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# **Epidemiology and outcomes of hospital-acquired bloodstream infections in intensive care unit patients: the EUROBACT-2 international cohort study**

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The members of the EUROBACT-2 study group are listed in the Acknowledgement section of the manuscript.

# Abstract

## Purpose:

In the critically ill, hospital-acquired bloodstream infections (HA-BSI) are associated with significant mortality. Granular data are required for optimizing management, and developing guidelines and clinical trials.

## Methods:

We carried out a prospective international cohort study of adult patients ( $\geq 18$  years of age) with HA-BSI treated in intensive care units (ICUs) between June 2019 and February 2021.

## Results:

2600 patients from 333 ICUs in 52 countries were included. 78% HA-BSI were ICU-acquired. Median Sequential Organ Failure Assessment (SOFA) score was 8 [IQR 5; 11] at HA-BSI diagnosis. Most frequent sources of infection included pneumonia (26.7%) and intravascular catheters (26.4%). Most frequent pathogens were Gram-negative bacteria (59.0%), predominantly *Klebsiella* spp. (27.9%), *Acinetobacter* spp. (20.3%), *Escherichia coli* (15.8%), and *Pseudomonas* spp. (14.3%). Carbapenem resistance was present in 37.8%, 84.6%, 7.4%, and 33.2%, respectively. Difficult-to-treat resistance (DTR) was present in 23.5% and pan-drug resistance in 1.5%. Antimicrobial therapy was deemed adequate within 24 h for 51.5%. Antimicrobial resistance was associated with longer delays to adequate antimicrobial therapy. Source control was needed in 52.5% but not achieved in 18.2%. Mortality was 37.1%, and only 16.1% had been discharged alive from hospital by day-28.

## Conclusions:

HA-BSI was frequently caused by Gram-negative, carbapenem-resistant and DTR pathogens. Antimicrobial resistance led to delays in adequate antimicrobial therapy. Mortality was high, and at day-28 only a minority of the patients were discharged alive from the hospital. Prevention of antimicrobial resistance and focusing on adequate antimicrobial therapy and source control are important to optimize patient management and outcomes.

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## Introduction

Hospital-acquired bloodstream infections (HA-BSI) are the healthcare-associated infection causing the highest burden in disability-adjusted life years [1]. They are relatively frequent in intensive care unit (ICU) patients and are associated with 36–42% mortality [2–5]. In 2012, the EURO-BACT-1 international cohort study highlighted the prevalence of multidrug resistant organisms and its association with higher risk of death in ICU patients with HABS.

In recent years, worrisome increases in antimicrobial resistance have been highlighted by agencies and scientific societies worldwide [6–8]. Indeed, antimicrobial resistance is associated with delays to adequate antimicrobial therapy, increased mortality, resource utilization and costs [2, 9, 10]. It leads to considerable increases in the use of broad-spectrum antimicrobials which in turn exacerbates the problem by selecting antimicrobial resistant micro-organisms. Given the frequency of sepsis, septic shock, and the high mortality in ICU patients with HA-BSI, large international studies are essential to identify potentially modifiable factors of poor prognosis. These data may inform patient care, the development of guidelines, and the design of clinical trials.

The EUROBACT-2 study was designed to update the epidemiology and main factors associated with day-28 mortality in ICU patients with HA-BSI by prospectively collecting granular center, patient, pathogen, treatment, and outcome data from ICUs worldwide.

## Methods

### Study design

EUROBACT-2 was a prospective international cohort study, registered with ClinicalTrials.org (NCT03937245) and reported in accordance with the STrengthening the Reporting of OBServational studies in Epidemiology (STROBE) guidelines [11]. The study was conducted across the first year of the pandemic caused by coronavirus disease 2019 (COVID-19). We reported the differences in the epidemiology of HABSIS in patients with COVID-19 separately [12]. Initial ethical approval as a low-risk research project with waiver of individual consent was granted by the Human Research Ethics Committee of the Royal Brisbane & Women's Hospital, Queensland, Australia (LNR/2019/ QRBW/48376). Each study site then obtained ethical and governance approvals according to national and/or local regulations.

### Setting

Endorsement, financial, and logistical support were obtained from the European Society of Intensive Care Medicine (ESICM) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) study Group for Infections in Critically Ill Patients (ESGCIP). The operational committee (AT, NB, FB, SR, QS, CD, JFT) oversaw study operations under the responsibility of the primary investigator (AT). Logistics were provided by the OUTCOMEREA non-profit research group (Paris, France). National coordinators recruited participating ICUs, applied for ethical and regulatory approvals, and facilitated communication within their country.

### Participants

We included adult ( $\geq 18$  years of age) patients with a HABSIS treated in the ICU. HA-BSI was defined as a positive blood culture sampled more than 48 h after hospital admission. Treatment in the ICU was defined as the blood culture having been either sampled in the ICU or the patient having been transferred to the ICU for the treatment of the HA-BSI. Detailed definitions are available in the electronic supplemental material (ESM).

For usually considered as common contaminants (list provided in the ESM), at least 2 blood cultures with the same antimicrobial susceptibility profile, or strong clinical grounds that it was not a contaminant (e.g., intravascular catheters or other infected material proven as a source for the HA-BSI) were mandatory. All possible contaminants were carefully reviewed for eligibility by the operational committee in collaboration with the local investigators and excluded if the above criteria were not met.

