conditions	3,129	(2867/262)	1.38	(0.87, 2.20)	0.17
Microbiological features					
Antibiotic resistance					
No resistance (reference)	2,447	(2234/213)			
ESBL	500	(462/38)	0.86	(0.60, 1.24)	0.42
Cefamicinase/AmpC	103	(98/5)	0.54	(0.22, 1.33)	0.18
Multirresistant	79	(73/6)	0.86	(0.37, 2.01)	0.73
Time to blood culture positivity (hours)	3,129	(2867/262)	0.99	(0.97, 1.00)	0.11

Table 4: Multivariate analysis of informative predictors of 30-day mortality in patients with bacteraemia caused by *Enterobacteriaceae.*

	OR (N = 2,609)	(95% CI)	P-value
Delayed information	2.22	(1.50, 3.30)	<0.001
Shock	5.20	(3.61, 7.51)	<0.001
Disseminated intravascular coagulation	4.08	(1.88, 8.83)	<0.001
Source of infection (reference: UTI)			
Abdominal	4.17	(2.70, 6.47)	<0.001
Catheter	2.44	(1.22, 4.90)	0.012
Gynecological	1		
Unknown	3.83	(2.40, 6.11)	<0.001
Iatrogenic	1		
Cutaneous	4.04	(1.43, 11.42)	0.008
Pulmonary	6.85	(3.12, 15.00)	<0.001
Other sources	1		<0.001
Drainage of source of infection	0.24	(0.14, 0.39)	<0.001
Persistent bacteraemia	2.73	(1.41, 5.30)	0.003
Potassium	1.37	(1.10, 1.71)	0.005
Acute renal failure	1.92	(1.33, 2.77)	<0.001
Haematological malignancy	2.44	(1.75, 3.42)	<0.001
Age (5 quantiles), years	1.28	(1.13, 1.45)	<0.001

OR: odds ratio; CI: confidence interval: C-statistic: 0.84; UTI**:** urinary tract infection

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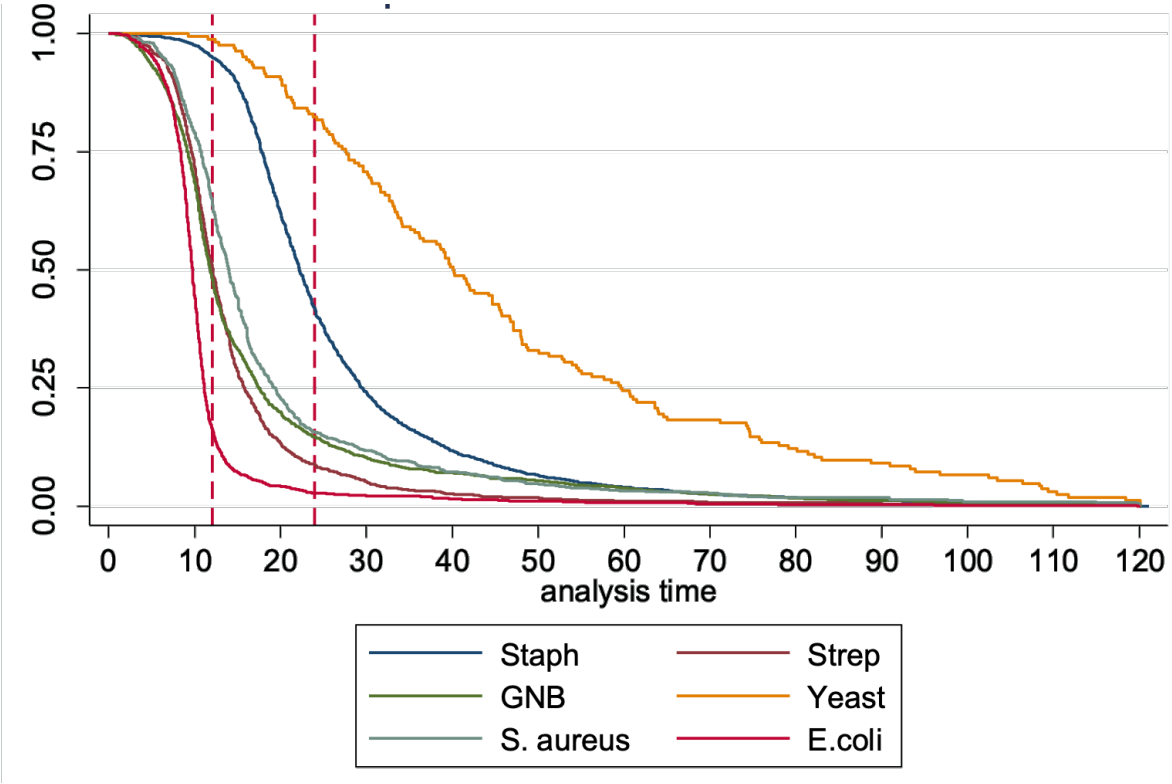
SUPPLEMENTARY MATERIAL

