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The role of centre and country factors on process and outcome indicators in critically ill patients with hospital-acquired bloodstream infections

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Abstract

Purpose: The primary objective of this study was to evaluate the associations between centre/country-based factors and two important process and outcome indicators in patients with hospital-acquired bloodstream infections (HABSI).

Methods: We used data on HABSI from the prospective EUROBACT-2 study to evaluate the associations between centre/country factors on a process *or* an outcome indicator: adequacy of antimicrobial therapy within the first 24 h or 28-day mortality, respectively. Mixed logistical models with clustering by centre identified factors associated with both indicators.

Results: Two thousand two hundred nine patients from two hundred one intensive care units (ICUs) were included in forty-seven countries. Overall, 51% ($n=1128$) of patients received an adequate antimicrobial therapy and the 28-day mortality was 38% ($n=839$). The availability of therapeutic drug monitoring (TDM) for aminoglycosides everyday [odds ratio (OR) 1.48, 95% confidence interval (CI) 1.03–2.14] or within a few hours (OR 1.79, 95% CI 1.34–2.38), surveillance cultures for multidrug-resistant organism carriage performed weekly (OR 1.45, 95% CI 1.09–1.93), and increasing Human Development Index (HDI) values were associated with adequate antimicrobial therapy. The presence of intermediate care beds (OR 0.63, 95% CI 0.47–0.84), TDM for aminoglycoside available everyday (OR 0.66, 95% CI 0.44–1.00) or within a few hours (OR 0.51, 95% CI 0.37–0.70), 24/7 consultation of clinical pharmacists (OR 0.67, 95% CI 0.47–0.95), percentage of vancomycin-resistant enterococci (VRE) between 10% and 25% in the ICU (OR 1.67, 95% CI 1.00–2.80), and decreasing HDI values were associated with 28-day mortality.

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Conclusion: Centre/country factors should be targeted for future interventions to improve management strategies and outcome of HABSI in ICU patients.

Keywords: Hospital-acquired bloodstream infections, Bacteraemia, Centre, Process indicator, Outcome indicator

Introduction

Hospital-acquired bloodstream infections (HABSI) are one of the hospital-acquired infections with the highest health burden measured in disability-adjusted life years [1, 2]. HABSI are frequently observed in the intensive care unit (ICU) setting and are associated with high morbidity, and increased hospital costs and length of stay. To investigate HABSI, initial adequate therapy and mortality represent one of the most important process and outcome indicators [3–5]. Interestingly, international cohorts investigating indicators focussed mostly on individual patient factors [6, 7]. Due to the difficulty to perform large multicentre cohorts, the role of centre-/country-based factors has been widely disregarded in the literature. Several surveys or international surveillance systems showed that the structure of the ICU and microbiological laboratory as well as epidemiological resistance data may substantially differ between different centres and countries [8–11]. However, associations between these structural indicators and the adequacy of antimicrobial therapy or mortality remain unknown due to the paucity of standardised data globally.

From 2019 to 2021, we conducted the EUROBACT-2 study, a prospective cohort that was designed to update the epidemiology and main factors associated with mortality in ICU patients with HABSI from ICUs worldwide [12]. We sought to use data from this high-quality cohort to evaluate the associations between centre-/country-based factors and two important process and outcome indicators, the adequacy of antimicrobial therapy within the first 24 h, and the 28-day mortality, respectively.

Take-home message

The role of different structural indicators or centre-/country-based factors has been widely disregarded in the literature
Therapeutic drug monitoring strategies, availability of clinical pharmacists, weekly screening for multidrug-resistant microorganism carriage, vancomycin-resistant enterococci prevalence in hospital-acquired bloodstream infections, and Human Development Index could be associated with adequacy of antimicrobial therapy and mortality

Material and methods

EUROBACT-2 study design

The EUROBACT-2 was a prospective multicontinental cohort study performed between September 2019 and June 2021 [12]. This clinical study was registered within ClinicalTrials.org (NCT03937245) and the results are reported in accordance with the STrengthening the Reporting of OBservational studies in Epidemiology guidelines [13].

Setting

Endorsement, logistic, and financial support was obtained from the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) study Group for Infections in Critically Ill Patients (ESGCIP) and the European Society of Intensive Care Medicine (ESICM). An operational committee (AT, JFT, FB, SR, and NB) oversaw all study operations. National coordinators (NCs) recruited participating centres, applied for regulatory and ethical approvals, and facilitated communication within different countries.

Centres and patients

The included centres were ICUs, defined as a unit specifically designed to manage patients with organ failure within an hospital and able to provide invasive mechanical ventilation for at least 24 h. The EUROBACT-2 study recruited centres with patients with HABSI from 1st June 2019 to 30th January 2021. For this specific analysis, amongst all EUROBACT-2 participating centres, we selected those that included a minimum of ten consecutive HABSI patients or those that recruited patients for a period > 2 months. A flexible start of the inclusion period was allowed for each centre to facilitate participation in the cohort.

Adult patients (≥ 18 years old) with a first episode of HABSI treated in ICU were enrolled. A HABSI was defined as a positive blood culture sampled 48 h after hospital admission. Treatment in the ICU was defined as either the blood culture having been sampled in the ICU or the patient having been transferred to the ICU (*i.e.* in 48 h) for the treatment of the HABSI.

Data collection, definitions, and indicators

Hospital, centre (ICU), and country data.

Data on hospital and centre characteristics were stratified into the following subgroups: (1) structure of the ICU (*i.e.* variables that described type of ICU, personal, [infra]structure and organisation), (2) organisation of the microbiology laboratory (*i.e.* microbiological processing and reporting) and infectious diseases (*i.e.* variables that

described availability of specialists, therapy drug monitoring [TDM] and institutional policy about treatments) and (3) aggregated ICU antimicrobial resistance (AMR)-related factors (*i.e.* variables that described or could influence AMR). We also collected data from countries of each of the included centres (e.g. geographical, life expectancy, education and income data). We extracted Human Development Index [HDI] data which is composite index of life expectancy, education and per capita income indicators [14, 15]. Further, country data from WHO Tripartite AMR Country Self-Assessment Survey [TrACSS] were also extracted [16, 17].