## **Data collection**

Centers prospectively recruited patients between the 1<sup>st</sup> of June 2019 and the 30th of January 2021, with a minimum of 10 consecutive patients or for a 3-month period, which on request could be extended. Hospital and ICU characteristics were recorded. Patient data were retrieved from the hospital charts without additional tests or interventions. Demographic data, the main diagnosis at ICU admission, and comorbidities were collected. Geographical regions and income categories were defined using the United Nations M49 standard [13]. Severity of illness was assessed at ICU admission by the Simplified Acute Physiology Score II (SAPS II) [14], and at HA-BSI diagnosis by the Sequential Organ Failure Assessment (SOFA) score [15]. Given all included patients had an infection, sepsis was defined at HA-BSI diagnosis according to Sepsis III criteria by a SOFA score  $\geq 2$ , and septic shock as sepsis plus v soproressor use plus lactate  $> 2$  mmol/L [16]. We focused on each patient's first episode of HA-BSI, collected pathogen with antibiogram, date and time of blood culture sampling and followed patients for 28 days, until hospital discharge, or death. Blood culture sampling represented the time zero of the study from which all timings were calculated (e.g., time to adequate antimicrobial therapy). Sources of HA-BSI were recorded in order of clinical likelihood according to the treating clinician. Primary HA-BSI was defined as no clear portal of entry or source of infection. Antimicrobials were collected from 2 days prior to HA-BSI to ICU discharge or day-28 follow-up. Carbapenem resistance for Enterobacterales was defined as resistance to at least one carbapenem [17]. Difficult-to-treat resistance (DTR) was defined as resistance to all first line antimicrobials [18], and pan-drugresistance (PDR) as resistance to all tested antimicrobials. To avoid over-reporting DTR and PDR for pathogens with incompletely reported antibiograms, the assessment required availability of antimicrobial susceptibility testing for at least one fluoroquinolone, one cephalosporin, one carbapenem, plus polymyxins for PDR. DTR and PDR were assessed for Enterobacterales, *Pseudomonas* spp., and *Acinetobacter* spp. Adequate antimicrobial therapy was defined as receiving at least 1 antimicrobial with invitro activity for the pathogen at the considered timepoint, with adequacy of antimicrobial selection, dosing and administration manually reviewed for all infections and sources of HA-BSI. Time to adequate antimicrobial therapy was defined as the time between sampling of the first positive blood culture and receipt of at least one adequate antibiotic for each pathogen. Source control was reported according to the source and intervention, with adequacy assessed by the investigator.

## **Statistical analysis**

As detailed in the ESM, and to ensure consistency, database lock was made on the 12/08/2021 after answering of all queries by the investigators, crosschecking with electronic controls, and careful reading of all the case-report forms by the operational committee.

**Table 1 Characteristics of participating ICUs and association with day-28 (D28) patient mortality**

Characteristics*	All ICUs (n = 333)*	All patients (n = 2600)	Dead on D28 (n = 966)	Alive on D28 (n = 1634)	OR [95% CI]	p value
<b>Geographic region</b>						0.824
Europe and Central Asia	184 (55.3)	1775 (68.3)	689 (71.3)	1086 (66.5)	1	
East Asia and Pacific	69 (20.7)	412 (15.8)	127 (13.1)	285 (17.4)	0.83 [0.54; 1.27]	
Middle East and North Africa	48 (14.4)	268 (10.3)	91 (9.4)	177 (10.8)	0.96 [0.61; 1.54]	
South Asia	14 (4.2)	54 (2.1)	24 (2.5)	30 (1.8)	1.29 [0.52; 3.2]	
Latin America and the Caribbean	11 (3.3)	52 (2)	17 (1.8)	35 (2.1)	0.78 [0.33; 1.85]	
Sub-Saharan Africa	5 (1.5)	20 (0.8)	6 (0.6)	8 (0.5)	1.7 [0.55; 5.21]	
North America	2 (0.6)	19 (0.7)	8 (0.8)	11 (0.7)	1.34 [0.34; 5.31]	
<b>National income</b>						0.145
High-income	202 (60.7)	1479 (56.9)	485 (50.2)	994 (60.8)	1	
Upper-middle-income	80 (24)	870 (33.5)	393 (40.7)	477 (29.2)	1.42 [0.99; 2.04]	
Low and lower-middle-income**	51 (14.1)	251 (9.2)	88 (9.1)	163 (10)	1.11 [0.72; 1.72]	
<b>Academic status of the hospital</b>						
Teaching hospital	270 (82.6)	2207 (85.4)	823 (85.4)	1384 (85.4)	1	0.122
Non-teaching hospital	57 (17.4)	378 (14.6)	141 (14.6)	237 (14.6)	1.28 [0.94; 1.76]	
<b>Type of ICU</b>						
Mixed (medical-surgical)	260 (79.5)	2040 (78.9)	732 (75.9)	1308 (80.7)	1	0.048
Medical	41 (12.5)	383 (14.8)	180 (18.7)	203 (12.5)	1.49 [1.07; 2.09]	
Surgical	26 (8)	162 (6.3)	52 (5.4)	110 (6.8)	0.9 [0.57; 1.43]	
<b>Number of ventilator equivalent beds in the ICU <math>\geq</math> 15</b>						0.081
176 (53.82)	1464 (56.63)	499 (51.8)	965 (59.5)	0.81 [0.65; 1.03]		
<b>Nurse to ventilator-bed ratio</b>						0.106
2 [1.3; 2.9]	2.2 [1.6; 2.8]	2.2 [1.6; 2.8]	2.2 [1.5; 2.9]	0.99 [0.97; 1]		
<b>Senior doctor to ventilator-bed ratio</b>						0.213
6.7 [4.3; 10]	6 [4; 9.5]	6 [4; 9]	6.3 [4.3; 9.5]	0.99 [0.97; 1.01]		
<b>Senior medical cover is available 24/7</b>						0.319
304 (93.3)	2355 (91.5)	869 (90.3)	1486 (92.1)	0.81 [0.53; 1.23]		
<b>General surgery is available 24/7</b>						0.637
321 (98.2)	2556 (98.9)	951 (98.7)	1605 (99)	0.8 [0.31; 2.05]		
<b>Infectious diseases specialist or clinical microbiologist are consulted</b>						
<b>24/7</b>						0.57
170 (54.8)	1479 (60)	566 (60.9)	913 (59.4)	1		
<b>During business hours</b>						
114 (36.8)	855 (34.7)	313 (33.7)	542 (35.3)	1.06 [0.82; 1.38]		
<b>Never or sporadically</b>						
26 (8.4)	131 (5.3)	50 (5.4)	81 (5.3)	1.29 [0.8; 2.09]		
<b>Clinical pharmacists are consulted</b>						
<b>24/7</b>						0.007
82 (25.5)	636 (25.1)	188 (19.9)	448 (28.2)	1		
<b>During business hours</b>						
129 (40.1)	811 (32)	284 (30.1)	527 (33.2)	1.32 [0.99; 1.78]		
<b>Never or sporadically</b>						
111 (34.5)	1084 (42.8)	471 (49.9)	613 (38.6)	1.64 [1.21; 2.24]		
<b>TDM of aminoglycosides is available</b>						
<b>Everyday</b>						0.002
171 (52.5)	1249 (48.5)	383 (39.8)	866 (53.7)	1		
<b>At least once a week</b>						
30 (9.2)	213 (8.3)	81 (8.4)	132 (8.2)	1.32 [0.88; 1.98]		



