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SPECIAL ARTICLE

Characteristics and determinants of outcome of hospital-acquired bloodstream infections in intensive care units: the EUROBACT International Cohort Study

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Abstract *Purpose:* The recent increase in drug-resistant micro-organisms complicates the management of hospital-acquired bloodstream infections (HA-BSIs). We investigated the epidemiology of HA-BSI and evaluated the impact of drug resistance on outcomes of critically ill patients, controlling for patient characteristics and infection management. *Methods:* A prospective, multicentre non-representative cohort study was conducted in 162 intensive care units (ICUs) in 24 countries. *Results:* We included 1,156 patients [mean ± standard deviation (SD) age, 59.5 ± 17.7 years; 65 % males; mean ± SD Simplified Acute Physiology Score (SAPS) II score, 50 ± 17] with HA-BSIs, of which 76 % were ICU-acquired. Median time to diagnosis was 14 [interquartile range (IQR), 7–26] days after hospital admission. Polymicrobial infections accounted for 12 % of cases. Among monomicrobial infections, 58.3 % were gram-negative, 32.8 % gram-positive, 7.8 % fungal and 1.2 % due to strict anaerobes. Overall, 629 (47.8 %) isolates were multidrug-resistant (MDR), including 270 (20.5 %) extensively resistant (XDR), and 5 (0.4 %) pan-drug-resistant (PDR). Micro-organism distribution and MDR occurrence varied significantly ($p < 0.001$) by country. The 28-day all-cause fatality rate was 36 %. In the multivariable model including micro-organism, patient and centre variables, independent predictors of 28-day mortality included MDR isolate [odds ratio (OR), 1.49; 95 % confidence interval (95 %CI), 1.07–2.06], uncontrolled infection source (OR, 5.86; 95 %CI, 2.5–13.9) and timing to adequate treatment (before day 6 since blood culture collection versus never, OR, 0.38; 95 %CI, 0.23–0.63; since day 6 versus never, OR, 0.20; 95 %CI, 0.08–0.47). *Conclusions:* MDR and XDR bacteria (especially gram-negative) are common in HA-BSIs in critically ill patients and are associated with increased 28-day mortality. Intensified efforts to prevent HA-BSIs and to optimize their management through adequate source control and antibiotic therapy are needed to improve outcomes.

Keywords Hospital acquired bloodstream infections · Critically ill patients · Antibiotic therapy · Prognosis · Multilevel models · Extensively resistant bacterias

Introduction

Bloodstream infection (BSI) is an important cause of severe sepsis and septic shock that is associated with high resource utilisation, morbidity and mortality [1–4]. Hospital-acquired bloodstream infection (HA-BSI) is recognised as a major patient-safety concern and a marker of quality of care [5]. Patients admitted to intensive care units (ICUs) have multiple risk factors for HA-BSIs including severe acute illness, co-morbidities and frequent use of invasive devices [6]. Many changes have occurred in the epidemiology of BSI in recent years, particularly with the emergence of drug-resistant organisms, which has increased the treatment-failure rate and

the risk of adverse patient outcomes [2, 6]. Although hospital-acquired infections in critically ill patients have been the focus of numerous reports worldwide [2–8], there is a paucity of contemporary multinational data on the epidemiology and outcome determinants of HA-BSIs in ICU patients [2, 4, 9].

The objective of this study is to describe the epidemiology of HA-BSIs treated in the ICU and to identify determinants of treatment failure and outcomes in Europe and internationally.

Methods

This study is reported in accordance with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines [10].

A prospective observational multicentre international cohort design was used. All participating ICUs obtained approval from their local ethics committees. The predefined goal was to include 1,100 ICU patients with HA-BSI.

Study protocol and definitions

Patients were enrolled if they had a new diagnosis of HA-BSI and were admitted to an ICU. The study focussed on the first episode of HA-BSI. Detailed definitions of HA-BSI are provided in the Electronic Supplement.

Data collected for each patient included the dates and times of collection and positivity of the first positive blood culture; source of infection; presence of sepsis; severity of illness; co-morbidities; and management including source control, antimicrobial drugs and adjunctive treatments. All study data were obtained from patient files, and no additional tests were performed for the purpose of the study. Severity of illness was defined at ICU admission and at HA-BSI diagnosis using SAPS II and Sequential organ failure assessment (SOFA) scores [11], respectively. Co-morbidities were assessed using the Charlson index and the five markers of the Chronic Health Evaluation of the APACHE II score reported by Knaus et al. [12, 13].

Clinical variables and relapses or new episodes of HA-BSI were recorded until ICU discharge, and all-cause mortality within 28 days since first positive blood culture was ascertained.

We recorded information on each ICU including type of hospital and ICU, number of beds and patients, and mortality rate in the previous year (2008). We also recorded factors possibly associated with antimicrobial use such as the availability of an infectious diseases specialist, procedures for antibiotic use and infection control protocols.

The organisms causing HA-BSI and their antimicrobial susceptibility test results were recorded according to local policies. Detailed definitions of adequate antimicrobial therapy are given in the Electronic Supplement.

Drug-resistant organisms were classified as susceptible (SUS), multidrug resistant (MDR), extensively resistant (XDR) and pan-drug resistant (PDR) according to the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) [14]. Each category was included within the previous category: all PDR organisms were XDR, and all XDR organisms were MDR. Definitions and worksheets can be downloaded from the European Centre for Disease Prevention and Control (ECDC) website [15]. According to this classification scheme, bacteria other than enterococci, *Staphylococcus aureus*, *Enterobacteriaceae* and non-fermenting gram-negative bacteria were considered susceptible. We arbitrarily classified yeasts among MDR organisms on the basis of their non-sensitivity to first-line empirical antimicrobial therapies.