Individual patient data and outcomes.

We collected patient data from the hospital charts and no additional tests or interventions were performed. Our primary process indicator was adequate antimicrobial therapy within the first 24 h after HABSI. It was defined as a therapy with at least one antimicrobial with in vitro activity for the microorganism at the first day, with adequacy of antimicrobial selection, dosing and administration manually reviewed for all infections and sources of HABSI by three experts (NB, AT and FB). Antimicrobials administered at ineffective or very low dose and/or route of administration, relative to the source of infection, were considered as not adequate.

Our primary outcome indicator was 28-day mortality. Patients were followed for up to 28 days or until hospital discharge and vital status was assessed on day 28.

Statistical analyses

Continuous variables were expressed as medians (interquartile range [IQR]) and categorical variables as absolute frequencies and percentages.

The statistical plan consisted of two steps. First, we described the differences in adequacy of antimicrobial therapy within the first 24 h and 28-day mortality using Chi-square (or Fisher) and Student *T* (or Wilcoxon) tests for categorical and numeric variables, respectively, for the following subgroups: (1) structure of the ICU, (2) organisation of the microbiology laboratory and infectious diseases, (3) aggregated ICU AMR-related factors and (4) country factors. Second, to identify factors associated with adequate antimicrobial therapy in the first 24 h or day-28 mortality, we built a two-tiered hierarchical logistic mixed model using the GLIMMIX procedure of the SAS software for each subgroup. The effects of centre-based variables were included as random intercepts. Multilevel modelling considered the hierarchical structure of the data, which may manifest as intraclass correlations. We performed mixed univariable and multivariable logistic models for each subgroup. All non-colinear clinically relevant variables with p values < 0.10 by univariate analysis were introduced into the multivariable model. A backward process was then used for further variable selection. To mitigate bias introduced by severity of patients at the time of HABSI diagnosis, we forced in our multivariable models the variable "presence of septic shock" at the individual level. Moreover, we performed sensitivity analysis excluding centres that recruited patients affected by coronavirus disease 2029 (COVID-19).

Further details on skin contaminants, centre/country or individual patient variables, data quality, definitions, missing data and statistical analyses are described in the electronic supplementary material (ESM).

Results

Participating ICUs and patients

Amongst the 333 ICUs included in the EUROBACT-2 cohort, we excluded 132 ICUs that included less than 10 patients or for a period < 3 months (eFigure 1), leaving 201 ICUs from 47 countries eligible for the study (eFigure 2). Half of them were located in Europe ($n = 105$, 52%) and two thirds were in Organization for Economic Cooperation and Development (OECD) member countries ($n = 137$, 68%).

We included 2209 patients with a HABSI. Most patients were male ($n = 1388$, 63%) with a median age of 64 (IQR 52; 73) years. The most common admission diagnoses were respiratory diseases ($n = 472$, 21%) and sepsis or septic shock ($n = 427$, 19%). Most HABSI ($n = 1766$, 80%) were acquired in ICU.

Overall, 51% ($n = 1128$) of patients received an adequate antimicrobial therapy within the first 24 h and 38% ($n = 839$) died in-hospital within 28 days.

Structure of the ICU

In descriptive analyses, patients recruited from teaching hospitals received less frequently adequate antimicrobial therapy within the first 24 h, whereas patients recruited from burn units and in ICUs with higher number of senior doctors received more frequently adequate antimicrobial therapy within the first 24 h (Table 1). However, when univariable and multivariable mixed logistic models were used, these variables were not associated with adequate therapy within the first 24 h (eTable 1).

In descriptive analyses, type of ICU, number of beds per doctor, number of senior doctors, number of beds in the ICU, number of ventilator and non-ventilator beds in the ICU, and recruitment from general and paediatric wards were associated with increased 28-day mortality (Table 1). Using multivariable mixed logistic models with adjustment

Table 1 Structure of the ICU

	All centres (*n* = 201)	All patients (*n* = 2209)	No adequate treatment (*n* = 1081)	24-h adequate treatment (*n* = 1128)	*p* value	Alive or discharge alive at day-28 (*n* = 1370)	28-day mortality (*n* = 839)	*p* value
Teaching hospital	168 (83.6)	1885 (85.3)	941 (87)	944 (83.7)	0.03	1168 (85.3)	717 (85.5)	0.90
Funding					0.88			0.59
Public	171 (85.1)	1888 (85.5)	928 (85.8)	960 (85.1)		1179 (86.1)	709 (84.5)	
Private	10 (5)	101 (4.6)	48 (4·4)	53 (4.7)		61 (4.5)	40 (4.8)	
Mixed	20 (10)	220 (10)	105 (9.7)	115 (10·2)		130 (9.5)	90 (10.7)	
Type of ICU					0.42			< 0.01
Medical	165 (82.1)	1772 (80.2)	879 (81.3)	893 (79.2)		1127 (82.3)	645 (76.9)	
Surgical	13 (6.5)	125 (5.7)	56 (5·2)	69 (6.1)		84 (6.1)	41 (4.9)	
Mixed	23 (11.4)	312 (14.1)	146 (13·5)	166 (14.7)		159 (11.6)	153 (18.2)	
Structure of the ICU					0.07			0.05
Closed ICU	156 (77.6)	1762 (79.8)	845 (78.2)	917 (81.3)		1111 (81.1)	651 (77.6)	
Open ICU	45 (22.4)	447 (20.2)	236 (21.8)	211 (18.7)		259 (18.9)	188 (22.4)	
Number of beds per nurse (miss = 5)	2.1 [1.5; 2.9]	2.3 [1.6; 2.8]	2.3 [1.7; 2.8]	2.2 [1.6; 2.9]	0.33	2.3 [1.6; 2.9]	2.3 [1.7; 2.6]	0.47
Number of beds per doctor[a] (miss = 3)	3 [1.9; 4.1]	2.8 [1.9; 4.1]	3 [1.9; 4.5]	2.7 [1.8; 4]	0.10	3 [1.9; 4.2]	2.6 [1.8; 4]	0.02
Number of junior or in training doctors (miss = 4)	3 [2; 6]	3.5 [2; 5.5]	3 [2; 6]	4 [2; 5]	0.73	3 [2; 6]	4 [2; 5]	0.31
Number of senior doctors (miss = 4)	3 [2; 5]	3 [2; 5]	3 [2; 4]	3 [2; 5]	< 0.01	3 [2; 5]	3 [2; 4]	0.02
Number of ventilator equivalent beds in the ICU (miss = 1)	15 [10; 22.5]	15 [11; 23]	15 [11; 24]	15 [11; 22]	0.34	15 [11; 24]	14 [11; 22]	< 0.01
Presence of intermediate care beds (miss = 1)	103 (51.5)	982 (44.6)	463 (42.9)	519 (46.2)	0.12	662 (48.5)	320 (38.2)	< 0.01
Number of beds in the ICU (miss = 1)	20 [12; 28.5]	20 [12; 28]	20 [12; 28]	20 [12; 28]	0.69	21 [13; 30]	18 [12; 27]	< 0.01
Recruitment: general or paediatric wards	188 (93.5)	2093 (94.7)	1033 (95.6)	1060 (94)	0.09	1285 (93.8)	808 (96.3)	0.01
Recruitment: cardiac surgery, coronary care or post-operative, neuro-surgical or trauma wards	162 (80.6)	1782 (80.7)	865 (80)	917 (81.3)	0.45	1124 (82)	658 (78.4)	0.04
Recruitment: burn wards	40 (19.9)	358 (16.2)	157 (14.5)	201 (17.8)	0.04	233 (17)	125 (14.9)	0.19
24-h medical coverage by senior level doctors	188 (93.5)	2021 (91.5)	977 (90.4)	1044 (92.6)	0.07	1262 (92.1)	759 (90.5)	0.18
24-h medical coverage by junior or in training doctors	171 (85.1)	1904 (86.2)	925 (85.6)	979 (86.8)	0.41	1190 (86.9)	714 (85.1)	0.24
General surgery team and operating theatre available 24/7	199 (99)	2196 (99.4)	1074 (99.4)	1122 (99.5)	0.72	1366 (99.7)	830 (98.9)	0.04

