Epidemiology and outcomes of hospital-acquired bloodstream infections in intensive care units: the EUROBACT II International Cohort Study

Electronic Supplemental Material (ESM)

Contents

Protocol and definitions

Timeline

The study start date was the 1st of August 2019. It was planned to continue for 1 year. Two pilot centers started recruitment on 1/06/2019. Delays caused by the COVID-19 pandemic led to extending the recruitment period up to the 30st of January 2021 for the date of HA-BSI. Centers could choose the study start date for their intensive care unit (ICU) between the date of obtention of all required ethical and regulatory approvals and the 31st of October 2020. The minimal study recruitment period was 3 months or 10 consecutive cases (whichever came first) and could be extended on request from the local investigator for up to the whole duration of the study. The database was closed on the 12th of August 2021.

Data quality processes

A dual verification and query process was used, including electronic verification of all collected data through a set of coherence routines, and reviewing of each case report form (CRF) by a group of experts (AT, NB, FB) assessing data quality and completeness. Complex cases were reviewed at regular meetings to resolve any disagreement. We excluded patients that did not meet the inclusion criteria and those missing core outcome data (i.e., dates of hospital-acquired bloodstream infection (HA-BSI) and hospital/ICU admission, discharge and/or death as applicable, pathogen and treatment inclusive of antimicrobials and source control as applicable). We ensured correlation between the recorded source, source control and microbiology results. Inserted intravascular catheters are often removed as a possible source of infection in patients who develop sepsis, septic shock, or HA-BSI, we reviewed each case with the investigators in light of clinical progress and microbiology data. We ensured that intravascular catheters that had been removed but ended up not being the source of HA-BSI were not recorded as catheter-related bloodstream infection. Particular attention was given to only include true infections with possible skin contaminants. Any question or incoherence was fed back to the investigator through eCRF-embedded queries and checked until satisfactory resolution. In the absence of a response, we attempted to contact the center, with assistance from the NC, for a minimum of three times. In extreme cases where no response was obtained, or the investigator became unavailable to respond, the patients and/or the center were excluded from the study.

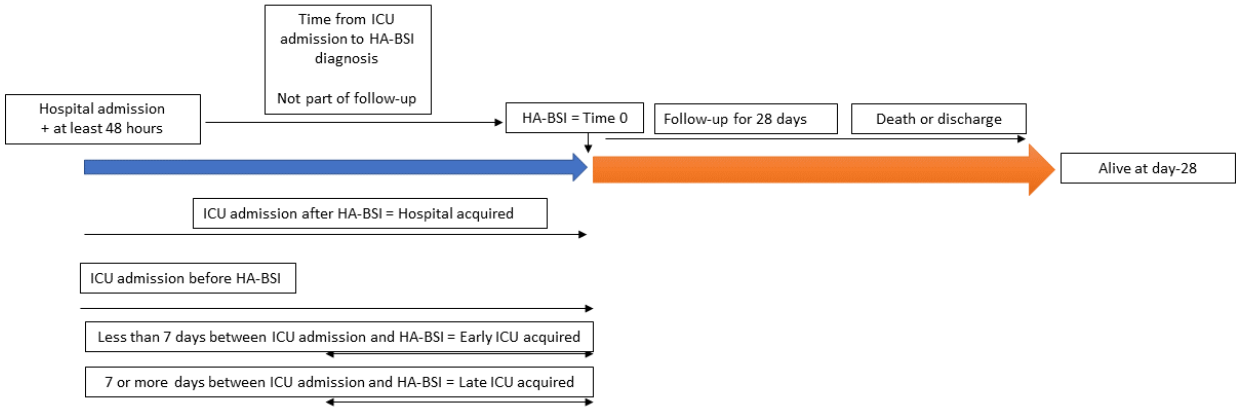
Definitions

- Intensive care unit: ICUs eligible to participate were defined as managing patients with organ failures within a health-care facility and able to provide invasive mechanical ventilation for a duration of at least 24 hours.
- Ventilator equivalent beds refers to the maximum number of ventilated patients the ICU can accommodate at one time.
- Admission source: refers to where was the patient prior to admission to the ICU.
- Primary diagnosis: The main reason for admission to the ICU. Only one primary diagnosis should be entered (see codes). If surgical admission the site of surgery should be entered as primary diagnosis.
- Type of admission: Surgical - defined as having surgery within 7 days of ICU admission. Elective surgery was defined as surgery scheduled > 24 hours in advance and emergency surgery as that scheduled within 24 hours of operation. All other admissions were considered medical.

- HA-BSIs were defined as isolation of a pathogenic organism from at least one blood culture 48 hours or more after hospital admission; the same 48-hour criterion was used to define ICU-acquired cases among HA-BSIs. For common skin contaminants (coagulase-negative staphylococci, *Corynebacterium* species, *Bacillus* species, *Propionibacterium* species, *Aerococcus* species, *Micrococcus* species), two blood cultures with the same antimicrobial susceptibility profile were mandatory or strong clinical grounds that it is not a contaminant. One example was infected material proven as a source for the HA-BSI. Where strong evidence supported HA-BSI but only one culture was positive (*e.g.,* positive catheter tip following line removal for suspected infection with prescription of additional treatment), all clinical and microbiological data were reviewed to decide whether the case should be included. Patients with BSIs acquired outside the ICU were eligible for inclusion if less than 2 days elapsed between collection of the first positive blood sample and ICU admission and/or if ICU admission was directly related to the consequences of HA-BSI. The inclusion date was the time of collection of the first positive blood culture.
- Comorbidities: Chronic diseases present prior to ICU admission. More than one can be chosen according to the following definitions:
- Metastatic cancer: Metastases proven by surgery, computed tomography or magnetic resonance scan, or any other method.
- Hematologic cancer: Lymphoma, Leukaemia.
- AIDS: HIV positive patients with clinical complications such as Pneumocystis carinii pneumonia, Kaposi's sarcoma, lymphoma, tuberculosis, or toxoplasma infection.
- Chronic renal failure: Defined as either chronic dialysis dependent renal failure or history of chronic renal insufficiency with a serum creatinine > 3.6 g/dL (300 µmol/L).
- Immunosuppression: Administration within the 6 months prior to ICU admission of corticosteroid treatment (at least 0.3 mg/kg/day prednisolone for at least one month) or other immunosuppressant drugs, severe malnutrition, congenital immune-humoral or cellular immune deficiency state.
- Chemotherapy/radiotherapy: If within 6 months prior to ICU admission.
- COPD / Chronic Pulmonary Disease Severe: Chronic restrictive, obstructive or vascular disease resulting in severe exercise limitation (*e.g.*, unable to climb stairs or perform household duties) or documented chronic hypoxia, hypercapnia, secondary polycythaemia, severe pulmonary hypertension (>40 mmHg) or home oxygen or non-invasive ventilation (NIV).
- Liver disease, severe: Biopsy-proven cirrhosis with portal hypertension; episodes of past upper gastro-intestinal bleeding attributed to portal hypertension; or prior episodes of hepatic failure, encephalopathy, or coma.
- For scoring purposes, we recorded minimal and maximal or worse biological and physiological values of the first 24 hours following ICU admission.
- For the Glasgow coma scale (GCS) we defined the following: For non-sedated patients, enter the lowest GCS during the 24 hours. For patients sedated, enter the GCS at the time of/just prior to sedation. If not available, please enter an estimated GCS score as it would be if the patient was not receiving sedation.

- Delirium: Delirium is defined as an acute or fluctuating mental state (which represents a change from the patient's normal baseline) and is characterized by inattention with altered level of consciousness, agitation or disorganized thought processes. It can be diagnosed by standardized assessment tools such as (but not limited to) the Confusion Assessment Method for ICU (CAM-ICU)
  Hyperactive delirium is characterized by agitation, restlessness, and attempts to remove tubes and lines. Hypoactive delirium is characterized by withdrawal, flat affect, apathy, lethargy, and decreased responsiveness. Mixed delirium is when patients fluctuate between the two.
- Decision to withhold or withdraw life-sustaining treatment was defined as the ethical decision to change goal of treatment from life-prolonging to palliative. It should only be entered if organ supportive therapy was stopped or not started when it would otherwise have been indicated
- Blood cultures, antimicrobial susceptibility testing, and interpretation were processed locally and following usual practice for each participating centre as detailed in eTable 3.
- Selective reporting of the antibiogram is a laboratory based antimicrobial stewardship process where the laboratory only reports a selection of the antimicrobials that were tested as susceptible for the pathogen. Selective reporting can be used to encourage the use of drugs that are appropriate for the site of infection, discourage the use of drugs for which susceptibility results may be misleading or drugs that may have negative consequences for a patient group or to avoid the overuse of broad-spectrum antibiotics. (see Pulcini et al. 2016 https://doi.org/10.1016/j.ijantimicag.2016.11.014).
- Methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant (coagulase-negative) *Staphylococcus epidermidis* (MRSE) were defined as resistance to methicillin/oxacillin.
- Vancomycin-resistant enterococci (VRE) were reported as the percentage of *Enterococcus faecium* resistant to vancomycin.
- Carbapenem resistance for Enterobacterales was defined as resistance to at least one carbapenem as recommended by the United States of America Center For Disease Control And Prevention [1].
- Adequate antimicrobial therapy was defined as receiving at least 1 antimicrobial with in-vitro 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 antimicrobial therapy for antimicrobials that were ongoing at time of HA-BSI was labelled as "Before BC sampling" and patients were categorized as having received adequate antimicrobial therapy ≤ 24 hours after HA-BSI. For the patients without susceptibility data or with incomplete antibiograms, antimicrobial therapy was considered adequate if the intrinsic organism characteristics and usual susceptibilities indicated a high likelihood of drug susceptibility. Antimicrobials administered at ineffective or very low dose and/or route of administration, relative to the source of infection, were considered as not adequate.
- Times are calculated from the time of blood culture sampling, which represents the time 0 of the study as shown in the diagram below.