Data management and statistical analysis

In each study ICU, data were entered into a password-protected and secured web-based server. Online data were managed in MySQL 5.1.41 (Oracle, Redwood Shores, CA, USA) and downloaded to SAS 9.2 (SAS Institute, Cary, NC, USA) for offline management and analysis. The electronic case-report form was developed locally using open-source software (PHP/MySQL) with the primary goal of ensuring easy and consistent data entry, data verification and easy communication between the coordinating centre (Albert Bonniot Institute, University Joseph Fourier, Grenoble, France) and each study ICU. At the coordinating centre, two investigators (A.T., D.K.) routinely checked the data for completeness and for consistency in definition use. All missing, extreme or implausible values were sent back to the study-ICU investigators for review. Where data could not be confirmed or remained questionable, the primary author (A.T.) made a final adjudication about study inclusion, in agreement with the main investigator (J.-F.T.). Doubtful cases were reviewed by two other investigators (J.-R.Z. and K.L.). Missing data were replaced by the median value, and missing times of sampling and of blood culture positivity by 12:00 a.m.

The statistical analyses considered only the first episode of HA-BSI, as information was fully collected only for these occurrences.

Means with standard deviation (SD) were used to describe normally or near-normally distributed continuous data and were compared using the *t* test. Medians with interquartile range (IQR) were computed for skewed data and were compared using the Mann–Whitney test. Fisher's exact test or the chi-square test was performed to compare categorical data.

In multivariable analyses, variables were organised into three tiers: country, ICU and patient. To identify factors associated with 28-day mortality, we built a three-tiered hierarchical logistic mixed model using the GLIMMIX procedure of the SAS software. The influence of country-based and ICU-based variables on the outcome was included through both fixed and random effects. Multilevel modelling takes into account the hierarchical structure of the data, which may manifest as intra-class correlations. To obtain a conservative estimate of the standard error, a separate random-error term should be specified for each level of the analysis [16]. Therefore, to avoid overestimating the significance of risk factors for death by day 28, we took intra-class correlations into account, and we specified a separate random-error term for each tier. Variables potentially associated with 28-day mortality (p values less than 0.10 on univariate analysis) were introduced into the multivariable model and selected using a backward approach. Two-way clinically relevant interactions were tested in the final model. In all analyses, two-sided p values less than 0.05 were deemed statistically significant. No correction for multiple testing was performed.

Results

We enrolled 1,156 patients from 162 ICUs in 120 cities in 24 countries (Fig. 1). Sixty-three ICUs accepted the study but did not participate, and 16 ICUs (30 patients) were excluded because of incomplete data. Of the 1,227 patients included initially, 71 were excluded prior to data analysis (34 incomplete files, 8 patients with community-acquired BSI and 29 patients with cultures positive for skin contaminants), leaving 1,156 patients for the study.

The study patients were located in many different geographic regions, although they predominated in European countries, particularly France (17.8 %) and Greece (24.9 %) (Fig. 1). No country-related factors were significantly associated with 28-day mortality (Table E1, Electronic Supplement).

Most of the ICUs (64 %) were university or university-affiliated. An infectious disease specialist was available in 86 % of the ICUs. Written antibiotic procedures were available in 71 % of ICUs and followed strictly in 23 %. Further details on ICU-related prognosis factors are presented in Table 1.

A total of 1,317 bloodstream isolates were cultured from the 1,156 study patients. A single organism was found in 1,016 (88 %) patients, two organisms in 120 (10 %) patients, three organisms in 19 (2 %) patients and four organisms in 1 (<1 %) patient.

HA-BSIs were diagnosed a median of 14 (IQR, 7–26) days after hospital admission. Among them, 76 % (877/1,156) were diagnosed in the ICU, with a median time from ICU admission to diagnosis of 8 (IQR, 3–16) days. Timing of acquisition had no significant influence on mortality. Patient characteristics are reported in Table 2 and details on the infections and treatment in Table 3.

The most common organisms causing HA-BSI and their resistance patterns are presented in Table 4. Of monomicrobial infections ($n = 1{,}016$), 592 (58.3 %) were gram-negative, 333 (32.8 %) gram-positive, 79 (7.8 %) fungal and 12 (1.2 %) due to strict anaerobes.

Carbapenem resistance was found in 110/166 (69 %) *Acinetobacter* spp., 59/156 (38 %) *Klebsiella pneumoniae*, 56/150 (37 %) *Pseudomonas* spp., 5/88 (5.7 %) *Enterobacter* spp. and 1/98 (1 %) *Escherichia coli*. Of the 119 *S. aureus* isolates, 57 (48 %) were methicillin-resistant; and of the 70 *Enterococcus faecium* isolates, 16 (23 %) were vancomycin-resistant (VRE). Isolates acquired in the ICU were more often drug resistant compared with other hospital-acquired isolates (413/992, 42 % versus 82/325, 25 %; $p < 0.0001$). The distribution of organisms differed significantly ($p < 0.001$) by country (Table E2, Electronic Supplement).

Among the 1,156 study patients, 608 (52.6 %) received adequate antibiotic therapy before or within 24 h following collection of the first positive blood culture, whereas 154 (13.3 %) did not receive adequate antibiotic therapy within 5 days or before ICU discharge or death. Patients who received adequate antimicrobials only after the fifth day had lower SOFA scores. Late adequate therapy was also associated with a longer time to blood-culture positivity (median [IQR], 100 h [23–144]). Resistance rates showed a significant positive association with failure to receive adequate antibiotic therapy. As shown in Fig. 2, time to adequate antibiotic therapy increased with antimicrobial resistance (chi-square for trends, $p < 0.001$).