ICU intensive Care Unit, *Miss* missing data. Of note, missing data are counted at centre level in this table

[a] Number of doctor included senior and junior doctors for this ratio

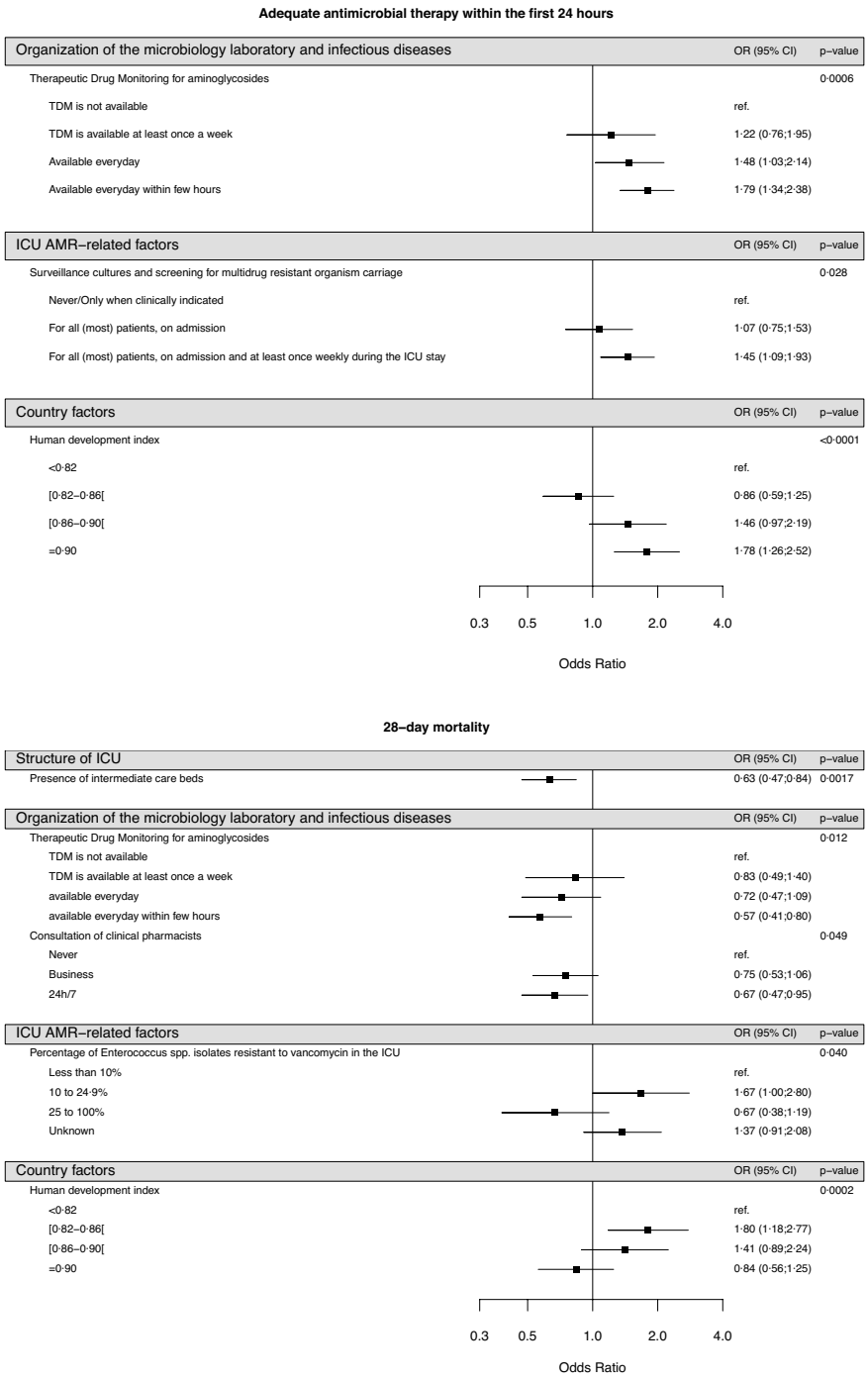

Fig. 1 Multivariable mixed logistical models for adequate antimicrobial therapy within the first 24 h and 28-day mortality. The first panel relates to adequate antimicrobial therapy within the first 24 h, the second panel 28-day mortality. *ICU* intensive care unit, *OR* odds ratio, *CI* confidence interval, *TDM* therapeutic drug monitoring, *AMR* antimicrobial resistance

for the presence of septic shock, the availability of intermediate care beds in the ICU was associated with decreased 28-day mortality (odds ratio [OR] 0.63, 95% confidence interval [CI] 0.47–0.84, $p = 0.0017$, Fig. 1, eTable 2).