**Table 1 (continued)**

Characteristics*	All ICUs (n = 333)*	All patients (n = 2600)	Dead on D28 (n = 966)	Allive on D28 (n = 1634)	OR [95% CI]	p value
Not available	125 (38.3)	1113 (43.2)	498 (51.8)	615 (38.1)	1.6 [1.23; 2.09]	
<b>TDM of vancomycin is available</b>						
Everyday	200 (61.3)	1419 (55.1)	462 (48)	957 (59.3)	1	0.012
At least once a week	43 (13.2)	319 (12.4)	120 (12.5)	199 (12.3)	1.07 [0.74; 1.53]	
Not available	83 (25.5)	837 (32.5)	380 (39.5)	457 (28.3)	1.55 [1.15; 2.07]	
<b>TDM of <math>\beta</math>-lactams is available</b>						
Everyday	35 (10.7)	256 (9.9)	87 (9)	169 (10.5)	1	0.255
At least once a week	51 (15.6)	408 (15.8)	117 (12.2)	291 (18)	0.81 [0.52; 1.27]	
Not available	240 (73.6)	1911 (74.2)	758 (78.8)	1153 (71.5)	1.1 [0.75; 1.62]	

Full report of center characteristics is available in ESM eTable 3. Results reported as n (%) for categorical variables and median [IQR] for continuous variables

\*All center data were missing for 6 ICUs and 7–12 did not provide staffing or stewardship data

\*\*There were 4 ICUs and 11 patients in the low-income category, 24/7: 24 h a day, 7 days a week. ICU: intensive care unit. TDM: therapeutic drug monitoring. Ventilator equivalent beds refers to the maximum number of ventilated patients the ICU can accommodate at one time

Linearity to the logit for continuous variables was checked with generalized additive models. Non-linear variables were discretised into categorical variables based on quartiles. Continuous variables were expressed as medians (interquartile range [IQR]) and categorical variables as absolute frequencies and percentage. Differences were tested by the Wilcoxon rank-sum test for continuous variables and Fisher's exact test for categorical variables.

To identify factors associated with day-28 death, we built a three-tiered hierarchical logistic mixed model and a subdistribution hazard frailty model that considered ICU discharge as a competing risk, as suggested by Fine and Gray [19]. Both are presented in the ESM as exploratory analyses, alongside sensitivity analysis excluding COVID-19 patients and investigating the role of carbapenem resistance in place of DTR. All analyses were two sided with *p* values less than 0.05 deemed statistically significant. Statistical analysis was done using SAS 9.4 statistical software (SAS Institute Inc., Cary, NC, USA) and R project version 4.04.

## Results

### Study population

We enrolled 2600 patients from 333 ICUs in 52 countries or territories (ESM eFigures 1–2, Table 1 and eTables 2–3). Most ICUs were in public (83.8%), teaching (82.6%) hospitals, with a mixed medical-surgical (79.5%) and general case mix (91.7%). Median [IQR] ICU size was 14 [10; 21] ventilator-equivalent beds with wide variability in infrastructure and factors related to antimicrobial stewardship.

ICUs recruited a median [IQR] of 6 [3, 10] patients. Most patients were males (63.7%), median [IQR] age was 64 [52;73] years, and 74.8% had at least one comorbidity (Table 2 and eTable 2). Most common ICU admission diagnoses were non-COVID-19-related respiratory failure (21.2%), sepsis or septic shock (20.4%), and COVID- 19 (12.9%).

Median [IQR] time from hospital admission to HABSI was 13 [8;25] days. Most HA-BSI (78.5%) were ICU acquired (median [IQR] time from ICU admission to diagnosis, 10 [5; 18] days). The median [IQR] SOFA score was 8 [5; 11] at HA-BSI diagnosis, with 4% of the patients not meeting the criteria for sepsis, while 64.2% and 31.7% met the criteria for sepsis and septic shock, respectively (Table 3).