The most frequently prescribed empirical antimicrobials and their adequacy against the causative organism are shown in Fig. 3a, and the first adequate treatment is shown in Fig. 3b. Carbapenems were the antimicrobials most frequently given in the first 24 h ($n = 212$; 19 %), followed by glycopeptides ($n = 172$; 15 %) and piperacillin-tazobactam ($n = 152$; 13 %). Treatment was adequate in the first 24 h with monotherapy in 339 (29 %) patients and combined therapy in 269 (23 %) patients. The 548 (47 %) remaining patients did not receive adequate antimicrobials in the first 24 h.

The 28-day all-cause mortality rate was 413/1,156 (35.7 %), with 381/413 (92 %) deaths occurring in the ICU. On day 28, 295/743 (40 %) survivors were still in the ICU. Among the 1,156 patients, 194 (17 %) had second and 44 (4 %) had third episodes of HA-BSI identified within the 28-day follow-up period. Patient- and ICU-related factors included in the univariate analysis are presented in Tables 1–3.

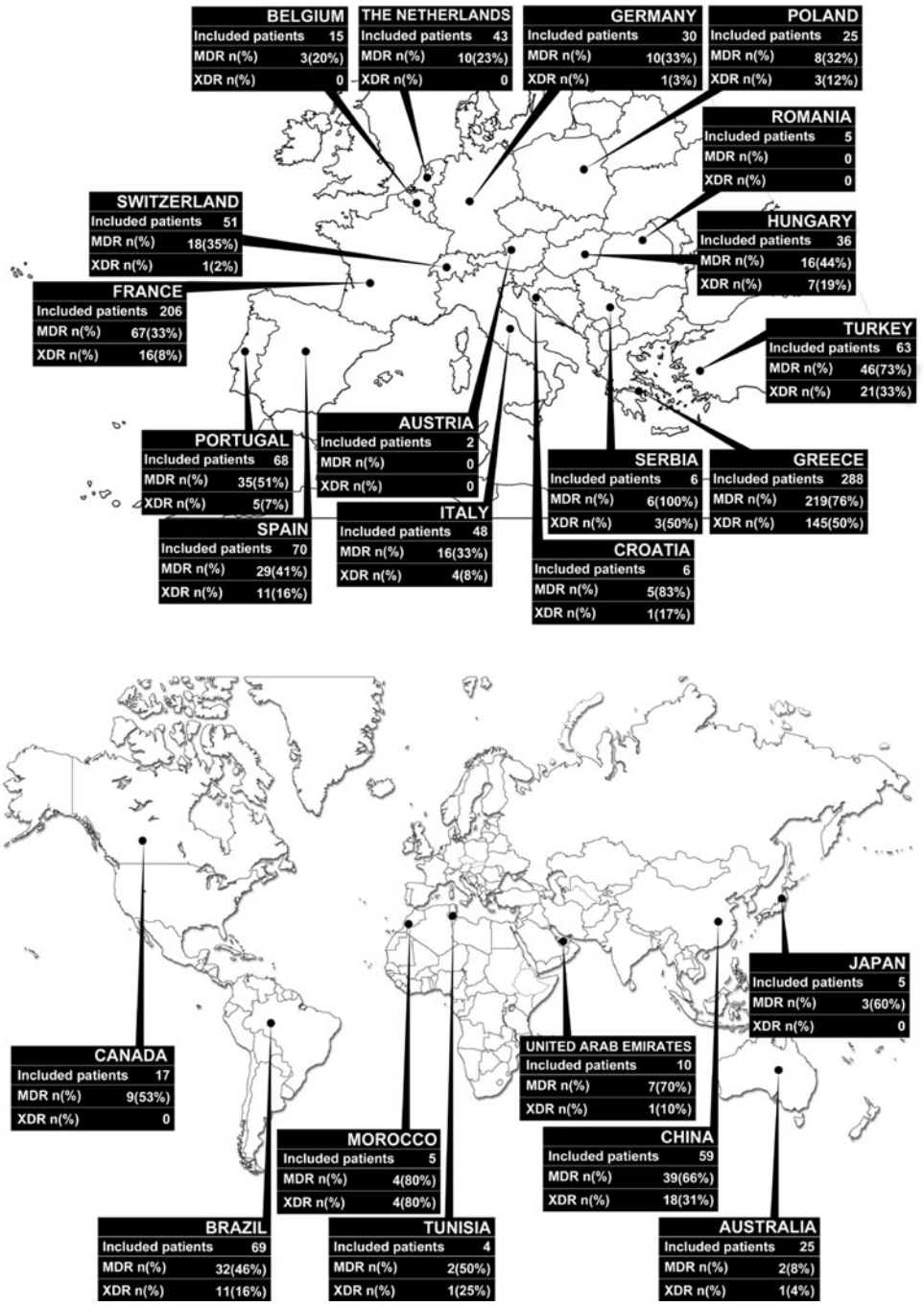

Fig. 1 Geographic distribution of included patient and antimicrobial resistance categories

On multivariable analysis (Table 5), factors significantly associated with higher 28-day mortality were turnover above the median value, higher mean ICU mortality rate in the previous year (2008) and several patient-related factors (Table 5). 28-day mortality was not significantly influenced by factors that may reflect antimicrobial stewardship (availability of an infectious diseases specialist, microbiological laboratory, written antibiotic protocols and/or infection-control protocols). 28-day mortality was significantly higher in older patients and in patients with chronic respiratory disease or immune deficiency. Intensity of the host response and organ dysfunctions as reflected by septic shock or a higher SOFA score at HA-BSI onset was an independent risk factor for 28-day mortality. The source of infection significantly affected 28-day mortality when introduced as a multiple-class variable (catheter, intra-abdominal, respiratory, urinary, multiple and other focus) ($p = 0.02$, data