- Time to adequate antimicrobial therapy was defined as the time between sampling of the study blood culture and receipt of one adequate antimicrobial for each pathogen in the blood culture.



Sources of Hospital acquired blood stream-infection and source control

The presumed source of the BSI was determined by the treating clinician from the following pre-defined list of categories and subcategories, and if multiple possible sources we requested ordering/numbering in order of likelihood.

- Primary: defined as no clear focus or portal of entry identified
- Catheter-related (Intra-vascular catheter only)
- Respiratory tract
    - Pneumonia
    - Pleural, empyema
    - Tracheobronchitis
- Intra-abdominal
    - Peritonitis
    - Biliary source
    - Other intra-abdominal
- Urinary tract
- Bone or soft tissues
    - Necrotizing fasciitis
    - Other soft tissue
    - Joint or bone
    - Spine
- Endocarditis
- Mediastinitis
- Central Nervous System

Source control was recorded according to the clinician's report as

- Not required
- Required, completed
- Source control required but not achieved

When it was required, we recorded the time, date and effectiveness of the intervention according to pre-defined categories, and if a specimen was sent for microbiology and if it was positive. When patients had multiple interventions we recorded the number of interventions, date of the last intervention and if it was deemed effective after the last intervention.

Source control interventions were recorded according to the following categories

Intravascular catheter Related

- Catheter removal
- Surgical vascular procedure (ligature)

Respiratory tract (pulmonary, pleural, empyema)

- Surgical thoracic
- Percutaneous thoracic (including chest drain)
- Percutaneous mediastinal

Vascular

- Surgical vascular
- Percutaneous vascular
- Other vascular

Cardiac and mediastinal

- Surgical cardiac
- Surgical mediastinal
- Percutaneous mediastinal
- other cardiac or mediastinal

Intra-abdominal

- Surgical abdominal
- Percutaneous abdominal
- Surgical other (mediastinal, pleural, …)
- Percutaneous other (mediastinal, pleural, …)

Urinary tract

- Surgical urinary (JJ stent)
- Surgical urinary (nephrectomy or other)
- Percutaneous urinary (nephrostomy)
- Other urinary

Bone or soft tissues

- Surgical skin
- Surgical bone
- Other bone or soft tissue

Other

- Percutaneous other
- Surgical other
- Other

eTable 1 Imputation of missing data.

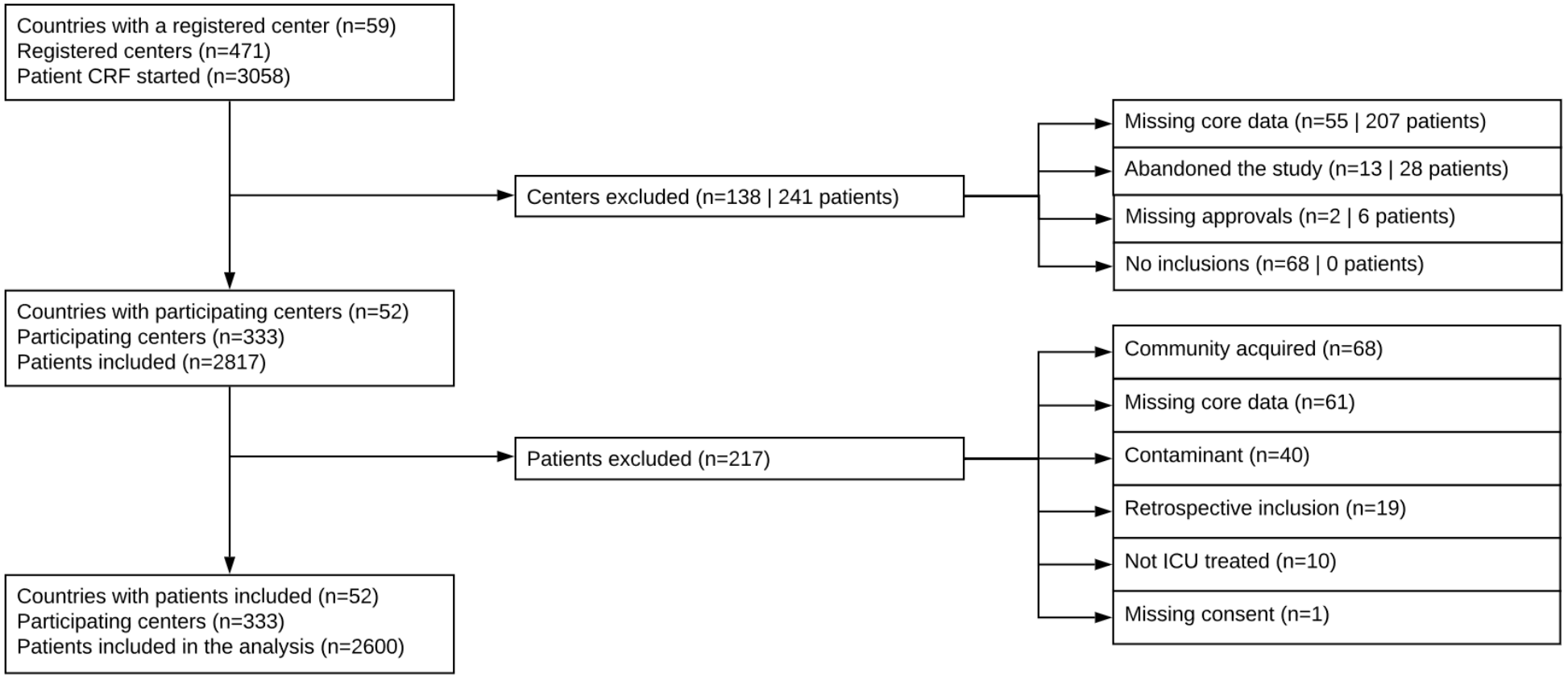
Variable	**Number of missing values**		**Imputed value**
	Center level	Patient level	
Type of ICU	6	15	Mixed (medical-surgical)
Clinical pharmacists are consulted	11	69	Available only during business hours
Aminoglycosides	7	25	TDM is available everyday
Vancomycin	7	25	TDM is available everyday
Number of ventilator-equivalent beds in the ICU ≥15	6	15	<15
Septic shock in class	n/a	8	No sepsis or sepsis without septic shock
Time before adequate treatment	n/a	2	24-48 hours

We used simple imputation of missing data to the median for continuous variables and to the mode for categorical variables.