Organisation of the microbiology laboratory and infectious diseases

Having an infectious diseases (ID) specialist in the ICU, scheduled ID rounds or multidisciplinary meetings with ID specialists, the presence of a clinical pharmacist as part of the permanent ICU staff, empirical antibiotic treatment determined by local infection treatment guidelines, TDM for aminoglycosides, vancomycin and beta-lactam, automated blood culture incubation, monitoring for positive blood cultures every 24 h and 7 days a week, and performing molecular tests in case of multidrug-resistant bacteria were associated with an increased percentage of adequate therapy within the first 24 h (Table 2). Using multivariable mixed logistic models with adjustment for the presence of septic shock, only TDM for aminoglycosides was associated with an increased probability of adequate therapy within the first 24 h (TDM available at least once a week, OR 1.22 [95% CI 0.76–1.95]; TDM available every day, OR 1.48 [95% CI 1.03–2.14]; TDM available every day within a few hours, OR 1.79 [95% CI 1.34–2.38]; $p < 0.01$, Fig. 1, eTable 3).

Scheduled ID rounds or multidisciplinary meetings, frequent consultation with clinical pharmacists, the presence of a clinical pharmacist as part of the permanent ICU staff, empirical antibiotic treatment determined by national/international or local guidelines, collection of microbiological surgical site or procedural site specimens, TDM for aminoglycosides, vancomycin and beta-lactam, results of positive blood culture reported on personal contact and 24/7, antibiotic susceptibility test directly performed from the positive blood culture, and molecular test performed in case of multidrug-resistant bacteria were associated with decreased 28-day mortality. Using multivariable mixed logistic models with adjustment for the presence of septic shock, TDM for aminoglycosides was associated with decreased probability of 28-day mortality (TDM available at least once a week, OR 0.81 [95% CI 0.48–1.36]; TDM available every day, OR 0.66 [95% CI 0.44–1.00]; TDM available every day within a few hours, OR 0.51 [95% CI 0.37–0.70]; $p < 0.01$, Fig. 1, eTable 4). Moreover, consultation of clinical pharmacists was associated with decreased 28-day mortality (24/7 consultation, OR 0.67 [95% CI 0.47–0.95]; business hours consultation, OR 0.75 [95% CI 0.53–1.06]).

ICU AMR-related factors

Selective oropharyngeal and/or digestive tract decontamination, surveillance cultures and screening for multidrug-resistant organism carriage, different percentage of vancomycin-resistant enterococci (VRE) and extended-spectrum beta-lactamase (ESBL)-producing Enterobacterales were associated with adequate therapy within the first 24 h (Table 3). Using multivariable mixed logistic models with adjustment for the presence of septic shock, surveillance cultures and screening for multidrug-resistant organism carriage were associated with an increased probability of adequate therapy within the first 24 h (screening for all patients on admission, OR 1.07 [95% CI 0.75–1.53]; screening for all patients on admission and at least once weekly, OR 1.45 [95% CI 1.09–1.93]; Fig. 1, eTable 5).

Surveillance cultures and screening for multidrug-resistant organism carriage, different percentage of methicillin-resistant *Staphylococcus aureus* (MRSA), VRE, ESBL-producing Enterobacterales and carbapenemase-producing Enterobacterales were associated with 28-day mortality (Table 3). Using multivariable mixed logistic models with adjustment for the presence of septic shock, percentage of VRE between 10 and 25% was associated with increased 28-day mortality (OR 1.67 [95% CI 1.00–2.80], Fig. 1, eTable 6).

Country factors

Median values of HDI and current health expenditure were increased in patients who received an adequate therapy within the first 24 h. Moreover, patients recruited in countries with training and professional education on AMR, in countries with data on reports from national surveillance system for AMR, and in countries with policies for optimising antimicrobial use implemented in most healthcare facilities had higher proportions of adequate therapy within the first 24 h (Table 4). Using multivariable mixed logistic models with adjustment for the presence of septic shock, increasing HDI values were associated with increased OR for adequate therapy within the first 24 h (Fig. 1, eTable 7).

Median values of HDI and current health expenditure were decreased in patients who died within 28 days (Table 4). Moreover, patients recruited in countries with training and professional education on AMR, in countries with data reports from national surveillance system for AMR and with policies for optimising antimicrobial use implemented in most healthcare facilities were associated with decreased 28-day mortality. Using multivariable mixed logistic