Table 1 Associations between ICU characteristics and 28-day mortality

Variable	Characteristics	All ICUs ($N = 162$)	All patients ($N = 1,156$)	Alive on D28 ($N = 743$)	Dead on D28 ($N = 413$)	p-Value[a]
Academic status of hospital	University	74 (45.7)	594 (51.4)	386 (49.5)	208 (50.4)	0.9
	University affiliated	30 (18.5)	199 (17.2)	128 (17.2)	71 (17.2)	
	General	58 (35.8)	363 (31.4)	229 (30.8)	134 (32.4)	
Funding of hospital	Public	145 (89.5)	1,042 (90.1)	670 (90.2)	372 (90)	1
	Private	17 (10.5)	114 (9.9)	73 (9.8)	41 (9.9)	
ICU recruitment	Medical	30 (18.5)	212 (18.3)	137 (18.4)	75 (18.1)	0.4
	Surgical	16 (9.9)	78 (6.7)	60 (8)	18 (4.3)	
	Medical + surgical	107 (66)	807 (69.8)	509 (68.5)	298 (72.1)	
	Cardiac	3 (1.9)	14 (1.2)	9 (1.2)	5 (1.2)	
	Other	6 (3.7)	45 (3.9)	28 (3.8)	17 (4.1)	
Type of ICU	Open	49 (30.2)	308 (26.6)	201 (27)	107 (25.9)	0.7
	Closed	113 (69.8)	848 (73.4)	542 (72.9)	306 (74.1)	
Number of ICU beds		12 [8]	14 [10]	14 [10]	14 [10]	0.5
Number of admissions/year		597 [458]	600 [748]	600 [750]	618 [737]	1
Number of admissions/bed/year	≤40	80 (49.4)	551 (47.7)	367 (49.4)	184 (44.6)	0.14
	>40	82 (50.6)	605 (52.3)	376 (50.6)	229 (55.4)	
Number of intensivists		6 [6]	7 [6]	7 [6]	7 [6]	0.5
Patient-to-nurse ratio		2 [1]	2.4 [1]	2.3 [1]	2.5 [1]	0.3
Overall ICU mortality rate in the past year (2008)		20 [13]	20 [13.4]	20 [13]	20.3 [12]	0.045
Availability of an infectious diseases specialist	No	22 (13.6)	139 (12)	84 (11.3)	55 (13.3)	0.3
	Consultant only	87 (53.7)	587 (50.8)	369 (49.7)	218 (52.8)	
	Yes	53 (32.7)	430 (37.2)	290 (39)	140 (33.9)	
Availability of an antibiotic committee	No	31 (19.1)	233 (20.2)	160 (21.5)	73 (17.7)	0.18
	Yes	131 (80.9)	923 (79.8)	583 (78.5)	340 (82.3)	
Written antibiotic procedures	No	47 (29)	307 (26.6)	195 (26.2)	112 (27.1)	0.17
	Yes, not strict	78 (48.1)	594 (51.4)	399 (53.7)	195 (47.2)	
	Yes, strict	37 (22.8)	255 (22.1)	149 (20)	106 (25.7)	
Infection prevention/control protocols	No	25 (15.4)	146 (12.6)	94 (12.6)	52 (12.6)	1.0
	Yes, not strict	64 (39.5)	495 (42.8)	318 (42.8)	177 (42.9)	
	Yes, strict	73 (45.1)	515 (44.6)	331 (44.5)	184 (44.6)	
Microbiological lab	24 h, in hospital	105 (64.8)	811 (70.2)	518 (69.7)	293 (70.9)	0.6
	24 h, outside hospital	12 (7.4)	61 (5.3)	42 (5.6)	19 (4.6)	
	Day only, in hospital	43 (26.5)	268 (23.2)	175 (23.5)	93 (22.5)	
	No	2 (1.2)	16 (1.4)	8 (1)	8 (1.9)	
Catheter tip culture	No	10 (6.2)	60 (5.2)	38 (5.1)	22 (5.3)	0.4
	Yes always	82 (50.6)	600 (51.9)	403 (54.2)	197 (47.7)	
	Yes, unless deceased	11 (6.8)	86 (7.4)	54 (7.2)	32 (7.7)	
	Yes, only for sepsis	59 (36.4)	410 (35.5)	248 (33.4)	162 (39.2)	

Results are shown as n (%), median [IQR] where applicable

[a] Hierarchical logistic regression with random effect for centre and country

not shown). Only abdominal source of infection was associated with 28-day mortality at the final step of variable selection. 28-day mortality was significantly higher in the event of inadequate antibiotic therapy or failure to control the infection source if required (absence of catheter removal, $n = 12$; surgical treatment for abdominal source of infection, $n = 22$; other sources, $n = 6$; multiple possible foci, $n = 5$).

Presence of an MDR/XDR/PDR organism was associated with a longer time to adequate antimicrobial therapy and with an increase in 28-day mortality. XDR or PDR resistance levels were not associated with higher 28-day mortality when compared with MDR levels. The results remained similar after exclusion of fungal HA-BSIs from the analysis (Table E3, Electronic Supplement) and when considering patients with a single episode of HA-BSI (Table E4, Electronic Supplement). The impact of inadequate antimicrobial treatment was not significantly different between episodes with and without MDR strains ($p = 0.54$).