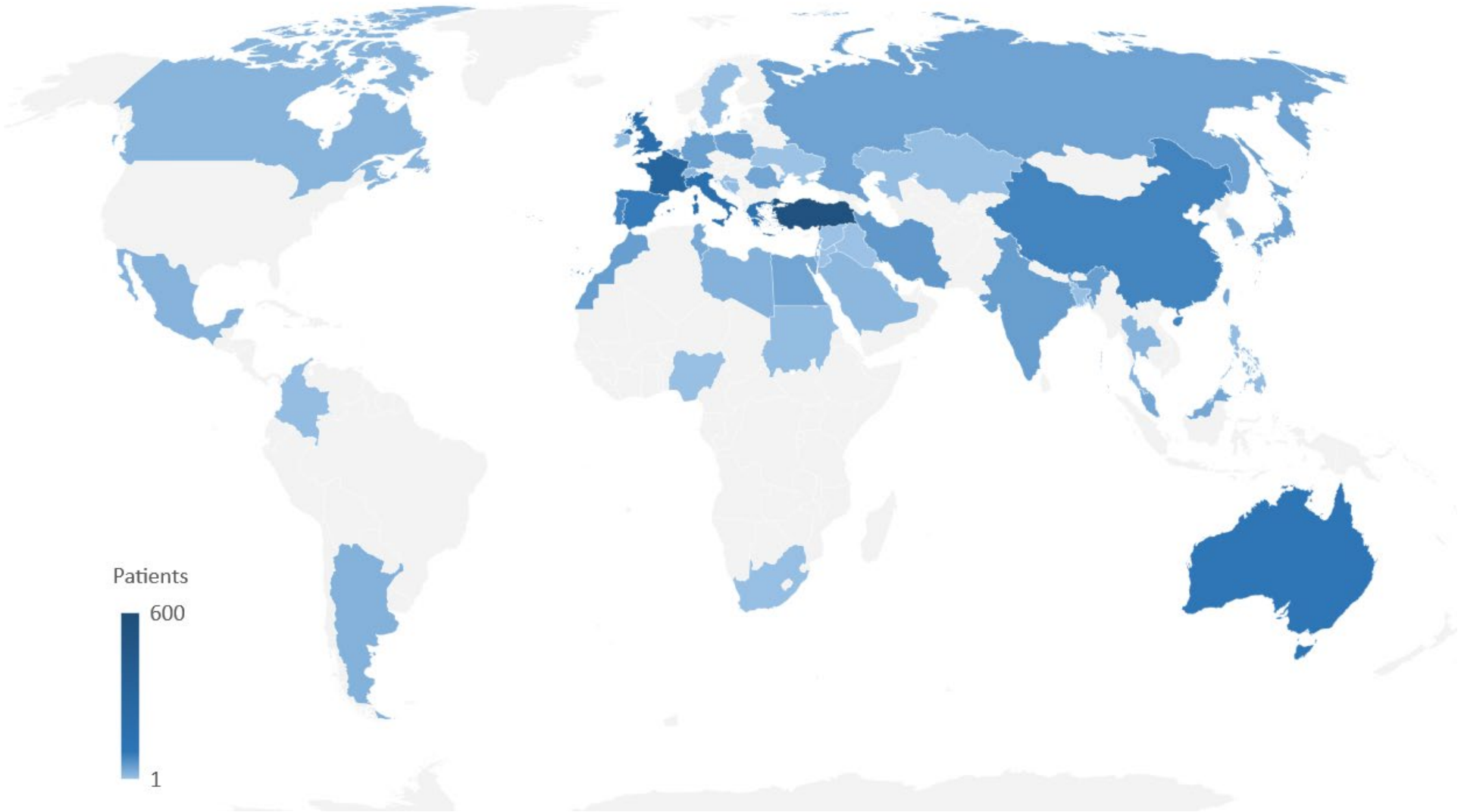
Missing times of blood culture sampling (n=26) and antibiotic start time (n=160) were imputed at 12:00 p.m.

TDM: therapeutic drug monitoring.

eFigure 1 Flowchart of the Eurobact II study



eFigure 2 Geographic distribution of participating ICUs and included patients



Legend: World-map participating countries and territories. Colour gradient denotes the number of included patients in each country.

eTable 2 Geographic distribution of participating ICUs

	ICUs	Patients		ICUs	Patients
East Asia and Pacific	**69**	**412**	**Europe and Central Asia**	**184**	**1775**
Australia	14	99	Belgium	12	64
Brunei	4	29	Bosnia and Herzegovina	1	10
China	15	80	Croatia	2	7
Hong Kong	1	5	France	35	288
Japan	11	44	Germany	6	46
Malaysia	6	36	Greece	19	144
Philippines	1	8	Italy	10	160
Republic of Korea	5	38	Kazakhstan	2	7
Singapore	6	18	Poland	6	41
Taiwan	4	35	Portugal	13	78
Thailand	2	20	Republic of Ireland	1	8
Middle East and North Africa	**48**	**268**	Romania	5	38
Dubai	1	10	Russian Federation	5	41
Egypt	7	38	Spain	13	92
Iran	13	54	Sweden	3	11
Iraq	1	2	Switzerland	2	20
Israel	2	19	Turkey	24	547
Lebanon	1	7	UK	24	172
Libya	5	22	Ukraine	1	1
Morocco	7	47	**North America**	**2**	**19**
Qatar	3	17	Canada	2	19
Saudi Arabia	3	15	**South Asia**	**14**	**54**
Syria	2	2	Bangladesh	2	6
Tunisia	2	33	India	12	48
Jordan	1	2	**Sub-Saharan Africa**	**5**	**20**
Latin America and the Caribbean	**11**	**52**	Nigeria	2	5
Argentina	4	23	South Africa	1	6
Colombia	1	8	Sudan	2	9
Mexico	6	21			

Legend: Number of participating ICUs and included patients in the Eurobact-2 database.

eTable 3 Characteristics of participating ICUs and patient outcomes

Characteristics *	All ICUs (n=333)*	All patients (N= 2600)	Dead on D28 (n= 966)	Alive on D28 (n= 1634)	OR [95% CI]	P value
Funding of the hospital						
Public	274 (83.8)	2198 (85)	808 (83.8)	1390 (85.7)	1	0.844
Private	35 (10.7)	263 (10.2)	108 (11.2)	155 (9.6)	1.06[0.73; 1.55]	.
Mixed	18 (5.5)	124 (4.8)	48 (5)	76 (4.7)	1.14[0.69; 1.88]	.
Structure of the ICU						
Closed-ICU	246 (75.2)	2039 (78.9)	739 (76.7)	1300 (80.2)	1	0.2
Open-ICU	81 (24.8)	546 (21.1)	225 (23.3)	321 (19.8)	1.19[0.91; 1.56]	.
Specific Recruitment **						
General ICU	300 (91.7)	2440 (94.4)	924 (95.9)	1516 (93.5)	1.46[0.9; 2.36]	0.124
Paediatric $	20 (6.1)	124 (4.8)	32 (3.3)	92 (5.7)	0.55[0.32; 0.93]	0.025
Cardiac-surgical	86 (26.3)	638 (24.7)	221 (22.9)	417 (25.7)	0.92[0.71; 1.2]	0.534
Coronary-care	89 (27.2)	559 (21.6)	194 (20.1)	365 (22.5)	0.99[0.76; 1.3]	0.955
Post-operative	235 (71.9)	1895 (73.3)	681 (70.6)	1214 (74.9)	0.76[0.59; 0.97]	0.031
Neuro-surgical	158 (48.3)	1373 (53.1)	503 (52.2)	870 (53.7)	0.77[0.61; 0.96]	0.024
Trauma	197 (60.2)	1574 (60.9)	584 (60.6)	990 (61.1)	0.9[0.71; 1.14]	0.389
Burns	65 (19.9)	446 (17.3)	161 (16.7)	285 (17.6)	1.07[0.8; 1.43]	0.629
Number of ventilator equivalent beds in the ICU	14 [10; 21]	15 [11; 22]	14 [11; 22]	15 [11; 23]	1 [0.99; 1]	0.415
Number high-dependency unit (HDU) beds in the ICU	0 [0; 6]	0 [0; 6]	0 [0; 5]	0 [0; 6]	0.99[0.98; 1.01]	0.227
Antibiotic choice is guided by **						
Local guidelines	194 (59.3)	1417 (54.8)	472 (49)	945 (58.3)	0.87[0.69; 1.11]	0.265
National/international guidelines	195 (59.6)	1570 (60.7)	551 (57.2)	1019 (62.9)	0.89[0.7; 1.12]	0.311
Surveillance cultures	157 (48)	1318 (51)	487 (50.5)	831 (51.3)	0.93[0.75; 1.17]	0.556
Consultation with ID, clinical microbiologists or pharmacists	135 (41.3)	1230 (47.6)	485 (50.3)	745 (46)	0.98[0.76; 1.25]	0.844
The treating physician	222 (67.9)	1648 (63.8)	572 (59.3)	1076 (66.4)	0.94[0.73; 1.22]	0.658
SOD or SDD						
In All ICU patients	58 (17.8)	296 (11.6)	180 (19)	342 (21.3)	1	0.211
In a selected group of patients	38 (11.7)	1735 (68)	95 (10)	201 (12.5)	0.97[0.63; 1.51]	.
Never			672 (71)	1063 (66.2)	1.23[0.92; 1.65]	
Inside the hospital or same campus	296 (90.5)	2378 (92)	897 (93)	1481 (91.4)	1	0.229
At another hospital with a partnership or agreement	25 (7.6)	178 (6.9)	52 (5.4)	126 (7.8)	0.79[0.5; 1.25]	
Off-site at an independent microbiology laboratory	6 (1.8)	29 (1.1)	15 (1.6)	14 (0.9)	1.93[0.74; 5.06]	
Selective reporting of antibiogram						
Not selective	155 (48)	1304 (50.9)	471 (49.1)	788 (49.2)	1	0.679
Selective	168 (52)	1259 (49.1)	489 (50.9)	815 (50.8)	0.95[0.75; 1.21]	
Recommendations used for the interpretation of antibiotic susceptibility testing						
EUCAST	194 (60.06)	1827 (71.56)	1121 (70.2)	706 (73.8)	1	0.802
CLSI	116 (35.91)	671 (26.28)	436 (27.3)	235 (24.6)	0.92 [0.69; 1.21]	
Other	13 (4.02)	55 (2.15)	39 (2.4)	16 (1.7)	0.89 [0.43; 1.85]	