Table 2 Organisation of the microbiology laboratory and infectious diseases

	All centres (*n* = 201)	All patients (*n* = 2209)	No adequate treatment (*n* = 1081)	24-h adequate treatment (*n* = 1128)	*p* value	Alive or discharge alive at day-28 (*n* = 1370)	28-day mortality (*n* = 839)	*p* value
Consultation of infectious diseases specialists or clinical microbiologists (miss = 28)					0.17			0.12
24 h/7 days	103 (59.5)	1275 (66.8)	647 (68.8)	628 (64.8)		766 (65.1)	509 (69.3)	
Business	58 (33.5)	540 (28.3)	248 (26.4)	292 (30.1)		345 (29.3)	195 (26.6)	
Never	12 (6.9)	95 (5)	46 (4.9)	49 (5.1)		65 (5.5)	30 (4.1)	
At least one ICU physician is an infectious diseases specialist	30 (14.9)	359 (16.3)	156 (14.4)	203 (18)	0.02	766 (65.1)	509 (69.3)	0.32
Scheduled infectious diseases rounds or multidisciplinary meetings	51 (25.4)	504 (22.8)	224 (20.7)	280 (24.8)	0.02	344 (25.1)	160 (19.1)	< 0.01
Consultation of clinical pharmacists (miss = 22)					0.33			< 0.01
24/7	56 (31.3)	578 (28.7)	270 (27.6)	308 (29.7)		402 (32.5)	176 (22.6)	
Business hours	53 (29.6)	477 (23.7)	226 (23.1)	251 (24.2)		300 (24.3)	177 (22.8)	
Never	70 (39.1)	960 (47.6)	483 (49.3)	477 (46)		535 (43.2)	425 (54.6)	
Clinical pharmacists available as part of the permanent staff of the ICU	36 (17.9)	341 (15.4)	149 (13.8)	192 (17)	0.04	249 (18.2)	92 (11)	< 0.01
Clinical pharmacists in scheduled multidisciplinary staff meetings	17 (8.5)	168 (7.6)	72 (6.7)	96 (8.5)	0.10	109 (8)	59 (7)	0.43
Empirical antibiotic treatment determined by national/international infection treatment guidelines	123 (61.2)	1349 (61.1)	644 (59.6)	705 (62.5)	0.16	864 (63.1)	485 (57.8)	0.01
Empirical antibiotic treatment determined by local infection treatment guidelines	119 (59.2)	1193 (54)	540 (50)	653 (57.9)	< 0.01	790 (57.7)	403 (48)	< 0.01
Empirical antibiotic treatment determined by surveillance cultures	99 (49.3)	1140 (51.6)	541 (50)	599 (53.1)	0.15	707 (51.6)	433 (51.6)	0.99
Empirical antibiotic treatment determined by routine consultation of infectious diseases specialists, microbiologists, or clinical pharmacists	85 (42.3)	1085 (49.1)	550 (50.9)	535 (47.4)	0.11	643 (46.9)	442 (52.7)	< 0.01
Empirical antibiotic treatment determined by the treating physician	131 (65.2)	1365 (61.8)	651 (60.2)	714 (63.3)	0.14	888 (64.8)	477 (56.9)	< 0.01
When infection is suspected, surgical site or procedural site specimens are collected and sent for culture (miss = 1)					0.05			< 0.01
Never or only when requested by the treating physician	31 (15.5)	409 (18.6)	177 (16.5)	232 (20.6)		209 (15.3)	200 (23.9)	
Most often	83 (41.5)	907 (41.2)	454 (42.3)	453 (40.2)		587 (43.1)	320 (38.2)	
Always	86 (43)	883 (40.2)	442 (41.2)	441 (39.2)		566 (41.6)	317 (37.9)	
TDM for aminoglycosides (miss = 1)					< 0.01			< 0.01

Table 2 (continued)

	All centres (*n* = 201)	All patients (*n* = 2209)	No adequate treatment (*n* = 1081)	24-h adequate treatment (*n* = 1128)	*p* value	Alive or discharge alive at day-28 (*n* = 1370)	28-day mortality (*n* = 839)	*p* value
Not available	71 (35.5)	962 (43.7)	530 (49.4)	432 (38.4)		525 (38.5)	437 (52.2)	
Available at least once a week	17 (8.5)	175 (8)	91 (8.5)	84 (7.5)		103 (7.6)	72 (8.6)	
Available every day within a few hours	78 (39)	740 (33.7)	306 (28.5)	434 (38.5)		517 (38)	223 (26.6)	
Available every day	34 (17)	322 (14.6)	146 (13.6)	176 (15.6)		217 (15.9)	105 (12.5)	
TDM for vancomycin (miss = 1)					< 0.01			< 0.01
Not available	51 (25.5)	758 (34.5)	405 (37.7)	353 (31.3)		418 (30.7)	340 (40.6)	
Available at least once a week	22 (11)	246 (11.2)	140 (13)	106 (9.4)		148 (10.9)	98 (11.7)	
Available every day within a few hours	88 (44)	842 (38.3)	363 (33.8)	479 (42.5)		554 (40.7)	288 (34.4)	
Available every day	39 (19.5)	353 (16.1)	165 (15.4)	188 (16.7)		242 (17.8)	111 (13.3)	
TDM for beta-lactams (miss = 1)					< 0.01			< 0.01
Not available	143 (71.5)	1630 (74.1)	830 (77.4)	800 (71)		972 (71.4)	658 (78.6)	
Available at least once a week	33 (16.5)	345 (15.7)	134 (12.5)	211 (18.7)		242 (17.8)	103 (12.3)	
Available every day within a few hours	8 (4)	84 (3.8)	47 (4.4)	37 (3.3)		56 (4.1)	28 (3.3)	
Available every day	16 (8)	140 (6.4)	62 (5.8)	78 (6.9)		92 (6.8)	48 (5.7)	
Blood cultures incubation started 24/ 7	149 (74.1)	1688 (76.4)	818 (75.7)	870 (77.1)	0.42	1025 (74.8)	663 (79)	0.02
Automated blood culture processing (miss = 1)	180 (90)	2003 (90.9)	965 (89.5)	1038 (92.2)	0.03	1232 (90.3)	771 (91.9)	0.19
Monitoring for positive blood cultures					< 0.01			0.47
24/7	103 (51.2)	1186 (53.7)	553 (51.2)	633 (56.1)		743 (54.2)	443 (52.8)	
Every day (including weekend), but not at night	77 (38.3)	790 (35.8)	392 (36.3)	398 (35.3)		491 (35.8)	299 (35.6)	
During business hours of weekdays only (neither weekends nor nights)	21 (10.4)	233 (10.5)	136 (12.6)	97 (8.6)		136 (9.9)	97 (11.6)	
Results of positive blood culture are reported 24/7 on personal contact	87 (43.3)	939 (42.5)	438 (40.5)	501 (44.4)	0.06	609 (44.5)	330 (39.3)	0.02
Perform of antibiotic susceptibility test (miss = 1)					0.04			< 0.01
Directly from the positive blood culture (unless the direct smear examination shows different bacteria)	111 (55.5)	1142 (51.8)	535 (49.6)	607 (53.9)		738 (54.1)	404 (48.2)	
From a sub-culture of the positive blood culture	89 (44.5)	1062 (48.2)	543 (50.4)	519 (46.1)		627 (45.9)	435 (51.8)	
MIC not performed (miss = 6)	14 (7.2)	146 (6.7)	87 (8.2)	59 (5.3)	< 0.01	80 (6)	66 (8)	0.06
In case of MDR bacteria phenotypic tests were performed	142 (70.6)	1484 (67.2)	713 (66)	771 (68.4)	0.23	954 (69.6)	530 (63.2)	< 0.01
In case of MDR bacteria molecular tests were performed	76 (37.8)	854 (38.7)	391 (36.2)	463 (41)	0.02	562 (41)	292 (34.8)	< 0.01