Sources of infection were predominantly respiratory (pneumonia) (26.7%) and intravascular catheters (26.4%), followed by the abdomen (15.1%). While primary HA-BSI were common (16.3%), one third of the patients (32.8%) had more than one possible source of HA-BSI.

### **Pathogens**

Most (88.8%) blood cultures were mono-microbial, with 10% containing two, and 1.2% more than two pathogens, resulting in a total of 2927 bacterial and fungal isolates. Pathogens were most commonly Gram-negative (1726/2927; 59%), with a predominance of *Klebsiella* spp. (482/1726; 27.9%), *Acinetobacter* spp. (350/1726; 20.3%), *Escherichia coli* (272/1726; 15.8%) and *Pseudomonas* spp. (247/1726; 14.3%) (Table 4 and ESM eFigure 3).

Carbapenem resistance was encountered in 37.8% (182/482) *Klebsiella* spp., 84.6% (296/350) *Acinetobacter* spp., 7.4% (20/272) *Escherichia coli* and 33.2% (82/247) *Pseudomonas* spp. When analysing Enterobacterales, *Pseudomonas* spp. and *Acinetobacter* spp., DTR was present in 23.5% (351/1492) and PDR in 1.5% (23/1492). Gram-positive pathogens (910/2972; 31.1%) were mainly *Enterococcus* spp. (314/910, 34.5%) and coagulase-negative staphylococci (273/910, 30%). Of the 27.6% (251/910) *Staphylococcus aureus*, 37.1% (93/251) were methicillin- resistant *Staphylococcus aureus* (MRSA). There were 2.1% (61/2927) strict anaerobe bacteria, and 7.9% (230/2927) fungi of which 39.6% (91/230) were *Candida albicans*, 57.8% (133/230) non-albicans *Candida* spp., and 6 (2.6%) other fungi.

### **Antimicrobial therapy and source control**

Adequate antimicrobial therapy was received by 51.5% within 24 h of blood culture sampling. As shown in Fig. 1, time to adequate antimicrobial therapy increased with antimicrobial resistance ( $p < 0.0001$ ). The 3 antimicrobials most frequently administered in the 24 h following HA-BSI diagnosis included meropenem 463/2600 (17.8%), piperacillin/tazobactam 380/2600 (14.6%), and vancomycin 266/2600 (10.2%). They were deemed adequate in 275/463 (59.4%), 244/380 (64.2%), and 132/266 (49.6%) prescriptions, respectively. Source control was deemed to be required for 52.5% of the patients and was effectively achieved in 81.8% of these, after a median of 24.5 [IQR 1;72] hours.

## **Mortality**

By day-28, 966 (37.1%) patients had died, 91% in the ICU and 9% after ICU discharge. Death was preceded by a decision to withhold or withdraw life-sustaining treatment for 268 (27.7%). At that time point, 38.7% of the survivors were still in the ICU, 35.7% had been discharged from the ICU, and 25.6% had been discharged from the hospital, which represents 16.1% of the total cohort.

Multiple factors were associated with day-28 mortality in the univariable analysis (Tables 1, 2, 3). At center level these included medical ICUs, lower availability of clinical pharmacists and of therapeutic drug monitoring (TDM) for aminoglycosides or vancomycin. Mortality was higher in patients with co-morbidities, medical and COVID-19 admissions, and those with higher severity of illness, including requirements for organ supportive therapy. Higher mortality was found in early ICU-acquired HA-BSI, respiratory sources, DTR Gram-negative bacteria or fungus, and patients who did not receive adequate antimicrobials or for whom source control was required but not achieved. There was no statistically significant association between time to adequate antimicrobial therapy and day-28 mortality.

Factors associated with death in the multivariable hierarchical logistic model and with an increased subdistribution hazard ratio (sHR) of death at day-28 in a competitive risk model are shown in eTable 5. In summary, factors that were statistically significant in both models included infrequent clinical pharmacist consultation, older age, severity of illness at HA-BSI, DTR Gram negative bacteria, and not achieving source control for patients who required an intervention. Conversely, achieving source control was protective in both analyses.

## **Discussion**

EUROBACT-2 provides an update on the epidemiology and prognostic factors of HA-BSI in the ICU by including 2600 patients from 333 ICUs in 5 continents. We report substantial day-28 mortality, especially in HA-BSI caused by DTR pathogens, patients with septic shock, and those who never received adequate antibiotics or source control. There was a broad range of sources of infection and pathogens. Gram-negative bacteria were frequently carbapenem resistant or DTR. Antibiotic resistance was associated with longer delays to adequate antibiotics. Center data showed important variability of service availability including for the variables related to antimicrobial stewardship.

To our knowledge, the EUROBACT-2 study represents the largest international study of HA-BSI s in ICU patients. Few large international studies have investigated this population, which limits possibilities for direct comparisons with our data. We conducted the EUROBACT- 1 study in 2010, with a similar methodology but a smaller group of ICUs [2]. The EPIC III point prevalence study investigated the prevalence and outcomes of ICU patients with infections in 2017 and was not limited to hospital-acquired or bloodstream infections [3]. As shown in Table 4, the two EUROBACT studies showed a predominance of Gram-negative bacteria. In comparison, bloodstream pathogens from the EPIC III cohort showed a higher proportion of Gram-positive bacteria, with more Staphylococcus spp. but less Enterococcus spp. The European Centre for Disease Prevention and Control (ECDC) epidemiological report of hospital-acquired infections in the ICU, computed from 2017 data, showed a predominance of Gram-positive pathogens in HA-BSI. There were 23.6% coagulase-negative staphylococci and 14.9% Enterococcus spp., followed by 12.4% Klebsiella spp. [20]. While some of these differences may be explained by the