Discussion

EUROBACT provides a contemporary analysis of the prognostic factors of HA-BSI among patients admitted to ICUs internationally. There was a predominance of patients included in France, Greece and southern Europe. Drug resistance rates were very high overall, and MDR was particularly common among gram-negative pathogens. Piperacillin + tazobactam, carbapenems, and

Table 2 Associations between baseline (admission to the ICU) patient characteristics and 28-day mortality

Variable	Characteristics	All patients (n = 1,156)	Alive on D28 (n = 743)	Dead on D28 (n = 413)	p-Value[a]
Age, years		59.5 ± 17.7	57.2 ± 18.3	63.7 ± 15.8	<0.0001
SAPS II		50 ± 17	47 ± 15	56 ± 17	<0.0001
Obesity (BMI >30 kg/m^2)		251 (22.1)	175 (69.7)	76 (30.3)	0.08
Malnutrition (BMI <18.5 kg/m^2)		43 (3.8)	24 (55.8)	19 (44.2)	0.18
Male		756 (65.4)	503 (66.5)	253 (33.5)	0.03
Charlson co-morbidity index	0	386 (33.4)	296 (76.7)	90 (23.3)	<0.0001
	1–2	404 (34.9)	263 (65.1)	141 (34.9)	
	3+	366 (31.7)	184 (50.3)	182 (49.7)	
Chronic illnesses					
Respiratory		98 (8.5)	50 (51)	48 (49)	0.008
Cardiovascular		117 (10.1)	71 (60.7)	46 (39.3)	0.5
Renal		61 (5.3)	34 (55.7)	27 (44.3)	0.19
Hepatic		44 (3.8)	21 (47.7)	23 (52.3)	0.017
Immunosuppression		151 (13.1)	68 (45)	83 (55)	<0.0001
Medical admission		672 (58.1)	398 (59.2)	274 (40.8)	0.0003
Organ dysfunctions at admission					
Neurological		354 (30.6)	236 (66.7)	118 (33.3)	0.5
Haemodynamic		591 (51.1)	342 (57.9)	249 (42.1)	<0.0001
Respiratory		937 (81.1)	586 (62.5)	351 (37.5)	0.009
Renal		155 (13.4)	86 (55.5)	69 (44.5)	0.01
No organ failure on admission		126 (10.9)	95 (75.4)	31 (24.6)	0.006
Septic shock at admission		267 (23.1)	139 (52.1)	128 (47.9)	<0.0001

BMI body mass index. Results are shown as n (%), mean ± SD where applicable

[a] Hierarchical logistic regression with random effect for centre and country

glycopeptides were extensively used both as initial empirical drugs and once the culture results were available. Mortality was higher in ICUs with higher turn-over rates. Inadequate antibiotic treatment and failure to control the source of infection were both associated with 28-day mortality, independently from age, chronic co-morbidities, severity of acute illness, shock and organ dysfunctions. Antimicrobial resistance was associated with a significantly longer time to adequate antimicrobial treatment and with a higher risk of death, even after controlling for adequacy of antimicrobial treatment.

The epidemiology of BSIs in ICU patients has changed over time. Gram-positive bacteria and yeasts have become major causes of BSI in the last two decades [1, 17]. MDR gram-negative bacteria are re-emerging [18], as confirmed by the present report. The most frequent pathogens in EUROBACT were *Acinetobacter*, *Klebsiella* and *Pseudomonas* spp., followed by enterococci, coagulase-negative staphylococci and *S. aureus*. The high prevalence of *Acinetobacter* in our study is probably related to the overrepresentation of southern European countries and may not reflect the situation worldwide. We observed significant variability in the distributions of organism groups and resistance patterns across countries, in accordance with European surveillance reports [15]. MDR organisms were ubiquitous, and three-quarters of the countries reported at least one XDR organism. These data are consistent with earlier reports [15]. Thus, XDR *Acinetobacter baumanii* and *P. aeruginosa* and carbapenemase-producing *K. pneumoniae* have been reported in southern Europe, as well as in South America and Asia, and have shown a tendency to spread rapidly throughout the world [18]. Moreover, with the expansion of international travel [19], no country is exempt from the risk of a major XDR outbreak.

The relationship between promptness of adequate therapy and prognosis is complex. Physicians prescribe early extended-spectrum antimicrobial therapy to patients with severe clinical presentations. In contrast, antimicrobial therapy is often delayed in patients without organ dysfunctions or with long times to blood-culture positivity. Finally, patients who die very early never receive antimicrobial therapy. These considerations explain why treatment adequacy was unrelated to outcomes in recent cohort studies [9, 20, 21]. Observational studies cannot provide proof of a causal relationship between treatment adequacy and outcome. In the present study, we found an association between time to adequate treatment and mortality even after adjustment for acute-illness severity at BSI onset. Further multistate models taking into account adequate antimicrobial therapy as a non-absorbing state and severity of the BSI are needed to definitely estimate the impact of delayed therapy. Although fluid resuscitation and adequate treatment of organ dysfunctions are key components of critical care, prompt adequate antimicrobial treatment remains a cornerstone of BSI management in the ICU [22].

Many studies, including the present one, have found that bacterial resistance decreased the chance of early

Table 3 Patient characteristics at the diagnosis of hospital-acquired bloodstream infection