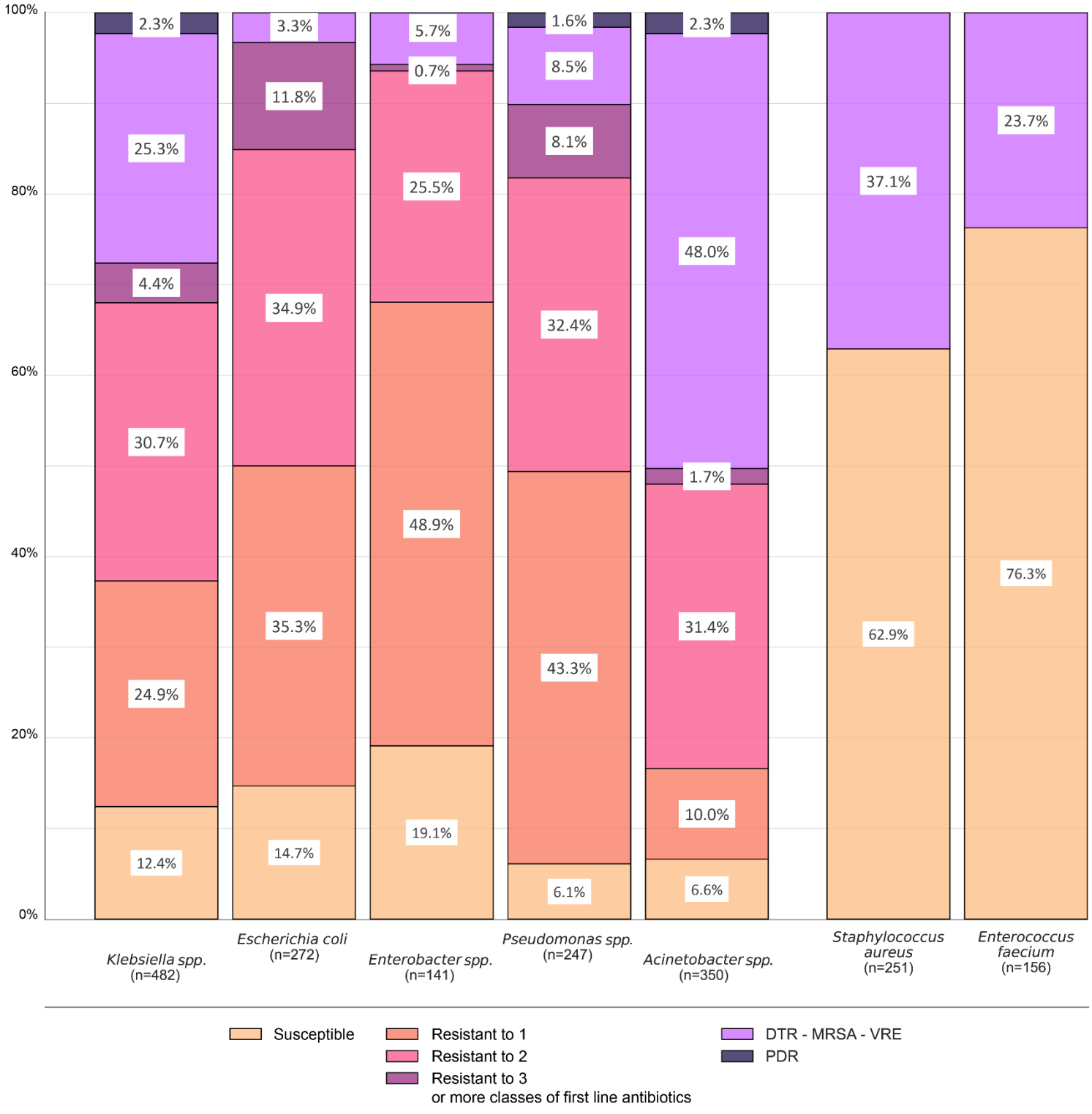
Legend: results reported as n (%) for categorical variables and median [IQR] for continuous variables; * All Center data was missing for 6 ICUs and 7 to 12 did not provide staffing or stewardship data. ** Percentage does not equate to 100% because multiple categories could be selected. $: Refers to ICUs with paediatric admission capacity – Only adult patients could be included in the study. *** There were 4 ICUs and 11 patients in the Low-income category Selective reporting of antibiogram results refers to the reporting to the clinician of a selection only of the tested antibiotics. 24/7: 24 hours a day, 7 days a week. ICU: intensive care unit, SOD: selective oral decontamination, SDD: selective digestive decontamination. TDM: therapeutic drug monitoring. Ventilator equivalent beds refers to the maximum number of ventilated patients the ICU can accommodate at one time.

eTable 4 Additional baseline (admission to the ICU) patient characteristics and day-28 mortality

Variable	All patients (N= 2600)	Dead on D28 (n= 966)	Alive on D28 (n= 1634)	OR [95% CI]	p-Value
Chronic illnesses*					
Moderate COPD	304 (11.7)	111 (11.5)	193 (11.8)	0.98 [0.76; 1.28]	0.905
Severe COPD	112 (4.3)	43 (4.5)	69 (4.2)	1.09 [0.72; 1.64]	0.685
Heart Failure (NYHA 3)	217 (8.3)	112 (11.6)	105 (6.4)	1.83 [1.35; 2.47]	<.001
Heart Failure (NYHA 4)	60 (2.3)	27 (2.8)	33 (2)	1.37 [0.79; 2.36]	0.26
Previous myocardial infarction	239 (9.2)	100 (10.4)	139 (8.5)	1.27 [0.95; 1.69]	0.102
Peripheral vascular disease	176 (6.8)	84 (8.7)	92 (5.6)	1.74 [1.25; 2.42]	0.001
Cerebrovascular disease	277 (10.7)	103 (10.7)	174 (10.6)	0.94 [0.71; 1.23]	0.631
Dementia	109 (4.2)	46 (4.8)	63 (3.9)	0.98 [0.64; 1.49]	0.919
Hemiplegia	70 (2.7)	20 (2.1)	50 (3.1)	0.64 [0.37; 1.11]	0.112
Diabetes without end organ damage	476 (18.3)	188 (19.5)	288 (17.6)	1.16 [0.94; 1.44]	0.174
Diabetes with end organ damage	272 (10.5)	118 (12.2)	154 (9.4)	1.15 [0.87; 1.51]	0.316
Renal disease, moderate	256 (9.8)	103 (10.7)	153 (9.4)	1.17 [0.88; 1.55]	0.282
Renal disease, severe (chronic dialysis)	129 (5)	51 (5.3)	78 (4.8)	1.09 [0.74; 1.59]	0.671
Connective tissue disease	67 (2.6)	31 (3.2)	36 (2.2)	1.54 [0.92; 2.59]	0.1
Ulcer disease (gastro-duodenal)	87 (3.3)	32 (3.3)	55 (3.4)	1.02 [0.63; 1.64]	0.949
Liver disease, mild to moderate	93 (3.6)	39 (4)	54 (3.3)	1.42 [0.91; 2.2]	0.119
Liver disease, severe	67 (2.6)	33 (3.4)	34 (2.1)	1.76 [1.06; 2.94]	0.03
Immunosuppression					
Steroids	134 (5.2)	60 (6.2)	74 (4.5)	1.49 [1.03; 2.16]	0.034
Chemotherapy/Radiotherapy within 6 months	220 (8.5)	93 (9.6)	127 (7.8)	1.37 [1.01; 1.85]	0.044
Targeted therapy for cancer	57 (2.2)	28 (2.9)	29 (1.8)	1.8 [1.03; 3.14]	0.039
Organ Transplant	73 (2.8)	26 (2.7)	47 (2.9)	0.93 [0.55; 1.56]	0.78
AIDS	16 (0.6)	7 (0.7)	9 (0.6)	1.73 [0.6; 5.01]	0.312
Other immunosuppression	95 (3.7)	39 (4)	56 (3.4)	1.21 [0.78; 1.88]	0.401
Source of ICU admission					
Hospital ward/floor, n (%)	1101 (42.3)	436 (45.1)	665 (40.7)	1	0.078
Emergency department	764 (29.4)	275 (28.5)	489 (29.9)	0.76 [0.61; 0.93]	
Other hospital, n (%)	352 (13.5)	136 (14.1)	216 (13.2)	0.92 [0.71; 1.2]	
Operating Room/recovery	286 (11)	89 (9.2)	197 (12.1)	0.75 [0.56; 1.01]	
Other intermediate care unit, n (%)	69 (2.7)	21 (2.2)	48 (2.9)	0.66 [0.37; 1.17]	
Other, n (%)	28 (1.1)	9 (0.9)	19 (1.2)	0.71 [0.3; 1.67]	
Primary diagnosis at ICU admission					
Sepsis or septic shock	530 (20.4)	189 (19.6)	341 (20.9)	1	<.001
Cardiac arrest	91 (3.5)	39 (4)	52 (3.2)	1.2 [0.75; 1.94]	
Cardio-vascular causes	137 (5.3)	45 (4.7)	92 (5.6)	0.86 [0.56; 1.31]	
Gastro-intestinal causes	85 (3.3)	36 (3.7)	49 (3)	1.27 [0.78; 2.07]	
Hypovolemic or Haemorrhagic shock	46 (1.8)	16 (1.7)	30 (1.8)	1.02 [0.53; 1.97]	
Metabolic causes	44 (1.7)	11 (1.1)	33 (2)	0.57 [0.27; 1.18]	
Multiple trauma (no TBI)	93 (3.6)	19 (2)	74 (4.5)	0.42 [0.24; 0.74]	
Neurologic causes	286 (11)	74 (7.7)	212 (13)	0.55 [0.39; 0.78]	
COVID-19**	336 (12.9)	195 (20.2)	141 (8.6)	2.04 [1.48; 2.83]	
Post-Operative admission	258 (9.9)	83 (8.6)	175 (10.7)	0.83 [0.6; 1.16]	
Renal failure	46 (1.8)	14 (1.4)	32 (2)	0.75 [0.38; 1.49]	
Respiratory admission	550 (21.2)	232 (24)	318 (19.5)	1.13 [0.87; 1.47]	
Traumatic brain injury	93 (3.6)	11 (1.1)	82 (5)	0.2 [0.1; 0.4]	
Other	5 (0.2)	2 (0.2)	3 (0.2)	1.14 [0.18; 7.35]	