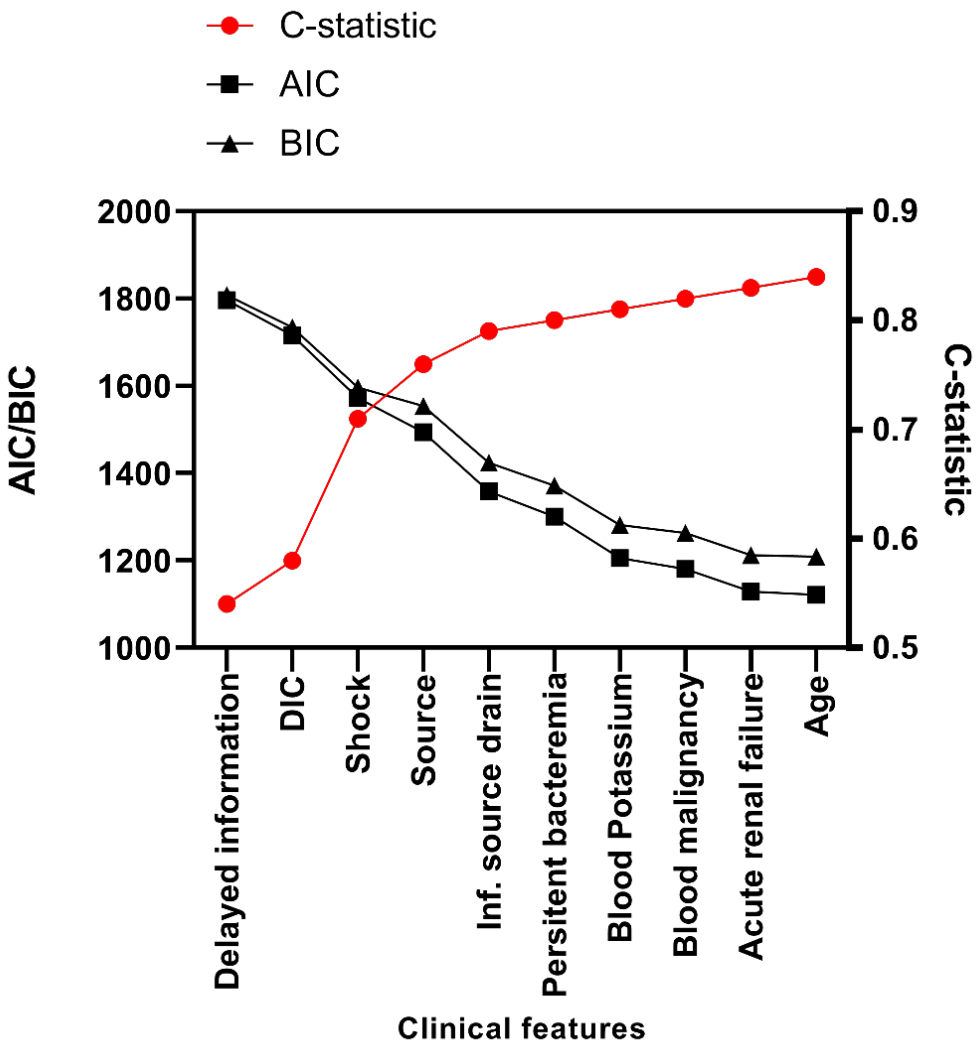
Information delay of significant bloodstream isolates and patient mortality: A retrospective analysis of 6,225 adult patients with bloodstream infection