Variable	Characteristics	All patients ($N = 1,156$)	Alive on D28 ($N = 743$)	Dead on D28 ($N = 413$)	p-Value[a]
Time from ICU admission to HA-BSI	Hospital-acquired, before ICU admission	279 (24.1)	168 (60.2)	111 (39.8)	0.01
	ICU-acquired, ≤7 days	281 (24.3)	186 (66.2)	95 (33.8)	
	ICU-acquired, >7 days	596 (51.6)	389 (65.3)	207 (34.7)	
Sepsis syndrome	SIRS/SEPSIS	150 (13)	110 (73.3)	40 (26.7)	<0.0001
	Severe sepsis	476 (41.2)	347 (72.9)	129 (27.1)	
	Septic shock	530 (45.8)	286 (54)	244 (46)	
SIRS score	0	24 (2.1)	15 (62.5)	9 (37.5)	0.7
	1	88 (7.6)	62 (70.5)	26 (29.5)	
	2	272 (23.5)	173 (63.6)	99 (36.4)	
	3	426 (36.9)	276 (64.8)	150 (35.2)	
	4	346 (29.9)	217 (62.7)	129 (37.3)	
Fever (>38.3 °C or 101 °F)	Yes	724 (62.6)	486 (67.1)	238 (32.9)	0.02
SOFA score		7 [6]	4 [5]	10 [6]	<0.0001
Mechanical ventilation		1,030 (89.1)	654 (63.5)	376 (36.5)	0.006
Hypotension		583 (50.4)	317 (54.4)	266 (45.6)	<0.0001
Gram-negative bacteria[d]		705 (61)	458 (65)	247 (35)	0.4
Gram-positive bacteria[d]		416 (36)	277 (66.6)	139 (33.4)	0.3
Fungus[d]		96 (8.3)	57 (59.4)	39 (40.6)	0.2
Anaerobes[d]		19 (1.6)	9 (47.4)	10 (52.6)	0.13
Susceptible organisms		570 (49.3)	401 (70.4)	169 (29.6)	<0.0001
MDR		586 (50.7)	342 (58.4)	244 (41.6)	<0.0001
XDR		254 (22)	151 (59.4)	103 (40.6)	0.09
Infection source	No clear source	274 (23.7)	181 (66.1)	93 (33.9)	0.0003
	Catheter-related	247 (21.4)	171 (69.2)	76 (30.8)	
	Intra-abdominal	134 (11.6)	64 (47.8)	70 (52.2)	
	Respiratory tract	244 (21.1)	145 (59.4)	99 (40.6)	
	Urinary tract	47 (4.1)	35 (74.5)	12 (25.5)	
	Other	73 (6.3)	55 (75.3)	18 (24.7)	
	Multiple sources	149 (12.9)	92 (67.2)	45 (32.8)	
Antimicrobial therapy[b]	Inadequate	154 (13.3)	79 (51.3)	75 (48.7)	0.0007
	Adequate	1,002 (86.7)	664 (66.3)	338 (33.7)	
Time to adequate treatment	<4 h	608 (52.6)	394 (64.8)	214 (35.2)	0.003
	24–48 h	166 (14.4)	109 (65.7)	57 (34.3)	
	Day 2–day 5	228 (19.7)	161 (70.6)	67 (29.4)	
	>Day 5 or never	154 (13.3)	79 (51.3)	75 (48.7)	
Source control	Not required	644 (55.7)	409 (63.5)	235 (36.5)	<0.0001
	Done	467 (40.4)	324 (69.4)	143 (30.6)	
	Required, not done	45 (3.9)	10 (22.2)	35 (77.8)	
Time to source control (days)		1.0 [2.5]	1 [2.8]	0.8 [2.0]	0.01

Data are n (%) or median [IQR]

SIRS Systemic inflammatory response syndrome

[a] Hierarchical logistic regression including random effects for country and centres

[b] Denotes no adequate anti-microbial treatment within 5 after collection of the first positive blood culture

[c] Polymicrobial episodes are counted in more than one category

adequate therapy [23, 24]. Bacterial resistance was also associated with mortality in recent, large, well-conducted epidemiological studies [2, 25]. However, when both bacterial resistance and adequacy of treatment are taken into account, treatment inadequacy is seen to make a larger contribution to the mortality increase than bacterial resistance [9, 26, 27]. One major finding from our study is the significant impact of MDR infections on patient outcome, even after adjustment on antimicrobial treatment adequacy, source control and all other ICU- and patient-related determinants of 28-day mortality. Interestingly, XDR infection did not have a greater influence on 28-day mortality than MDR infection, despite a further increase in time to adequate therapy. This finding is consistent with experimental studies suggesting that resistance to antimicrobial agents may be associated with decreases in bacterial fitness, metabolic activity [28] or virulence [29].

The strong relationship between absence of source control and mortality in our study further supports the widely recognised importance of source control in patients with infection or sepsis [22]. To the best of our knowledge, although this importance is widely accepted by clinicians, it has not been demonstrated in previous studies, except in necrotising fasciitis [30].

In the present study, an intra-abdominal source was an independent risk factor for mortality, in keeping with

Table 4 Isolates found in hospital-acquired bloodstream infections in patients in intensive care units

	Susceptible, *n* (%)	MDR,[a] *n* (%)	XDR,[a] *n* (%)	PDR,[a] *n* (%)	Total	28-day mortality
Gram-negative					759 (57.6 %)	264 (34.8 %)
Acinetobacter spp.	13 (8.1 %)	147 (91.9 %)	114 (71.3 %)	1 (0.6 %)	160 (12.2 %)	55 (34.4 %)
Klebsiella spp.	46 (29.5 %)	110 (70.5 %)	76 (48.7 %)	3 (1.9 %)	156 (11.9 %)	52 (33.3 %)
Pseudomonas spp.	95 (63.3 %)	55 (36.7 %)	41 (27.3 %)	1 (0.7 %)	150 (11.4 %)	60 (40 %)
Escherichia coli	57 (58.2 %)	41 (41.8 %)	5 (5.1 %)	0 (0 %)	98 (7.4 %)	34 (34.7 %)
Enterobacter spp.	48 (54.6 %)	40 (45.5 %)	17 (19.3 %)	0 (0 %)	88 (6.7 %)	29 (33 %)
Other gram-negative	69 (64.5 %)	38 (35.5 %)	15 (14.0 %)	0 (0 %)	107 (8.1 %)	34 (31.8 %)
Gram-positive					440 (33.4 %)	149 (33.9 %)
Enterococcus spp	103 (71.5 %)	41 (28.5 %)	2 (1.4 %)	0 (0 %)	144 (10.9 %)	61 (42.4 %)
Coagulase-negative staphylococci and other staphylococci	141 (100 %)	0 (0 %)	0 (0 %)	0 (0 %)	141 (10.7 %)	41 (29.1 %)
Staphylococcus aureus	60 (50.4 %)	59 (49.6 %)	0 (0 %)	0 (0 %)	119 (9 %)	37 (31.1 %)
Other gram-positive	36 (100 %)	0 (0 %)	0 (0 %)	0 (0 %)	36 (2.7 %)	10 (27.8 %)
Anaerobes					20 (1.5 %)	10 (50 %)
Bacteroides spp.	13 (100 %)	0 (0 %)	0 (0 %)	0 (0 %)	13 (1 %)	6 (46.2 %)
Other anaerobes	7 (100 %)	0 (0 %)	0 (0 %)	0 (0 %)	7 (0.5 %)	4 (57.1 %)
Fungi					98 (7.4 %)	40 (40.8 %)
Candida albicans	0 (0 %)	56 (100 %)	0 (0 %)	0 (0 %)	56 (4.3 %)	23 (41.1 %)
Candida non-*albicans*	0 (0 %)	39 (100 %)	0 (0 %)	0 (0 %)	39 (3 %)	14 (35.9 %)
Other	0 (0 %)	3 (100 %)	0 (0 %)	0 (0 %)	3 (0.2 %)	3 (100 %)
Total (patient)[b]	570 (49.3 %)	586 (50.7 %)	254 (22 %)	5 (0.43 %)	1,156	413 (35.7 %)
Total (micro-organisms)	688 (52.2 %)	629 (47.8 %)	270 (20.5 %)	5 (0.38 %)	1,317	