Legend: Continuous variables are presented as median [IQR] and categorical variables as n(%). COPD: chronic obstructive pulmonary disease, ICU: intensive care unit, NYHA: New York heart association, AIDS: acquired immunodeficiency syndrome, TBI: Traumatic brain injury ** Respiratory admission refers to admission for respiratory failure other than COVID-19 that has been categorized separately.

eFigure 3 Proportion of drug resistant pathogens



Legend: Resistant to 1, 2 or 3 or more first line antibiotics was assessed among carbapenem, β-lactam, and fluoroquinolone categories and if tested piperacillin-tazobactam and ampicillin-sulbactam (*Acinetobacter spp.* ly) and aztreonam (not applicable for *Acinetobacter spp.*). DTR = difficult to treat resistance, PDR = Pandrug resistant (resistant to all tested antibiotics). DTR assessment requires antibiogram results for ≥1 carbapenem, ≥1 extended-spectrum cephalosporin, and ≥1 fluoroquinolone. PDR status only assessed for DTR pathogens. All PDR micro-organisms are DTR. MRSA= methicillin resistant *Staphylococcus aureus*

Multivariable models

Statistical methods for the multivariable models

To identify factors associated with day-28 death, we built a three-tiered hierarchical logistic mixed model using the GLIMMIX procedure of the SAS software. The variables were organized into 3 tiers: country, ICU, and patient. The effects of country-based and center-based variables on the day28 survival were included as random intercepts. Multilevel modelling takes into account the hierarchical structure of the data, which may manifest as intraclass correlations [2]. To obtain a conservative estimate of the standard error, a separate random-error term was specified for each level of the analysis. Therefore, to avoid overestimating the significance of risk factors of day-28 mortality, we took intraclass correlations into account, and we specified a separate random-error term for each tier. Variables potentially associated with death were introduced into the multivariable model. The hierarchical model comprised three levels: country (level 3), center (level 2), and patient (level 1). All variables not obviously correlated (e.g., SOFA score and vasopressor use, age or temperature and SAPS II excluding age related points) with P-values less than 0.10 by univariate analysis were introduced into the multivariable model. We did not correct for multiplicity of statistical tests. Owing to the low number of missing values, simple imputation to the median for continuous variables and to the mode for categorical variables was used (ESM eTable 1). The COVID-19 status was not included in the multivariable analysis because of co-linearity of the admission diagnosis with sepsis or septic shock. To mitigate the bias (*i.e.*, high mortality and different epidemiology of HA-BSI) introduced by patients infected with SARS-CoV-2 [3], we performed a sensitivity analysis excluding the 276 COVID-19 patients. Following the peer review process, and to mitigate the risk of bias introduced by logistic regression with day-28 mortality as an outcome variable (*i.e.,* a substantial part of the cohort was still in the ICU), we computed a competing-risk, subdistribution hazard frailty model as suggested by Fine and Gray [4]. We introduced ICU discharge as a competing risk and a random centre effect to model cluster dependence on the cumulative incidence function of the event of interest in the presence of competing events using the finalfit() package of the R software

Variable selection for the multivariable models.

Variable selection for the multivariable models used full pre-specification and was performed as follows:

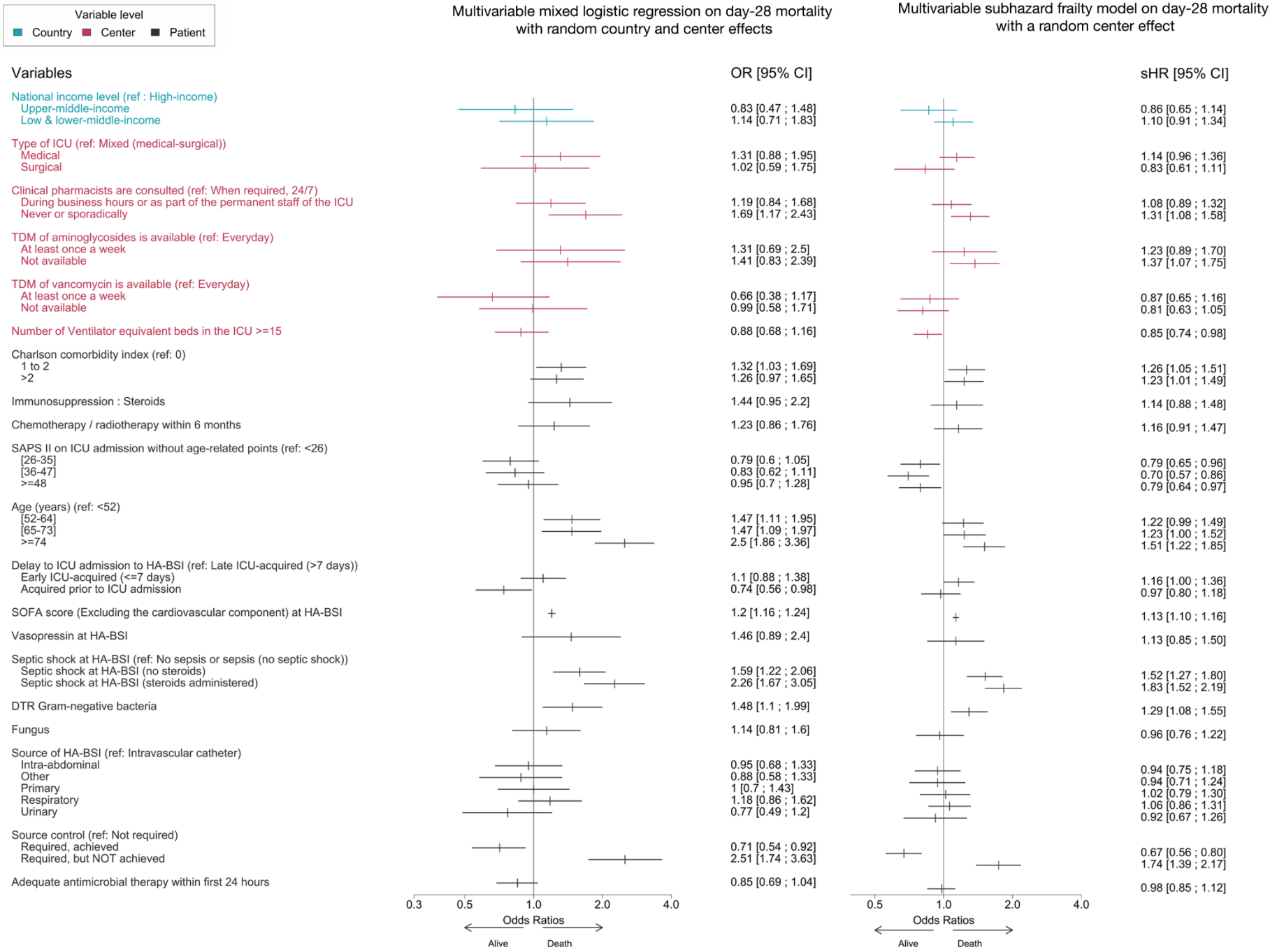
At database close a selection of clinically relevant variables was made to be presented in the manuscript and in the multivariable model. All candidate variables that were statistically significant with a threshold of 10% were included in the multivariable model. There was no stepwise process. We excluded variables that involved less than 5% of the cohort and those that were deemed collinear because of overlapping or used in the calculation of scores as shown in the table below.