Table 2 (continued)

	All centres ($n=201$)	All patients ($n=2209$)	No adequate treatment ($n=1081$)	24-h adequate treatment ($n=1128$)	*p* value	Alive or discharge alive at day-28 ($n=1370$)	28-day mortality ($n=839$)	*p* value
Results of susceptibility testing and the antibiogram are reported on electronic system	171 (85.1)	1951 (88.3)	958 (88.6)	993 (88)	0.67	1224 (89.3)	727 (86.7)	0.06
Susceptibility results are routinely provided by the laboratory as sensitive/resistant (without further detail)	134 (66.7)	1406 (63.6)	696 (64.4)	710 (62.9)	0.48	891 (65)	515 (61.4)	0.08
Susceptibility results are routinely provided by the laboratory as inhibition zones diameter with interpretation S/I/R	58 (28.9)	669 (30.3)	332 (30.7)	337 (29.9)	0.68	424 (30.9)	245 (29.2)	0.39
Susceptibility results are routinely provided by the laboratory as MIC data	132 (65.7)	1530 (69.3)	724 (67)	806 (71.5)	0.02	943 (68.8)	587 (70)	0.58

ICU intensive care unit, *TDM* therapeutic drug monitoring, *MIC* minimum inhibitory concentration, *MDR* multidrug resistance, *S/I/R* susceptible/intermediate/resistant, *Miss* missing data; of note, missing data are counted at centre level in this table

models with adjustment for the presence of septic shock, decreasing values of HDI were associated with increased 28-day mortality (Fig. 1, eTable 8).

Sensitivity analysis excluding the centres that recruited COVID-19 patients

A sensitivity analysis excluding centres ($n=59$) that recruited COVID-19 patients (980 patients, 319 patients with COVID-19) during the study period showed similar results regarding the structure of the ICU factors, organisation of the microbiology laboratory and infectious diseases, ICU AMR-related and country factors for both indicators (eFigure 3).

Discussion

Using a large international prospective cohort, we provided a detailed description of the organisation of ICUs, microbiology laboratories and antimicrobial stewardship processes worldwide. We showed that several factors related to the centre and country were associated with the adequacy of antimicrobial therapy and mortality in critically ill patients with HABSI. To our knowledge, such an in-depth analysis on centre- and country-specific factors has never been performed. Compared to the initial EUROBACT-2 publication [12], this analysis differs in the study population by including only the largest centres, centre-related factors were investigated in detail that were not investigated in the initial publication, including those relevant to the organisation of the microbiology laboratory, infectious diseases and AMR, as were country-level factors. Individual HABSI data were used only as adjustment factors, and this analysis provides an in-depth analysis of a process indicator (*i.e.* adequacy of antimicrobial therapy).

Indeed, cohort studies analysing adequacy of antimicrobial therapy or mortality have mostly focussed on individual risk factors [18, 19].

Aminoglycoside TDM was associated with an increased probability of adequate antimicrobial therapy within the first 24 h and with decreased mortality. TDM is frequently used to optimise exposure whilst minimising toxicity in antibiotics with complex pharmacokinetics or those with a narrow therapeutic window [20]. Aminoglycosides could lead to acute kidney injury due to acute tubular necrosis; therefore, pharmacokinetically monitored aminoglycoside therapy in critically ill patients may reduce toxicity [20]. In addition, aminoglycoside TDM could optimise antibiotic dosing in an attempt to achieve pharmacokinetic/pharmacodynamic targets and outcomes of severe infections in critically ill patients [20, 21]. It is, therefore, possible that the frequency of TDM may be associated with reduced mortality. However, TDM for aminoglycoside may simply

Table 3 Antimicrobial resistance-related factors in the ICU

	All centres (*n* = 201)	All patients (*n* = 2209)	No adequate treatment (*n* = 1081)	24 h adequate treatment (*n* = 1128)	*p* value	Alive or discharge alive at day-28 (*n* = 1370)	28-day mortality (*n* = 839)	*p* value
Selective oropharyngeal and/or digestive tract decontamination (miss centre = 2)					< 0.01			0.07
Never	134 (67.3)	1439 (66.1)	680 (64.1)	759 (68)		871 (64.3)	568 (69.1)	
In a selected group of patients	25 (12.6)	266 (12.2)	121 (11.4)	145 (13)		174 (12.8)	92 (11.2)	
In All ICU patients	40 (20.1)	472 (21.7)	260 (24.5)	212 (19)		310 (22.9)	162 (19.7)	
Surveillance cultures and screening for multidrug-resistant organism carriage					< 0.01			0.04
Never/only when clinically indicated	69 (34.3)	753 (34.1)	405 (37.5)	348 (30.9)		475 (34.7)	278 (33.1)	
For all (most) patients, on admission	42 (20.9)	405 (18.3)	207 (19.1)	198 (17.6)		269 (19.6)	136 (16.2)	
For all (most) patients, on admission and at least once weekly during the ICU stay	90 (44.8)	1051 (47.6)	469 (43.4)	582 (51.6)		626 (45.7)	425 (50.7)	
Percentage of *Staphylococcus aureus* isolates resistant to methicillin in the ICU					0.27			< 0.01
Less than 10%	96 (47.8)	988 (44.7)	476 (44)	512 (45.4)		644 (47)	344 (41)	
10 to 24·9%	40 (19.9)	456 (20.6)	225 (20.8)	231 (20.5)		282 (20.6)	174 (20.7)	
25 to 100%	38 (18.9)	513 (23.2)	267 (24.7)	246 (21.8)		288 (21)	225 (26.8)	
Unknown	27 (13.4)	252 (11.4)	113 (10.5)	139 (12.3)		156 (11.4)	96 (11.4)	
Percentage of *Enterococcus* spp· isolates resistant to vancomycin in the ICU					0.04			< 0.01
Less than 10%	140 (69.7)	1496 (67.7)	757 (70)	739 (65.5)		961 (70.1)	535 (63.8)	
10 to 24·9%	16 (8)	235 (10.6)	98 (9.1)	137 (12.1)		112 (8.2)	123 (14.7)	
25 to 100%	16 (8)	128 (5.8)	66 (6.1)	62 (5.5)		87 (6.4)	41 (4.9)	
Unknown	29 (14.4)	350 (15.8)	160 (14.8)	190 (16.8)		210 (15.3)	140 (16.7)	