inclusion of community-acquired infections in EPIC III, the lower proportion coagulase-negative staphylococci in our study is probably secondary to the careful review of each case and discussion with the investigators, leading to the exclusion of all potential blood culture contaminants that did not meet the inclusion criteria. Between EUROBACT-1 and 2, the proportion of MRSA has decreased by 10%, and the proportion of vancomycin resistant *Enterococcus* (VRE) has remained stable. Interestingly, there has been an increase in the proportion of non-albicans *Candida* spp., which have now become dominant. Carbapenem resistance has substantially increased, especially for *Enterobacter* spp. and *Acinetobacter* spp., leading to a substantial proportion of DTR in Gram-negative pathogens, and up to 1.6% PDR for *Pseudomonas* spp. and 2.3% for *Acinetobacter* spp. In keeping with previous reports, and as shown in eTables 5 and 7, carbapenem resistance and DTR in Gram-negative bacteremia were associated with mortality, highlighting the importance of strategies aimed at preventing and treating infections caused by multidrug resistant pathogens [2, 18, 21, 22]. A detailed description of the of the pathogens causing HA-BSI in the COVID-19 population is reported separately [12].

Ten years after the first EUROBACT-2 study, we observed comparable delays to adequate antimicrobial therapy as around half of the patients received such within 24 h of blood culture sampling. Antimicrobial resistance was associated with delays. In the setting of widespread resistance to broad-spectrum antibiotics, molecular rapid diagnostic testing may be a key for earlier adequate antimicrobial treatment [23, 24]. That delays to adequate antimicrobial therapy were not associated with day-28 mortality may be subsequent to multiple confounders and should be interpreted with caution. Indeed, the relationship between time to antimicrobial therapy and mortality in observational research is complicated [25]. On the one hand, the clinical impression of severity may be a driver for earlier administration of broader spectrum antimicrobials to patients with an increased risk of death. Moreover, a non-negligible proportion of patients with sepsis may inexorably die, regardless of the antibiotic treatment. Others may have died before antibiogram results could be acted upon, eliminating an opportunity for antimicrobial adequacy. On the other hand, patients identified at lower risk may have been treated later, when positive microbiology was reported [26]. Another source of immortal-time bias may be present as some patients with HA-BSI may have never been diagnosed or included in the study. Some may have died before they could be transferred to the ICU, underestimating mortality, while others may have rapidly improved, before ICU admission, overestimating mortality of HA-BSI. These findings do not challenge the recommendation for early adequate antimicrobial therapy for patients with sepsis or septic shock [27]. Indeed, while we need to avoid antibiotic overuse and its associated harms [28], early adequate antimicrobial therapy is one of the most important interventions for HA-BSI [27].

How can these observations improve clinical practice? The exploratory analysis suggests a protective effect of source control and a possible detrimental effect of infrequent clinical pharmacist consultation. These highlight the importance of a multidisciplinary approach for managing critically ill patients with HA-BSI, and by extension, severe infections. Hospitals require integrated pathways, protocols, and educational programs targeting recognition, diagnosis, and treatment of sepsis, including prediction of antimicrobial resistance, antimicrobial prescription, and source control [27, 29, 30]. The optimisation of antimicrobial therapy in critically ill patients involves a multifaceted approach. Pharmacodynamic/pharmacokinetic optimisation and adequate exposure at the source of infection requires optimal dosing and delivery, considering potential interactions, modified volume of distribution, and decreased or augmented renal clearance [31]. Integrated antimicrobial stewardship programs may facilitate clinically relevant advice and recommendations for therapeutic drug monitoring, and a discussion on source control [6, 27, 32].