Level	Variable	Selected for multivariable analysis	reason
Country	National income	Yes	
Center	Type of ICU	Yes	
Center	Paediatric	No	Collinear with type of ICU
Center	Post-operative	No	
Center	Neuro-surgical	No	
Center	Number of Ventilator equivalent beds in the ICU >=15	Yes	
Center	Clinical pharmacists are consulted	Yes	
Center	TDM of aminoglycosides is available	Yes	
Center	TDM of vancomycin is available	Yes	
Patient	Age	Yes	
Patient	SAPS-II on admission, excluding Age related points	Yes	SAPS-II score was computed excluding age related points to avoid collinearity with the variable Age.
Patient	Charlson co-morbidity index in class	Yes	
Patient	Solid-tumours – Proven metastasis	No	Already included as part of the computation of the SAPS-II score.
Patient	Haematological malignancy (Leukaemia or lymphoma)	No	
Patient	Immunosuppression: Steroids	Yes	
Patient	Chemotherapy / radiotherapy within 6 months	Yes	
Patient	Targeted Cancer Therapy (ongoing)	No	Size < 5%
Patient	Type of ICU admission	No	Already included as part of the computation of the SAPS-II score.
Patient	Primary ICU admission diagnosis	No	Collinear with sepsis / septic shock as 20.4% patients were admitted for sepsis or septic shock
Patient	Time from ICU admission to HA-BSI	Yes	
Patient	Temperature at HA-BSI (max) in class	No	Already included as part of the computation of the SAPS-II score.
Patient	SOFA score without the cardiovascular component at HA-BSI	Yes	The SOFA score cardiovascular component includes the use of dopamine, epi. or norepi. and as such is collinear with septic shock. We have included in the multivariable analysis a SOFA score excluding the cardiovascular component to avoid this issue.
Patient	SOFA score at HA-BSI	No	
Patient	Ventilation status	No	Collinear with the SOFA score
Patient	Vasopressors (adrenaline or noradrenaline)	No	Collinear with sepsis / septic shock
Patient	ECMO (VA OR VV)	No	Size < 5%
Patient	Vasopressin	Yes	This variable is not included in the SOFA score or in sepsis / septic shock.
Patient	Septic shock in class	Yes	
Patient	DTR Gram-negative pathogen	Yes	
Patient	Fungus	Yes	
Patient	Source of HA-BSI	Yes	
Patient	Source control	Yes	
Patient	Time to adequate antimicrobial therapy	Yes	

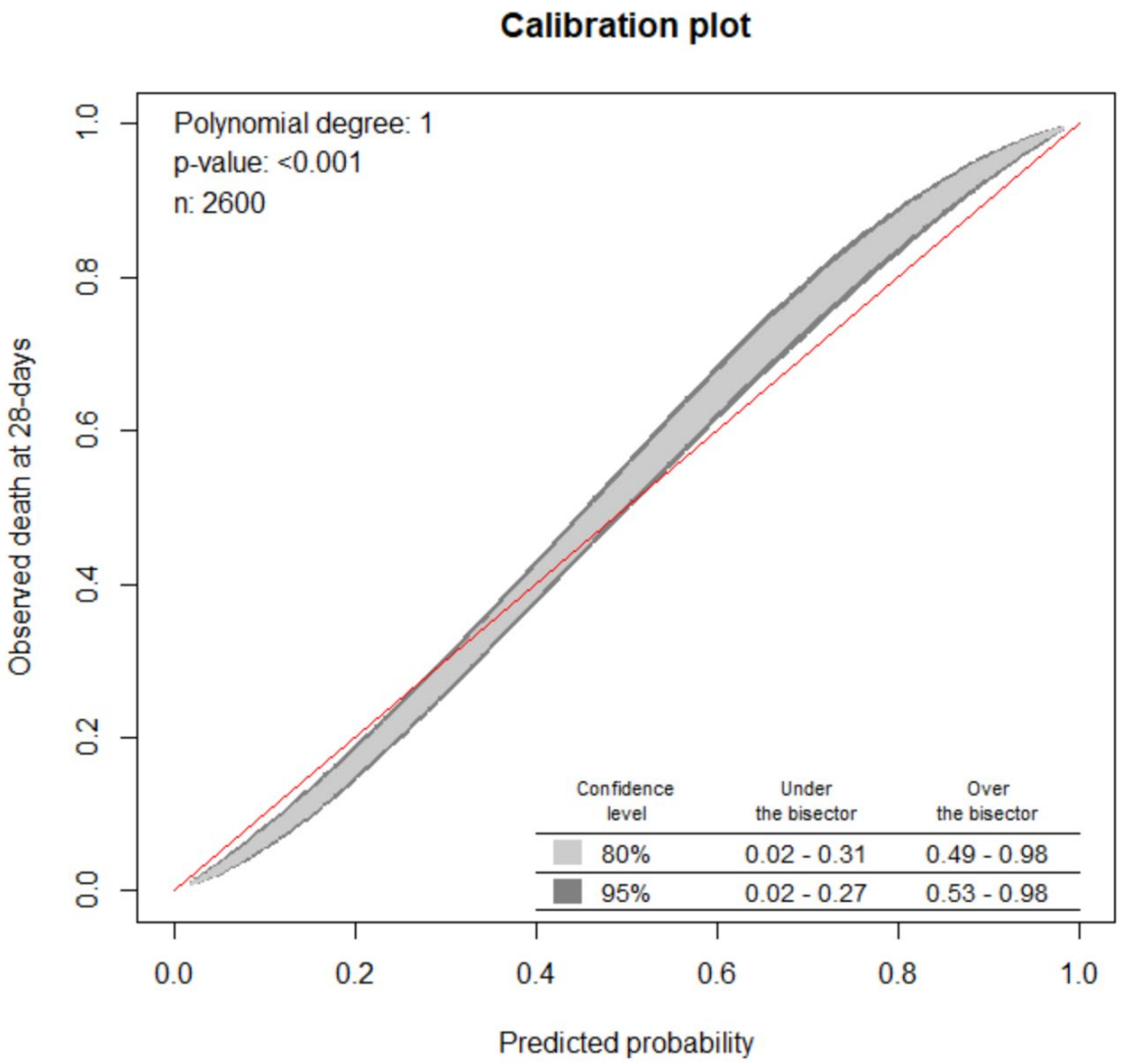
eTable 5 Competing-risks frailty model and comparison with hierarchical logistic model

		Hierarchical logistic mixed model	Competing-risks frailty model (Fine & Gray)
Variable	**items**	OR [CI 95%]	sHR [CI 95%]
National income level	High-Income	1	1
	Upper-middle-income	0.83 [0.47;1.48]	0.86 [0.65;1.14]
	Low & Lower-middle-income	1.14 [0.71;1.83]	1.10 [0.91;1.34]
Type of ICU	Mixed (medical-surgical)	1	1
	Medical	1.31 [0.88;1.95]	1.14 [0.96;1.36]
	Surgical	1.02 [0.59;1.75]	0.83 [0.61;1.11]
Clinical pharmacists are consulted	When required, 24/7	1	1
	During business hours or part of the ICU staff	1.19 [0.84;1.68]	1.08 [0.89;1.32]
	Never or sporadically	1.69 [1.17;2.43]	1.31 [1.08;1.58]
TDM of aminoglycosides is available	Everyday	1	1
	At least once a week	1.31 [0.69;2.5]	1.23 [0.89;1.70]
	Not available	1.41 [0.83;2.39]	1.37 [1.07;1.75]
TDM of vancomycin is available	Everyday	1	1
	At least once a week	0.66 [0.38;1.17]	0.87 [0.65;1.16]
	Not available	0.99 [0.58;1.71]	0.81 [0.63;1.05]
Number of Ventilator equivalent beds in the ICU ≥15		0.88 [0.68;1.16]	0.85 [0.74;0.98]
Charlson comorbidity index	0	1	1
	1 to 2	1.32 [1.03;1.69]	1.26 [1.05;1.51]
	>2	1.26 [0.97;1.65]	1.23 [1.01;1.49]
Immunosuppression: Steroids		1.44 [0.95;2.2]	1.14 [0.88;1.48]
Chemotherapy / radiotherapy within 6 months		1.23 [0.86;1.76]	1.16 [0.91;1.47]
SAPS II on ICU admission without age-related points	< 26	1	1
	[26-35]	0.79 [0.6;1.05]	0.79 [0.65;0.96]
	[36-47]	0.83 [0.62;1.11]	0.70 [0.57;0.86]
	>=48	0.95 [0.7;1.28]	0.79 [0.64;0.97]
Age (years)	<52	1	1
	[52-64]	1.47 [1.11;1.95]	1.22 [0.99;1.49]
	[65-73]	1.47 [1.09;1.97]	1.23 [1.00;1.52]
	>=74	2.5 [1.86;3.36]	1.51 [1.22;1.85]
Time from ICU admission to HA-BSI	Late ICU-acquired (>7 days)	1	1
	Early ICU-acquired (≤7 days)	1.1 [0.88;1.38]	1.16 [1.00;1.36]
	Acquired prior to ICU admission	0.74 [0.56;0.98]	0.97 [0.80;1.18]
SOFA score (Excluding the cardiovascular component) at HA-BSI		1.2 [1.16;1.24]	1.13 [1.10;1.16]
Vasopressin at HA-BSI		1.46 [0.89;2.4]	1.13 [0.85;1.50]
Septic shock at HA-BSI	No sepsis or sepsis (no septic shock)	1	1
	Septic shock at HA-BSI (no steroids)	1.59 [1.22;2.06]	1.52 [1.27;1.80]
	Septic shock at HA-BSI (received steroids)	2.26 [1.67;3.05]	1.83 [1.52;2.19]
DTR Gram-negative bacteria		1.48 [1.1;1.99]	1.29 [1.08;1.55]
Fungus		1.14 [0.81;1.6]	0.96 [0.76;1.22]
Most likely source of infection	Intravascular catheter	1	1
	Intra-abdominal	0.95 [0.68;1.33]	0.94 [0.75;1.18]
	Other	0.88 [0.58;1.33]	0.94 [0.71;1.24]
	Primary	1 [0.7;1.43]	1.02 [0.79;1.30]
	Respiratory	1.18 [0.86;1.62]	1.06 [0.86;1.31]
	Urinary	0.77 [0.49;1.2]	0.92 [0.67;1.26]
Source control	Not required	1	1
	Required, achieved	0.71 [0.54;0.92]	0.67 [0.56;0.80]
	Required, but NOT achieved	2.51 [1.74;3.63]	1.74 [1.39;2.17]
Adequate antimicrobial therapy within 24h of HA-BSI		0.85 [0.69;1.04]	0.98 [0.85;1.12]