Berta Fidalgo[1], Laura Morata [3,4], Celia Cardozo [3,4], Ana del Río [3,4], Javier Morales [1], Mariana Fernández-Pittol[1], José Antonio Martínez[3,4,5], Josep Mensa [3,4], Jordi Vila [1,2,5], Alex Soriano [3,4,5], Climent Casals-Pascual[1,2,5]

sFigure 1. Time to positivity (in hours) of the most frequently isolated microorganisms using an automated blood culture system. Staph: includes *S. aureus* and other Staphylococci; GNB: Gram-negative bacteria (including *E.coli*); Strep: includes all significant bacteraemia caused by Streptococci. Vertical dotted lines represent: 12h and 24h.



sFigure2. Explanatory model for the introduction of clinical features significantly associated with 30-day mortality. C-statistic (Harrel's C) is equivalent to the area under the curve for the model. AIC: Akaike's information criterion; BIC: Bayesian information criterion.



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476 **sTable 1. Microorganisms causing BSI in the population described.**
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Microorganisms	All patients N/Total	Real-time information N/Total	Delayed information N/Total	P-value
Escherichia coli	1808/6225	593/2130	1215/4095	0.13
***Klebsiella* spp**	849/6225	260/2130	589/3611	0.02
Staphylococcus aureus	487/6225	158/2130	344/3611	0.18
***Enterococcus* spp**	719/6225	263/2130	456/3611	0.16
Pseudomonas aeruginosa	531/6225	177/2130	354/3611	0.65
Other *Enterobacteriaceae*	609/6225	201/2130	408/3611	0.51
Other Gram Negative bacteria (no enterobacteriaceae)	156/6225	74/2130	82/3611	0.00
Other Gram Positive cocci (no *Staphylococcus aureus,* no *Enterococcus* spp)	1126/6225	410/2130	716/3611	0.09
***Candida* spp**	212/6225	64/2130	148/3611	0.21
Polymicrobial*	530/6225	159/2130	371/3611	0.03

478 *Polymicrobial bacteraemia: *E.coli +Enterococcus spp* (52/530; 9.8%); *E.coli+*
479 *Klebsiella spp* (47/530; 8,9%); *Klebsiella spp+ Enterococcus spp* (40/530; 7.5%),
480 other (391/530; 73,7%).
481
482

sTable 2. Time-to-positivity and clinical outcome.

Bacteraemia aetiology	**N**	***Time to positivity (all episodes) median (q1,q3)**	**N**	**Time to positivity (death episodes) median (q1,q3)**	**N**	**Time to positivity (alive episodes) median (q1,q3)**	**§P-value**
All	6225	11.3(8.9, 16)	625	11.4 (8.3, 16.7)	5600	11.3 (9, 15.9)	0.27
Enterobacteriaceae	3129	9.8 (8.1, 11.6)	262	8.9 (6.9, 10.8)	2867	9.9 (8.2, 11.7)	0.00
Escherichia coli	1808	9.6 (8.1, 11.2)	148	8.4 (6.2, 10.2)	1660	9.7 (8.2, 11.2)	0.00
Klebsiella pneumoniae complex	781	9.7 (7.7, 11.5)	73	8.8 (6.9, 10.9)	708	9.8 (7.8, 11.6)	0.06
Pseudomonas aeruginosa	531	14.8 (11.2, 17.8)	65	14.9 (12.3, 17.3)	466	14.7 (11, 17.9)	0.75
Staphylococcus aureus	502	12.4 (9.5, 15.8)	72	11.7 (8.2, 14.8)	430	12.5 (9.6, 15.9)	0.23
***Enterococcus spp* (*E.faecalis* and *E.faecium*)**	719	12.1 (9.4, 14.9)	94	12.5 (10.1, 15.2)	625	12.1 (9.3, 14.8)	0.37