**Table 3 Patient characteristics at diagnosis of hospital-acquired bloodstream infection and day-28 mortality**

Characteristics	All patients (N = 2600)	Dead on D28 (n = 966)	Alive on D28 (n = 1634)	OR [95% CI]	p value
<b>Time from ICU admission to HA-BSI</b>					
Acquired prior to ICU admission	558 (21.5)	188 (19.5)	370 (22.6)	1.03 [0.82; 1.29]	0.017
Early ICU-acquired (≤7 days)	810 (31.2)	327 (33.9)	483 (29.6)	1.32 [1.08; 1.6]	
Late ICU-acquired (>7 days)	1232 (47.4)	451 (46.7)	781 (47.8)	1	
<b>Maximum temperature</b>					
< 38.2 °C	1412 (54.5)	588 (61.2)	824 (50.6)	1	< 0.001
≥ 38.2 °C	1179 (45.5)	373 (38.8)	806 (49.4)	0.72 [0.6; 0.86]	
<b>Sepsis or septic shock</b>					
No sepsis or sepsis without shock	1776 (68.5)	538 (55.9)	1238 (76)	1	< 0.001
Septic shock—no steroids	446 (17.2)	213 (22.1)	233 (14.3)	2.38 [1.89; 2.99]	
Septic shock—steroids administered	370 (14.3)	211 (21.9)	159 (9.8)	3.85 [2.98; 4.97]	
<b>SOFA score</b>	8 [5; 11]	10 [7; 13]	7 [5; 10]	1.21 [1.19; 1.24]	< 0.001
<b>Ventilation status</b>					
Low flow oxygen or no oxygen	493 (19)	104 (10.8)	389 (23.8)	1	< 0.001
High flow oxygen nasal canula	163 (6.3)	50 (5.2)	113 (6.9)	1.69 [1.11; 2.57]	
Non-invasive mechanical ventilation or CPAP	153 (5.9)	50 (5.2)	103 (6.3)	1.84 [1.2; 2.81]	
Invasive Mechanical Ventilation	1791 (68.9)	762 (78.9)	1029 (63)	2.81 [2.18; 3.61]	
<b>ECMO (VA or VV)</b>	41 (1.6)	21 (2.2)	20 (1.2)	1.92 [0.99; 3.72]	0.053
<b>Vasopressors (adrenaline or noradrenaline)</b>	1376 (52.9)	614 (63.6)	762 (46.6)	2.44 [2.04; 2.93]	< 0.001
<b>Vasopressin</b>	113 (4.3)	61 (6.3)	52 (3.2)	2.89 [1.89; 4.4]	< 0.001
<b>Gram-negative bacteria<sup>a</sup></b>	1623 (62.4)	608 (62.9)	1015 (62.1)	0.98 [0.82; 1.17]	0.823
DTR Gram-negative	350 (13.5)	185 (19.2)	165 (10.1)	1.71 [1.33; 2.21]	< 0.001
<b>Gram-positive bacteria<sup>a</sup></b>	859 (33)	312 (32.3)	547 (33.5)	0.98 [0.82; 1.17]	0.821
Resistant Gram-positive (MRSA, MRSE or VRE)	323 (12.4)	112 (11.6)	211 (12.9)	0.86 [0.66; 1.11]	0.248
<b>Fungus<sup>a</sup></b>	227 (8.7)	102 (10.6)	125 (7.6)	1.39 [1.04; 1.86]	0.026
<b>Strict anaerobe bacteria<sup>a</sup></b>	57 (2.2)	15 (1.6)	42 (2.6)	0.76 [0.41; 1.41]	0.382
<b>Polymicrobial blood culture</b>	290 (11.2)	106 (11)	184 (11.3)	1 [0.77; 1.32]	0.973
<b>Source of HA-BSI</b>					
Intravascular catheter	686 (26.4)	239 (24.7)	447 (27.4)	1	0.027
Intra-abdominal	392 (15.1)	145 (15)	247 (15.1)	1.33 [1; 1.76]	
Other	217 (8.3)	69 (7.1)	148 (9.1)	1.01 [0.71; 1.44]	
Primary	425 (16.3)	169 (17.5)	256 (15.7)	1.26 [0.96; 1.65]	
Respiratory	694 (26.7)	288 (29.8)	406 (24.8)	1.39 [1.09; 1.77]	
Urinary	186 (7.2)	56 (5.8)	130 (8)	0.9 [0.62; 1.3]	
More than 1 possible source of infection	853 (32.8)	322 (33.3)	531 (32.5)	1.14 [0.94; 1.37]	0.191
<b>Time to adequate antimicrobial therapy</b>					
≤ 24 h, n (%)	1339 (51.5)	463 (47.9)	876 (53.6)	1	< 0.001
[24;48] hours, n (%)	336 (12.9)	117 (12.1)	219 (13.4)	1.03 [0.79; 1.34]	
[48;120] hours, n (%)	396 (15.2)	134 (13.9)	262 (16)	0.96 [0.74; 1.23]	
> 120 h, n (%)	125 (4.8)	38 (3.9)	87 (5.3)	0.72 [0.47; 1.09]	
Never, n (%)	403 (15.5)	214 (22.2)	189 (11.6)	1.98 [1.55; 2.53]	
<b>Source control</b>					
Not required	1235 (47.5)	488 (50.5)	747 (45.7)	1	< 0.001
Required, achieved	1117 (43)	321 (33.2)	796 (48.7)	0.63 [0.52; 0.76]	
Required, but NOT achieved	248 (9.5)	157 (16.3)	91 (5.6)	2.6 [1.92; 3.51]	

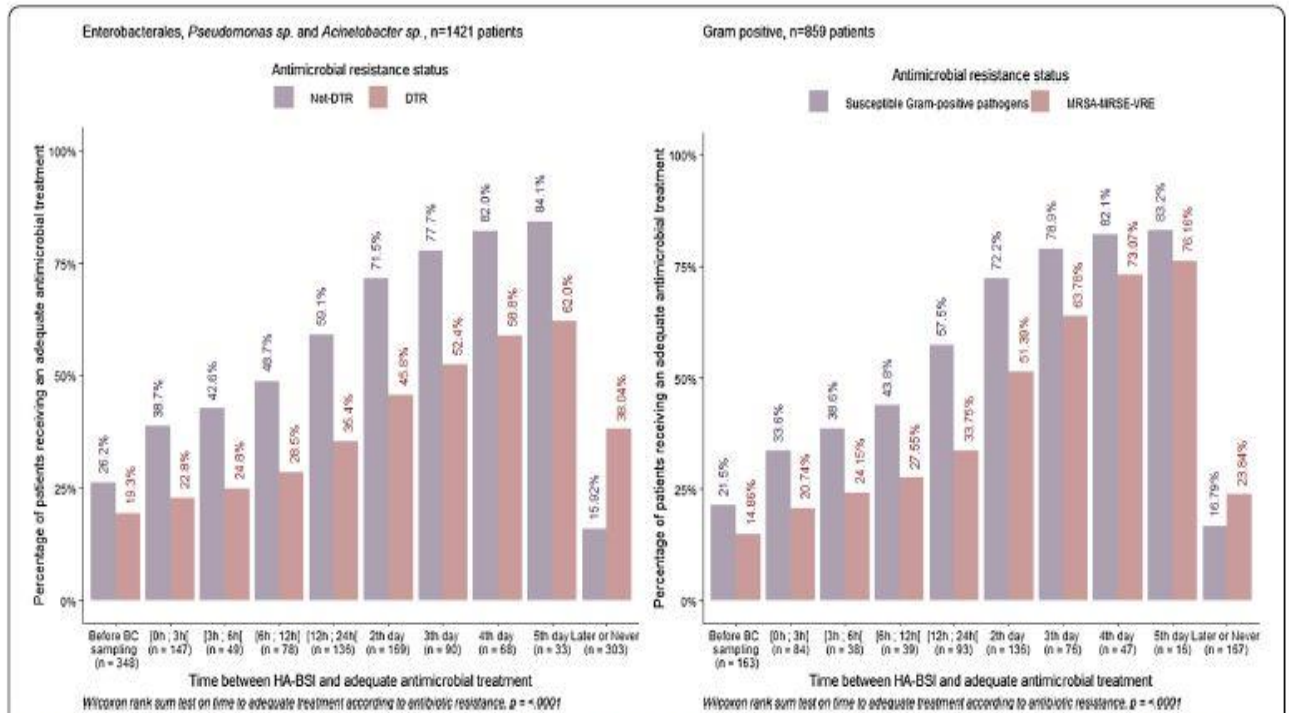
Continuous variables are presented as median [IQR] and categorical variables as n (%). Closed brackets [ ] denote inclusive of the end of the range and open brackets; [ denote the exclusion of the end of the range. HA-BSI: hospital-acquired blood stream infection, CPAP: continuous positive airway pressure ECMO: extra-corporeal membrane oxygenation, VA: venoarterial, VV: venovenous. DTR: Difficult to treat resistance MRSA: methicillin-resistant *Staphylococcus aureus*, MRSE: methicillin-resistant *Staphylococcus epidermidis* and includes all coagulase negative staphylococcus reported as non-susceptible to methicillin, VRE: vancomycin-resistant *Enterococcus*