Table 3 (Continued)

	All centres (*n* = 201)	All patients (*n* = 2209)	No adequate treatment (*n* = 1081)	24 h adequate treatment (*n* = 1128)	*p* value	Alive or discharge alive at day-28 (*n* = 1370)	28-day mortality (*n* = 839)	*p* value
Percentage of Enterobacterales isolates producing extended-spectrum beta-lactamase in the ICU					< 0.01			< 0.01
Less than 10%	60 (29.9)	574 (26)	259 (24)	315 (27.9)		390 (28.5)	184 (21.9)	
10 to 24·9%	45 (22.4)	469 (21.2)	223 (20.6)	246 (21.8)		318 (23.2)	151 (18)	
25 to 100%	60 (29.9)	841 (38.1)	452 (41.8)	389 (34.5)		460 (33.6)	381 (45.4)	
Unknown	36 (17.9)	325 (14.7)	147 (13.6)	178 (15.8)		202 (14.7)	123 (14.7)	
Percentage of Enterobacterales isolates producing carbapenemases in the ICU					0.09			< 0.01
Less than 10%	111 (55.2)	1093 (49.5)	523 (48.4)	570 (50.5)		732 (53.4)	361 (43)	
10 to 249%	25 (12.4)	285 (12.9)	157 (14.5)	128 (11.3)		160 (11.7)	125 (14.9)	
25 to 100%	31 (15.4)	519 (23.5)	259 (24)	260 (23)		282 (20.6)	237 (28.2)	
Unknown	34 (16.9)	312 (14.1)	142 (13.1)	170 (15.1)		196 (14.3)	116 (13.8)	

ICU intensive care unit, *AMR* antimicrobial resistance, *Miss* missing data; Of note, missing data are counted at centre level in this table

represent a proxy measure for access to a highly functional laboratory system in a mature healthcare setting with multiple other protective factors. Further analysis showed that 64% ($n=128$) of centres administered aminoglycoside during the study period and, amongst them, 35% ($n=45$) did not perform TDM for aminoglycoside. Interestingly, models conducted in this subpopulation showed similar results (eTables 9–10).

We observed that frequent consultation with clinical pharmacists was significantly associated with decreased 28-day mortality. Up to now, a positive impact of pharmacy consultation for ICU patients with severe infections has been reported only from retrospective database linkage [22], or by small localised studies [23, 24]. By ensuring optimal drug choice, avoiding interactions and improving delivery with pharmacodynamic/pharmacokinetic optimisation, clinical pharmacists could have a significant role in providing safe and effective care to ICU patients with severe infections.

In settings with a low prevalence of multidrug-resistant microorganisms, screening for multidrug-resistant organism carriage could prevent the spread of such microorganisms by allowing a prompt implementation of infection prevention and control measures, thus decreasing the risk of cross-transmission [25]. We also found that screening for multidrug-resistant organism carriage was associated with an increased probability of adequate therapy within the first 24 h. This association was significant when multidrug microorganisms were tested on admission and at least once weekly. Awareness of multidrug-resistant microorganism colonisation in critically ill patients could, therefore, be crucial for the implementation of the best therapeutic management strategies. In this context, a recent systematic review and meta-regression analysis showed that patients colonised with carbapenem-resistant microorganisms were at increased risk of subsequent infection [26]. Interestingly, one third of patients included in the EUROBACT-2 study were not screened for multidrug-resistant organism carriage, highlighting room for improvement in several centres. Further discussion on ICU AMR factors associated with mortality is described in the supplementary material.

Our study showed an association between the presence of intermediate care beds in the ICU and 28-day mortality in the EUROBACT-2 cohort. The role of intermediate care beds combined with ICU beds has been debated in the literature in the last 2 decades [27]. On one hand, intermediate care beds could provide more intensive monitoring and patient management than the general ward, thus impacting prognosis [27]. In this context, a large cohort study highlighted the benefits of intermediate care beds in term of prognosis for severely ill patients [28] and our international study underlined the importance of the presence of these beds, especially during COVID-19 pandemic. On the other hand, the presence of intermediate care beds may simply represent a less-severe patient population. However, after adjusting for severity on admission, we observed a significant association with mortality, thus refuting this hypothesis.

Country factors were also associated with our process and outcome indicators. We showed that decreasing values of HDI were associated with a low probability of adequate antimicrobial therapy and increased probability of mortality, respectively. To our knowledge, country factors have not been investigated as dependent variables on process and outcome indicators in critically ill patients with HABSI due to difficult to obtain worldwide data. HDI includes long and healthy life expectancy, education, and a decent standard of living measured by gross national income per capita [29]: our findings clearly highlighted the need for policy-mediated large-scale improvements even for critically ill patients.