Legend: Initially planned the hierarchical logistic mixed model and comparison with a competing risk frailty model. The covariance parameters for the logistic model (3-level hierarchical logistic regression) are as follows: Country-Level 3 (estimate: 0.08314, Standard error (SE) 0.09173), Center-Level 2 (estimate 0.4104, SE 0.1037). The c-statistic for the primary model was 0.8279 (95% CI 0.8119; 0.8439), indicating good discrimination. Calibration was tested using a calibration belt as shown below. Income level categories were defined using the United Nations M49 standard. HA-BSI: Hospital-acquired bloodstream infection, SAPS II: Simplified Acute Physiology Score II, TDM: Therapeutic drug monitoring, SOFA: Sequential Organ Failure Assessment. Closed brackets [;] denote inclusive of the end of the range and open brackets]; [denote the exclusion of the end of the range.


Variable level
Country
Center
Patient
Multivariable mixed logistic regression on day-28 mortality with random country and center effects
Multivariable subhazard frailty model on day-28 mortality with a random center effect
Variables
OR [95% CI]
sHR [95% CI]
National income level (ref : High-income)
Upper-middle-income
0.83 [0.47 ; 1.48]
0.86 [0.65 ; 1.14]
Low & lower-middle-income
1.14 [0.71 ; 1.83]
1.10 [0.91 ; 1.34]
Type of ICU (ref: Mixed (medical-surgical))
Medical
1.31 [0.88 ; 1.95]
1.14 [0.96 ; 1.36]
Surgical
1.02 [0.59 ; 1.75]
0.83 [0.61 ; 1.11]
Clinical pharmacists are consulted (ref: When required, 24/7)
During business hours or as part of the permanent staff of the ICU
1.19 [0.84 ; 1.68]
1.08 [0.89 ; 1.32]
Never or sporadically
1.69 [1.17 ; 2.43]
1.31 [1.08 ; 1.58]
TDM of aminoglycosides is available (ref: Everyday)
At least once a week
1.31 [0.69 ; 2.5]
1.23 [0.89 ; 1.70]
Not available
1.41 [0.83 ; 2.39]
1.37 [1.07 ; 1.75]
TDM of vancomycin is available (ref: Everyday)
At least once a week
0.66 [0.38 ; 1.17]
0.87 [0.65 ; 1.16]
Not available
0.99 [0.58 ; 1.71]
0.81 [0.63 ; 1.05]
Number of Ventilator equivalent beds in the ICU >=15
0.88 [0.68 ; 1.16]
0.85 [0.74 ; 0.98]
Charlson comorbidity index (ref: 0)
1 to 2
1.32 [1.03 ; 1.69]
1.26 [1.05 ; 1.51]
>2
1.26 [0.97 ; 1.65]
1.23 [1.01 ; 1.49]
Immunosuppression : Steroids
1.44 [0.95 ; 2.2]
1.14 [0.88 ; 1.48]
Chemotherapy / radiotherapy within 6 months
1.23 [0.86 ; 1.76]
1.16 [0.91 ; 1.47]
SAPS II on ICU admission without age-related points (ref: <26)
[26-35]
0.79 [0.6 ; 1.05]
0.79 [0.65 ; 0.96]
[36-47]
0.83 [0.62 ; 1.11]
0.70 [0.57 ; 0.86]
>=48
0.95 [0.7 ; 1.28]
0.79 [0.64 ; 0.97]
Age (years) (ref: <52)
[52-64]
1.47 [1.11 ; 1.95]
1.22 [0.99 ; 1.49]
[65-73]
1.47 [1.09 ; 1.97]
1.23 [1.00 ; 1.52]
>=74
2.5 [1.86 ; 3.36]
1.51 [1.22 ; 1.85]
Delay to ICU admission to HA-BSI (ref: Late ICU-acquired (>7 days))
Early ICU-acquired (<=7 days)
1.1 [0.88 ; 1.38]
1.16 [1.00 ; 1.36]
Acquired prior to ICU admission
0.74 [0.56 ; 0.98]
0.97 [0.80 ; 1.18]
SOFA score (Excluding the cardiovascular component) at HA-BSI
1.2 [1.16 ; 1.24]
1.13 [1.10 ; 1.16]
Vasopressin at HA-BSI
1.46 [0.89 ; 2.4]
1.13 [0.85 ; 1.50]
Septic shock at HA-BSI (ref: No sepsis or sepsis (no septic shock))
Septic shock at HA-BSI (no steroids)
1.59 [1.22 ; 2.06]
1.52 [1.27 ; 1.80]
Septic shock at HA-BSI (steroids administered)
2.26 [1.67 ; 3.05]
1.83 [1.52 ; 2.19]
DTR Gram-negative bacteria
1.48 [1.1 ; 1.99]
1.29 [1.08 ; 1.55]
Fungus
1.14 [0.81 ; 1.6]
0.96 [0.76 ; 1.22]
Source of HA-BSI (ref: Intravascular catheter)
Intra-abdominal
0.95 [0.68 ; 1.33]
0.94 [0.75 ; 1.18]
Other
0.88 [0.58 ; 1.33]
0.94 [0.71 ; 1.24]
Primary
1 [0.7 ; 1.43]
1.02 [0.79 ; 1.30]
Respiratory
1.18 [0.86 ; 1.62]
1.06 [0.86 ; 1.31]
Urinary
0.77 [0.49 ; 1.2]
0.92 [0.67 ; 1.26]
Source control (ref: Not required)
Required, achieved
0.71 [0.54 ; 0.92]
0.67 [0.56 ; 0.80]
Required, but NOT achieved
2.51 [1.74 ; 3.63]
1.74 [1.39 ; 2.17]
Adequate antimicrobial therapy within first 24 hours
0.85 [0.69 ; 1.04]
0.98 [0.85 ; 1.12]
0.3
0.5
1.0
2.0
4.0
Odds Ratios
Alive
Death
0.5
1.0
2.0
4.0
Odds Ratios
Alive
Death

eFigure 4: Calibration belt for the hierarchical logistic model.



Legend: Calibration belt, following the recommendations by Nattino et al. (2017), showing poor calibration. Given that our primary goal was to describe clinical features of HA-BSI patients and associations with mortality, we chose to fully pre-specify clinically relevant variables to be introduced in the model and have not attempted to improve model calibration through addition or deletion of variables, techniques of handling variables or other model specifications. Our preference was to present clinically relevant variables and their associations with mortality that physicians may use at the bedside.

eTable 6 Sensitivity analysis: Hierarchical logistic mixed model with random effects for country and ICU, excluding the 276 patients with a COVID-19 diagnosis.