<sup>a</sup> Sum of percentages exceed 100 because a patient may have had several pathogens in the blood culture, referring to the 11.2% polymicrobial blood cultures

**Table 4 Characteristics of the pathogens in the initial blood culture in EUROBACT-2 and comparison with EUROBACT-1 and EPIC III studies**

Pathogens	EUROBACT-2 n = 2927 (%)	EUROBACT-1 (n = 1317)*	EPIC III BSI (n = 1239)**
<b>Gram-negative bacteria</b>	1726 (59)	759 (57.6)	515 (44.6)
<i>Klebsiella</i> spp.	482 (27.9)	156 (20.1)	144 (28)
Carbapenem resistant	182 (37.8)	59 (37.8)	86 (59.7)
DTR*	133 (27.6)	.	.
PDR*	11 (2.3)	3 (1.9)	.
<i>Escherichia coli</i>	272 (15.8)	98(12.9)	116 (22.5)
Carbapenem resistant	20 (7.4)	1(1)	32 (27.6)
DTR*	9 (3.3)	.	.
PDR*	0 (0)	0(0)	.
<i>Enterobacter</i> spp.	141 (8.2)	88 (11.6)	.
Carbapenem resistant	31 (22)	5 (5.7)	.
DTR*	8 (5.7)	.	.
PDR*	0 (0)	0(0)	.
<i>Pseudomonas</i> spp.	247 (14.3)	150 (19.7)	67 (13)
Carbapenem resistant	82 (33.2)	56 (37.3)	10 (14.9)
DTR*	25 (10.1)	.	.
PDR*	4 (1.6)	0(0)	.
<i>Acinetobacter</i> spp.	350 (20.3)	160 (21.1)	68 (13.2)
Carbapenem resistant	296 (84.6)	110 (68.7)	53 (77.9)
DTR*	176 (50.3)	.	.
PDR*	8 (2.3)	1 (0.6)	.
<b>Other Gram-negative bacteria</b>	234 (13.6)	107 (14.1)	177 (34.4)
Carbapenem resistant	24 (12.5)	.	.
<b>Gram-positive bacteria</b>	910 (31.1)	440 (33.4)	494 (42.7)
<i>Enterococcus</i> spp.	314 (34.5)	144 (32.7)	58 (11.7)
<i>Enterococcus faecium</i>	156 (49.7)	70 (48.6)	.
VRE	37 (23.7)	16 (22.9)	.
<i>Coagulase-negative Staphylococcus</i>	273 (30)	141(32)	182 (36.8)
MRSE	200 (73.3)	.	73 (40.1)
<i>Staphylococcus aureus</i>	251 (27.6)	119 (27)	180 (36.4)
MRSA	93 (37.1)	57 (47.9)	54 (30)
Other Gram-positive bacteria	72 (7.9)	36 (8.2)	40 (8.1)
<b>Strict anaerobe bacteria</b>	61 (2.1)	20 (1.5)	19 (1.6)
Bacteroides	29 (47.5)	.	.
Other anaerobes	32 (52.5)	.	.
<b>Fungi</b>	230 (7.9)	98 (7.4)	126 (10.9)
<i>Candida albicans</i>	91 (39.6)	56 (57.1)	71 (56.3)
<i>Candida non-albicans</i> spp.	133 (57.8)	39 (39.8)	53 (42.1)
Other fungi	6 (2.6)	.	4 (3.2)