Our study has several limitations. Centres were predominantly from high-income and upper-middle-income countries, which limits the generalisability of our results. Second, data collection continued during the first year of the COVID-19 pandemic, whereas the management of HABSI in the different centres may have been modified during this period. For this reason, we performed a sensitivity analysis excluding centres that recruited COVID-19 patients. Third, data collection was performed by individual investigators in several ICUs, without on-site monitoring. We mitigated the risk of inconsistencies with online checks through the electronic case report file, and by a close monitoring of the data quality and coherence within each case report by at least one expert. Fourth, for our multivariable models, we used backward selection which could be sensitive to the sample size, the order of variables, the correlation amongst variables, and the significance level. Fifth, aggregated AMR ICU data on *Acinetobacter* spp. and *Pseudomonas* spp. were not available in the EUROBACT-2 database. Sixth, adequacy within 24 h may be a debatable process outcome and could only represent a proxy for the true adequacy of antimicrobial treatment. Of note, a recent meta-analysis showed that 24 versus 48 h cut-off showed similar impact on mortality [30]. Seventh, the number of HABSI included in each centre was low, thus decreasing reliability of adjusted analyses.

Conclusion

Using a large high-quality international database, we showed that TDM strategies, availability of clinical pharmacists, weekly screening for multidrug-resistant microorganisms carriage, VRE prevalence in HABSI and

Table 4 Country factors

	All centres (*n* = 201)	All patients (*n* = 2209)	No adequate treatment (*n* = 1081)	24 h adequate treatment (*n* = 1128)	*p* value	Alive or discharge alive at day-28 (*n* = 1370)	28-day mortality (*n* = 839)	*p* value
OECD member	137 (68.2)	1681 (76.1)	810 (74.9)	871 (77.2)	0.21	1040 (75.9)	641 (76.4)	0.79
Human Development Index	0.88 [0.82; 0.90]	0.86 [0.82; 0.90]	0.83 [0.82; 0.90]	0.89 [0.82; 0.90]	< 0.01	0.89 [0.82; 0.90]	0.83 [0.82; 0.90]	< 0.01
National action plan on AMR (miss = 4)					0.03			< 0.01
Not implemented	79 (40.1)	1008 (46.5)	523 (48.8)	485 (44.2)		580 (43.3)	428 (51.8)	
Developed and implemented	118 (59.9)	1160 (53.5)	548 (51.2)	612 (55.8)		761 (56.7)	399 (48.2)	
Training and professional education on AMR (miss = 8)					< 0.01			< 0.01
Never/in some pre-service training and continuing professional development	74 (38.3)	1048 (49.2)	571 (54.2)	477 (44.2)		576 (43.7)	472 (58)	
In all relevant pre-service training and continuing professional development	119 (61.7)	1084 (50.8)	483 (45.8)	601 (55.8)		742 (56.3)	342 (42)	
National monitoring system for consumption and rational use of antimicrobials (miss = 4)					0.05			0.12
None	7 (3.6)	64 (3)	26 (2.4)	38 (3.5)		41 (3.1)	23 (2.8)	
National sales and consumption	17 (8.6)	111 (5.1)	54 (5)	57 (5.2)		62 (4.6)	49 (5.9)	
National and/or sub-national sales and consumption	46 (23.4)	554 (25.6)	263 (24.6)	291 (26.5)		359 (26.8)	195 (23.6)	
Prescribing practises and antibiotic use	15 (7.6)	114 (5.3)	70 (6.5)	44 (4)		61 (4.5)	53 (6.4)	
Prescribing practises, antibiotic use, national sales, and consumption	112 (56.9)	1325 (61.1)	658 (61.4)	667 (60.8)		818 (61)	507 (61.3)	
National surveillance system for AMR[a] (miss = 9)					< 0.01			< 0.01
No reports	51 (26.6)	886 (41.5)	492 (46.9)	394 (36.4)		486 (36.9)	400 (49)	
Collects data and produces reports	141 (73.4)	1247 (58.5)	558 (53.1)	689 (63.6)		830 (63.1)	417 (51)	

Table 4 (Continued)

	All centres (*n* = 201)	All patients (*n* = 2209)	No adequate treatment (*n* = 1081)	24 h adequate treatment (*n* = 1128)	*p* value	Alive or discharge alive at day-28 (*n* = 1370)	28-day mortality (*n* = 839)	*p* value
Policies for optimising antimicrobial use (miss = 4)					< 0.01			< 0.01
None or in some healthcare facilities, n (%)	91 (46.2)	1197 (55.2)	628 (58.6)	569 (51.9)		682 (50.9)	515 (62.3)	
In most healthcare/guidelines implemented for all, n (%)	106 (53.8)	971 (44.8)	443 (41.4)	528 (48.1)		659 (49.1)	312 (37.7)	
Region					0.22			0.01
The Americas	6 (3)	46 (2.1)	22 (2)	24 (2.1)		30 (2.2)	16 (1.9)	
East Asia and Pacific	34 (16.9)	304 (13.8)	132 (12.2)	172 (15.2)		210 (15.3)	94 (11.2)	
Europe and Central Asia	130 (64.7)	1608 (72.8)	799 (73.9)	809 (71.7)		966 (70.5)	642 (76.5)	
Middle East and Africa	24 (11.9)	214 (9.7)	106 (9.8)	108 (9.6)		144 (10.5)	70 (8.3)	
South Asia	7 (3.5)	37 (1.7)	22 (2)	15 (1.3)		20 (1.5)	17 (2)	

OECD Organisation for Economic Co-operation and Development, *AMR* antimicrobial resistance, *Miss* missing data; of note, missing data are counted at centre level in this table

Human Development Index could substantially be associated with process and outcome indicators. Centre- and country-specific factors should be included in further prospective international studies investigating severe infections in critically ill patients.

Supplementary Information

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Author contributions
NB, SR, AT and JFT designed and conceptualised the study. All co-authors acquired the data in their countries. SR, NB, NS and JFT did the statistical analysis. SR performed data curation. JFT and AT acquired funding. NB, SR, AT and JFT analysed and interpreted the data. NB, AT, NS and JFT drafted the manuscript. All authors critically reviewed the manuscript and approved the final report.

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

Declarations

Conflicts of interest
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Ethics approval
The initial ethical approval as a low-risk research project with waiver of individual consent was granted by the Ethics Committee of the Royal Brisbane & Women's Hospital, Queensland, Australia (number: LNR/2019/QRBW/48376). Each study centre obtained ethical, governance and any other relevant approvals according to regional and/or national regulations.

Consent for publication
Not applicable.

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