Legend:

		Hierarchical logistic mixed model
Variable	**items**	OR [CI 95%]
National income level	High-Income	1
	Upper-middle-income	0.9 [0.5;1.61]
	Low & Lower-middle-income	1.18 [0.73;1.91]
Type of ICU	Mixed (medical-surgical)	1
	Medical	1.38 [0.92;2.07]
	Surgical	1.12 [0.65;1.91]
Clinical pharmacists are consulted	When required, 24/7	1
	During business hours or part of the ICU staff	1.14 [0.81;1.62]
	Never or sporadically	1.64 [1.13;2.38]
TDM of aminoglycosides is available	Everyday	1
	At least once a week	1.41 [0.75;2.69]
	Not available	1.52 [0.89;2.59]
TDM of vancomycin is available	Everyday	1
	At least once a week	0.67 [0.38;1.17]
	Not available	0.89 [0.52;1.52]
Number of Ventilator equivalent beds in the ICU ≥15		0.86 [0.65;1.14]
Charlson comorbidity index	0	1
	1 to 2	1.29 [0.99;1.68]
	>2	1.19 [0.9;1.58]
Immunosuppression: Steroids		1.52 [0.98;2.35]
Chemotherapy / radiotherapy within 6 months		1.29 [0.9;1.84]
SAPS II on ICU admission without age-related points	< 26	1
	[26-35]	0.71 [0.52;0.98]
	[36-47]	0.84 [0.61;1.16]
	>=48	0.96 [0.69;1.34]
Age (years)	<52	1
	[52-64]	1.54 [1.14;2.08]
	[65-73]	1.43 [1.04;1.95]
	>=74	2.6 [1.91;3.55]
Time from ICU admission to HA-BSI	Late ICU-acquired (>7 days)	1
	Early ICU-acquired (≤7 days)	1.13 [0.89;1.45]
	Acquired prior to ICU admission	0.81 [0.6;1.08]
SOFA score (Excluding the cardiovascular component) at HA-BSI		1.23 [1.19;1.28]
Vasopressin at HA-BSI		1.56 [0.95;2.58]
Septic shock at HA-BSI	No sepsis or sepsis (no septic shock)	1
	Septic shock at HA-BSI (no steroids)	1.52 [1.15;2]
	Septic shock at HA-BSI (received steroids)	2.08 [1.51;2.87]
DTR Gram-negative bacteria		1.38 [1.01;1.89]
Fungus		1.4 [1.01;1.92]
Most likely source of infection	Intravascular catheter	1
	Intra-abdominal	1.06 [0.75;1.5]
	Other	0.99 [0.65;1.52]
	Primary	1 [0.68;1.48]
	Respiratory	1.18 [0.83;1.66]
	Urinary	0.87 [0.55;1.39]
Source control	Not required	1
	Required, achieved	0.75 [0.57;0.99]
	Required, but NOT achieved	2.59 [1.77;3.8]
Adequate antimicrobial therapy within 24h of HA-BSI		0.84 [0.68;1.04]

Sensitivity analysis conducted on 2324 patients after exclusion of the 276 patients with a COVID-19 diagnosis, Income level categories were defined using the United Nations M49 standard. DTR: difficult-to-treat resistance, HA-BSI: Hospital-acquired Bloodstream Infection, ICU: intensive care unit, SAPS II: Simplified Acute Physiology Score II, SOFA: Sequential Organ Failure Assessment, TDM: Therapeutic drug monitoring. Closed brackets [;] denote inclusive of the end of the range and open brackets]; [denote the exclusion of the end of the range.

eTable 7 Sensitivity analysis: Hierarchical logistic mixed model with random effects for country and ICU, investigating carbapenem resistance instead of difficult to treat resistance.

		Hierarchical logistic mixed model
Variable	**items**	OR [CI 95%]
National income level	High-Income	1
	Upper-middle-income	0.83 [0.46;1.48]
	Low & Lower-middle-income	1.14 [0.71;1.84]
Type of ICU	Mixed (medical-surgical)	1
	Medical	1.3 [0.87;1.94]
	Surgical	1.02 [0.59;1.75]
Clinical pharmacists are consulted	When required, 24/7	1
	During business hours or part of the ICU staff	1.19 [0.84;1.68]
	Never or sporadically	1.68 [1.16;2.42]
TDM of aminoglycosides is available	Everyday	1
	At least once a week	1.31 [0.69;2.49]
	Not available	1.39 [0.82;2.38]
TDM of vancomycin is available	Everyday	1
	At least once a week	0.67 [0.38;1.18]
	Not available	1 [0.58;1.72]
Number of Ventilator equivalent beds in the ICU ≥15		0.88 [0.67;1.16]
Charlson comorbidity index	0	1
	1 to 2	1.32 [1.03;1.69]
	>2	1.27 [0.97;1.65]
Immunosuppression: Steroids		1.41 [0.93;2.16]
Chemotherapy / radiotherapy within 6 months		1.24 [0.86;1.77]
SAPS II on ICU admission without age-related points	< 26	1
	[26-35]	0.79 [0.6;1.05]
	[36-47]	0.84 [0.62;1.12]
	>=48	0.95 [0.7;1.29]
Age (years)	<52	1
	[52-64]	1.48 [1.11;1.96]
	[65-73]	1.47 [1.1;1.98]
	>=74	2.52 [1.88;3.38]
Time from ICU admission to HA-BSI	Late ICU-acquired (>7 days)	1
	Early ICU-acquired (≤7 days)	1.1 [0.88;1.38]
	Acquired prior to ICU admission	0.74 [0.56;0.98]
SOFA score (Excluding the cardiovascular component) at HA-BSI		1.23 [1.18;1.27]
Vasopressin at HA-BSI		1.49 [0.91;2.43]
Septic shock at HA-BSI	No sepsis or sepsis (no septic shock)	1
	Septic shock at HA-BSI (no steroids)	1.58 [1.22;2.05]
	Septic shock at HA-BSI (received steroids)	2.26 [1.67;3.06]
Carbapenem resistant enterobacterales		1.31 [1.02;1.68]
Fungus		1.15 [0.81;1.62]
Most likely source of infection	Intravascular catheter	1
	Intra-abdominal	0.95 [0.68;1.33]
	Other	0.88 [0.58;1.33]
	Primary	1 [0.7;1.43]
	Respiratory	1.18 [0.86;1.62]
	Urinary	0.77 [0.49;1.2]
Source control	Not required	1
	Required, achieved	0.71 [0.55;0.92]
	Required, but NOT achieved	2.48 [1.72;3.59]
Adequate antimicrobial therapy within 24h of HA-BSI		0.85 [0.7;1.04]

Legend: Sensitivity analysis computed by imputing carbapenem resistance in Gram-negative pathogens in place of DTR. Income level categories were defined using the United Nations M49 standard. DTR: difficult-to-treat resistance, HA-BSI: Hospital-acquired Bloodstream Infection, ICU: intensive care unit, SAPS II: Simplified Acute Physiology Score II, SOFA: Sequential Organ Failure Assessment, TDM: Therapeutic drug monitoring. Closed brackets [;] denote inclusive of the end of the range and open brackets]; [denote the exclusion of the end of the range.

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Hong Kong

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Japan

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Malaysia

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Philippines

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Republic Of Korea

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Thailand

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Middle East and North Africa

Dubai

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Egypt

National Coordinator: Dr. Adel Alsisi

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Iran

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Iraq

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Israel

National Coordinator: Prof. Pierre Singer

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Jordan

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Lebanon

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Libya

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Morocco

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Palestine

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Qatar

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Saudi Arabia

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Syria

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Tunisia

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Latin America and The Caribbean

Argentina

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Colombia

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Mexico

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Europe And Central Asia

Belgium

National Coordinator: Dr. Liesbet De Bus

Scientific Committee: Prof. Jan De Waele

Recruitment of participating ICUs worldwide: Mr. Guy Francois

Participating ICUs: Ghent University Hospital, Intensive Care Unit: Dr Liesbet De Bus, Dr Jan De Waele. A.S.Z., Iz: Dr Isabelle Hollevoet. Az Nikolaas, Icu: Dr Wouter Denys. Az Sint-Jan Av Brugge - Oostende Campus Brugge, Icu: Dr Marc Bourgeois. Az Sint-Lucas, Department of Intensive Care: Dr Sofie F.M. Vanderhaeghen. Centre Hospitalier De Jolimont, Soins Intensifs : Dr Jean-Baptiste Mesland, Dr Pierre Henin. Chu Ambroise Paré, Unité Des Soins Intensifs : Dr Lionel Haentjens. Chu Charleroi, Medico-Surgical Icu: Dr Patrick Biston, Mrs Cindérella Noel. Chu Liège, Soins Intensifs : Dr Nathalie Layos, Dr Benoît Misset. Clinique Saint-Pierre, Intensive Care Unit : Dr Nicolas De Schryver, Dr Nicolas Serck. Cliniques Universitaires Saint-Luc, UCLouvain, Soins Intensifs : Dr Xavier Wittebole. Uzbrussel, Intensieve Zorgen: Prof Elisabeth De Waele, Mrs Godelive Opdenacker.

Bosnia And Herzegovina

National Coordinator: Dr Pedja Kovacevic

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Croatia

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France

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Germany

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Kazakhstan

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Greece

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Italy

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Poland

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Republic Of Ireland

National Coordinator: Prof Ignacio Martin-Loeches

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Portugal

National Coordinator: Prof. José Artur Paiva

Scientific Committee: Prof. Pedro Póvoa

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