Percentages of *SUS* susceptible, *MDR* multidrug-resistant, *XDR* extensively drug resistant and *PDR* pan-drug-resistant strains of each pathogen are shown. The "Total" column shows the percentage of each pathogen in the cohort

[a] Each category is included within the previous category: all PDR organisms are XDR, and all XDR organisms are MDR

[b] In case of BSI due to more than one micro-organism, the most resistant one was taken into account to classify the patient

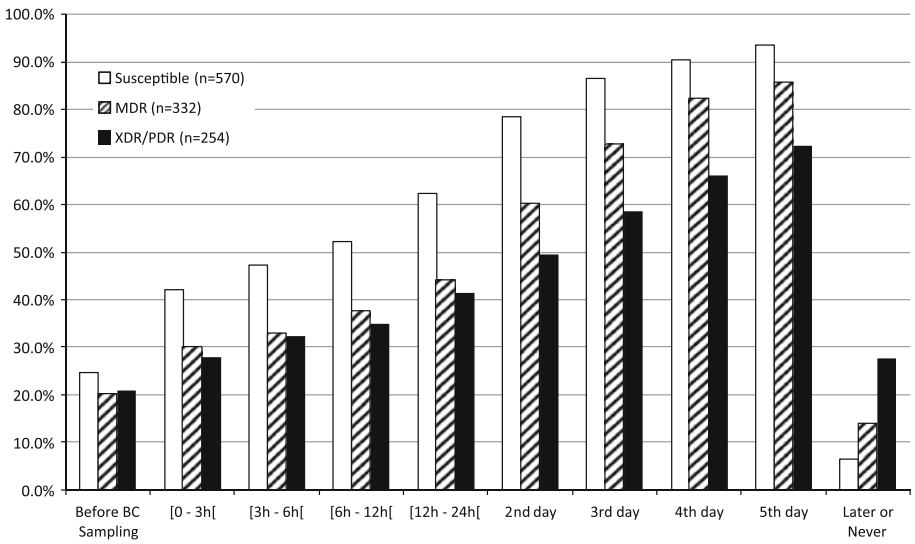

Fig. 2 Cumulative percentage of patients receiving at least one adequate antimicrobial, on each calendar day before and after the date of collection of the first positive blood culture, shown by antimicrobial resistance status (trend chi-square, $p < 0.001$). The calendar day (without details on time) was available in 46 patients for blood collection and 67 patients for treatment initiation; a time of 12:00 a.m. was assigned in these patients

previously reported evidence that intra-abdominal sources of bacteraemia were associated with higher mortality [26, 31].

The influence of centre-related characteristics on patient outcomes deserves some commentary. In ICUs with more than 40 admissions/bed/year, mortality rates in patients with HA-BSI were higher. This finding may reflect delayed diagnosis, inappropriate symptomatic or aetiological treatment, unidentified factors or chance alone. Among the ICU-related factors that might influence antimicrobial use, availability of an infectious diseases specialist, antibiotic committee or written antibiotic therapy procedures did not significantly influence 28-day mortality in our study. The effectiveness of antibiotic stewardship programs in ICUs remains debated [32]. In our studies, the large proportion of ICUs having at least one physician with special training in infectious diseases may have limited our ability to detect a positive