Percentages shown for the relevant pathogen or category. \*denotes unavailable or not comparable data. MRSA and MRSE denotes the % of *Staphylococcus aureus* and *Coagulase negative Staphylococcus* resistant to methicillin, VRE the % of enterococcus faecium resistant to vancomycin. Carbapenem resistant is defined as at least one carbapenem has been tested and the isolate is resistant to all the carbapenems that have been tested. DTR: Difficult to treat resistance. PDR: Pan-drug resistant (resistant to all tested antibiotics). DTR status is determined on Enterobacteriaceae, *Pseudomonas* and *Acinetobacter* species and requires require antibiogram results for  $\geq 1$  carbapenem,  $\geq 1$  extended-spectrum cephalosporin, and  $\geq 1$  fluoroquinolone. *Candida* unknown species have been classified in non-albicans. All PDR pathogens are DTR, and all DTR are carbapenem-R, thus the count and proportion of DTR and carbapenem-R micro-organisms includes that of the more resistant categories. EUROBACT-1 reported susceptibilities on monomicrobial infections. EPIC III reported the pathogens from 1154 bacterial or fungal bloodstream infections, not restricted to hospital-acquired infections. Sum of percentages exceeds 100 because patients may have had more than 1 infection



**Fig. 1** Relationship between resistance and timing of adequate antimicrobial therapy. Cumulative percentage of patients receiving at least one adequate antimicrobial, on each time-period before and after the date of collection of the first positive blood culture, shown by antimicrobial resistance status. MRSA, methicillin-resistant *Staphylococcus aureus*; MRSE, methicillin-resistant *Staphylococcus epidermidis* includes all methicillin resistant coagulase-negative staphylococcus, VRE: vancomycin-resistant *Enterococcus*. Closed brackets [ ] denote inclusive of the end of the range and open brackets [ ] denote the exclusion of the end of the range  
 Wilcoxon rank sum test on time to adequate treatment according to antibiotic resistance.  $p = <.0001$

There are important limitations to this study. Firstly, ICUs were predominantly from the Europe and Central Asia and the East Asia and Pacific regions, and from high-income and upper-middle-income countries, thus limiting the generalizability of our results. Second, we started data collection before and continued during the first year of the COVID-19 pandemic. This likely influenced the patient population, microorganism distribution, antimicrobial resistance and mortality [33, 34]. Some ICUs were unable to start or complete the study, leading to multiple exclusions. However, we report similar patient severity, pathogen distribution, and mortality to the EUROACT-1 study, validating the current report. Thirdly, pathogen identification and antimicrobial susceptibility testing relied on each laboratory, with possible differences in interpretation leading to inconsistencies. The patients at risk of late onset BSI had to stay in the ICU for more than 7 days to be exposed to this risk, leading to potential selection bias. The method used for the multivariable analysis led to poor calibration, which is now presented in the ESM. Moreover, data collection was performed by individual investigators in 330 ICUs, without on-site monitoring. We improved the risk of inconsistencies with online checks through the electronic case report file, and by closely monitoring data quality and coherence for each case-report.

## Interpretation

HA-BSI in ICU patients was mainly caused by Gramnegative bacteria, with widespread carbapenem resistance and DTR. Antibiotic resistance was associated with longer delays to adequate antimicrobial therapy. HA-BSI was associated with 37.1% mortality, and by day-28 only 16.1% of the patients had been discharged alive from the hospital. Multifaceted programs to decrease multidrug resistance as well as prevent, recognize, and manage HABSIs, with a focus on antimicrobial adequacy and source control are suggested to improve patient management and outcomes.

In this study, hospital-acquired bloodstream infections were frequently caused by Gram-negative, carbapenem resistant or with difficult to treat resistance pathogens. Antibiotic resistance was associated with delays to antimicrobial therapy. Mortality was 37% at day-28.

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The datasets used and/or analysed during the current study are available from the OUTCOMEREA organisation on reasonable request.

**Declarations****Conflict of interest**

AT has nothing to disclose, NB has nothing to disclose, QS has nothing to disclose, SR has nothing to disclose, MA reports honoraria paid to his university for educational activities by Pfizer, Sanofi, MSD and Astra Zeneca, ATA has nothing to disclose, ML reported consulting and lecture fees from Amomed Pharma, Aspen, LFB and Gilead, ACM has received payment for speaking on behalf of Boston Scientific and sits on the Scientific Advisory Board of Cambridge Infection Diagnostics, a start-up seeking to develop novel diagnostics for infectious diseases, MB received advisory board, speaker activities from Angelini, Bayer, Biomerieux, Cidara, Gilead, Menarini, MSD, Pfizer, Roche, Shionogi, study grants from: Angelini, Shionogi, Cidara, Gilead, Pfizer, and MSD, KA has nothing to disclose, JL has received lecture fees and honoraria from MSD, RF reports Payment for lectures, speakers bureaus or advisory boards from Grifols, MSD, Pfizer, Gilead, Shionogi, Thermofisher, Hill Rom, AOP Health, BD, HQ has nothing to disclose, JAP reports consulting, advisory boards or lectures fees and honoraria for MSD, Pfizer, Astra-Zeneca, Gilead, Jansen, Cepheid, AOP Orphan Pharmaceuticals, PP reported advisory boards participation for Gilead, Technophage and Sanofi, lectures fees from MSD, Gilead and Pfizer, and research grant from Abionic, LDB has nothing to disclose, JdW has consulted for Pfizer, MSD (honoraria paid to institution), FZ has nothing to disclose, MG has nothing to disclose, AA has nothing to disclose, KA has nothing to disclose, HB has nothing to disclose, YH has nothing to disclose, KJ has nothing to disclose, ME has nothing to disclose, FB reported consulting and lecture fees, conference invitation from MSD and lecture fees from BioMérieux, J-FT reported advisory boards participation for Merck, Gilead, Beckton-Dickinson, Pfizer, Shinogi, Medimune, Paratek, research grants from Merck, Pfizer, Thermofischer.

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