*All blood cultures where incubated for 120 hours or until positivity. Time to positivity was calculated from the time elapsed between the blood culture bottle was introduced into the automatic system until the first bottle became positive. § P values were calculated using the Mann-Whitney test.

sTable 3: Multivariate analysis of informative predictors of 14-day mortality in patients with bacteraemia caused by *Enterobacteriaceae.*

	OR (N = 2,609)	(95% CI)	P-value
Delayed information	2.05	(1.27, 3.32)	0.00
Shock	6.84	(4.40, 10.63)	0.00
Disseminated intravascular coagulation	4.29	(1.89, 9.72)	0.00
Source of infection (reference: UTI)			
Abdominal	3.59	(2.16, 5.99)	0.00
Catheter	0.81	(0.23, 2.87)	0.743
Gynecological	1		
Unknown	2.84	(1.64, 4.90)	0.00
Iatrogenic	1		
Cutaneous	2.24	(0.52, 8.87)	0.29
Pulmonary	4.75	(1.95, 11.57)	0.00
Other sources	1		
Drainage of source of infection	0.11	(0.05, 0.24)	0.00
Persistent bacteraemia	1.14	(0.40,3.34)	0.80
Potassium	1.33	(1.03, 1.71)	0.03
Acute renal failure	2.00	(1.28, 3.12)	0.00
Haematological malignancy	2.58	(1.70, 3.92)	0.00
Age (5 quantiles), years	1.38	(1.18, 1.62)	0.00

OR: odds ratio; CI: confidence interval; UTI**:** urinary tract infection

sTable 4: Multivariate analysis of informative predictors of 7-day mortality in patients with bacteraemia caused by *Enterobacteriaceae.*

	OR (N = 2,609)	(95% CI)	P-value
Delayed information	1.92	(1.09, 3.40)	0.02
Shock	11.28	(6.53, 19.47)	0.00
Disseminated intravascular coagulation	5.13	(2.20, 11.98)	0.00
Source of infection (reference: UTI)			
Abdominal	3..07	(1.68, 5.63)	0.00
Catheter	0.90	(0.19, 4.20)	0.90
Gynecological	1		
Unknown	2.94	(1.55, 5.57)	0.00
Iatrogenic	1		
Cutaneous	1.50	(0.24, 9.40)	0.67
Pulmonary	2.78	(0.94, 8.22)	0.07
Other sources	1		
Drainage of source of infection	0.11	(0.05, 0.28)	0.00
Persistent bacteraemia	0.85	(0.23,3.22)	0.82
Potassium	1.51	(1.13, 2.02)	0.01
Acute renal failure	2.03	(1.18, 3.48)	0.00
Haematological malignancy	2.16	(1.32, 3.53)	0.00
Age (5 quantiles), years	1.44	(1.19, 1.74)	0.00

OR: odds ratio; CI: confidence interval; UTI**:** urinary tract infection

552 **sTable 5: Evolution of mortality (Enterobacteriaceae) from 2013 to 2019**
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		2013 (%)	2014 (%)	2015 (%)	2016 (%)	2017 (%)	2018 (%)	2019 (%)
Real time information	Death	6/112 (5.4)	6/111 (5.4)	5/93 (5.4)	15/200 (7.5)	11/168 (6.5)	9/167 (5.4)	6/164 (3.7)
	Alive	106/112 (94.6)	105/111 (94.5)	88/93 (94.6)	185/200 (92.5)	157/168 (93.5)	158/167 (94.6)	158/164 (96.3)
Delayed information	Death	37/333 (11.1)	37/351 (10.5)	33/355 (9.2)	25/314 (8)	21/268 (7.8)	24/232 (10.3)	27/261 (10.3)
	Alive	296/333 (88.9)	314/351 (89.5)	256/282 (90.8)	289/314 (92)	247/268 (92.2)	208/232 (89.7)	234/261 (89.7)
Overall mortality		**43/445 (9.7)**	**43/462 (9.3)**	**38/448 (8.5)**	**40/514 (7.8)**	**32/436 (7.3)**	**33/399 (8.3)**	**33/425 (7.8)**