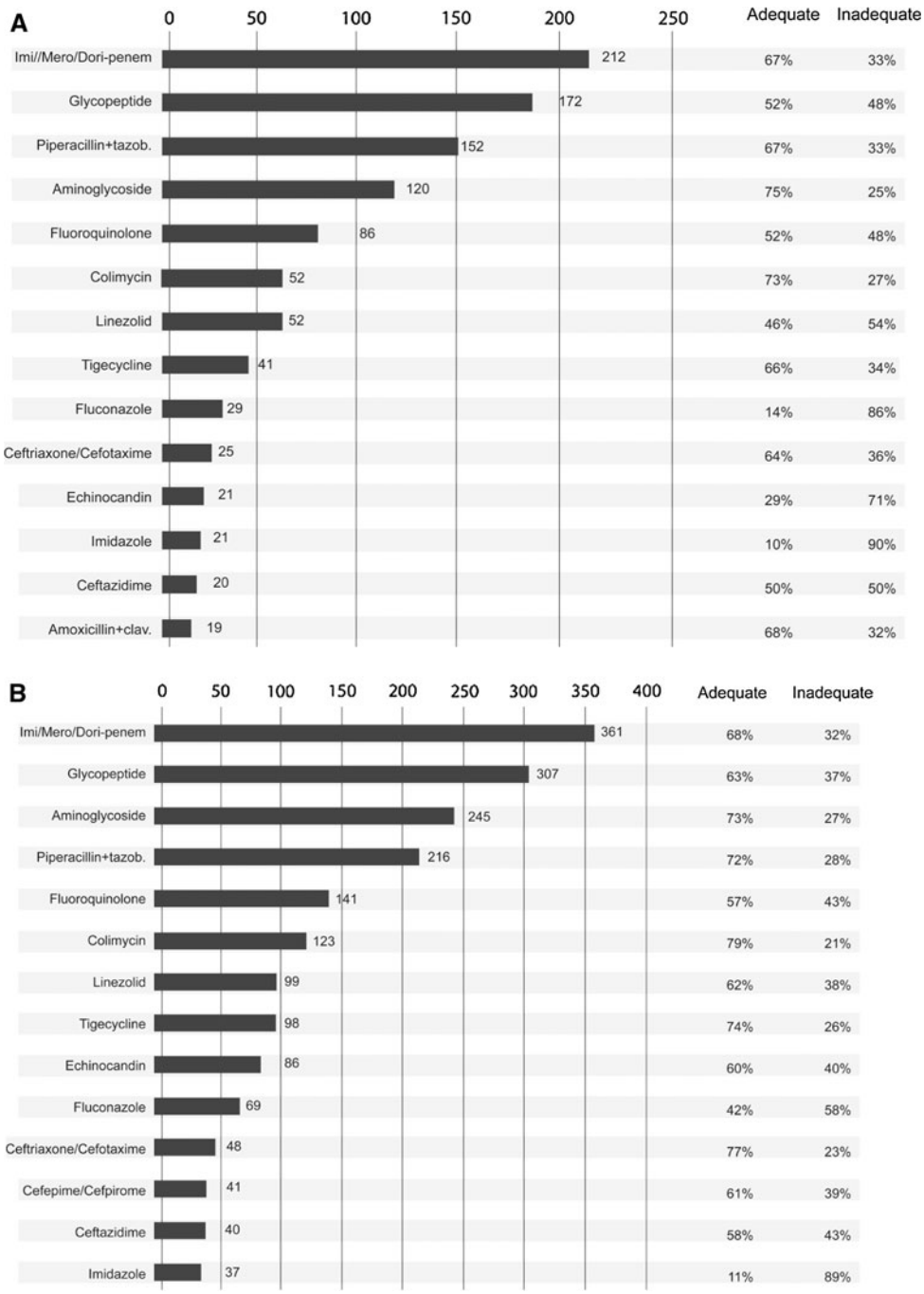

Fig. 3 Antibiotic use. **a** Most frequent empiric antimicrobials, reported as the number of patients receiving the antimicrobial in the 12 h before, to 24 h after collection of the first positive blood culture. **b** Antimicrobials most frequently used in the 5 days following HA-BSI diagnosis, reported as the number of patients receiving the treatment. "Adequate" and "inadequate" show the percentage of cases in which the organism recovered from blood cultures was susceptible to each molecule

impact of antibiotic stewardship programs on patient outcomes. Studies have established that reducing antimicrobial pressure via antimicrobial stewardship programs improves the antimicrobial susceptibility of pathogens. Although such programs did not significantly influence mortality in our study, they are likely to diminish the risk for drug resistance and should be further promoted.

Several limitations of the EUROBACT study merit discussion. First, the distribution of the participating ICUs is not representative of the populations or healthcare systems in the 24 participating countries. In some countries, the number of included patients was very small. As a result, the distributions of pathogens and resistance rates reported here should be interpreted with caution. Second, each participating ICU performed laboratory tests according to their own local protocols, as opposed to sending the isolates to a central laboratory for standardised susceptibility testing. Furthermore, molecular testing of strain relatedness or confirmation of specific resistance mechanisms was not feasible in this large multinational

Table 5 Hierarchical logistic regression model of the effect of patient- and centre-related variables on 28-day mortality following hospital-acquired bloodstream infection

Variable	Estimate (SE)	OR [95 %CI]	*p*-Value[a]
Centres			
ICU mortality in 2008 (per percentage point)	0.02 (0.01)	1.02 [1.00–1.04]	0.03
Turn-over >40 admissions/bed/year (median ICU turn-over)	0.49 (0.21)	1.64 [1.08–2.49]	0.02
Patients			
Female	0.29 (0.15)	1.34 [1.01–1.79]	0.046
Medical patient	0.34 (0.15)	1.40 [1.04–1.90]	0.03
Age (per year)	0.02 (0.005)	1.02 [1.01–1.03]	0.0002
SAPS II (per point)[b]	0.01 (0.005)	1.01 [1.00–1.02]	0.01
Chronic respiratory disease	0.56 (0.24)	1.75 [1.09–2.80]	0.02
Chronic immunological disease	0.75 (0.21)	2.11 [1.40–3.19]	0.0004
SOFA without cardiovascular points (per point)[c]	0.18 (0.03)	1.20 [1.14–1.26]	<0.0001
Septic shock	0.38 (0.15)	1.46 [1.09–1.96]	0.01
Intra-abdominal source	0.48 (0.21)	1.61 [1.07–2.44]	0.023
Organism resistance[c]			0.043
Non-resistant organisms	Ref.		
MDR	0.40 (0.17)	1.49 [1.07–2.06]	
XDR/PDR	0.35 (0.20)	1.42 [0.95–2.11]	
Timing to adequate treatment			<0.0001
Never	Ref.		
Before day 6[d]	−0.97 (0.25)	0.38 [0.23–0.63]	
Since day 6[d]	−1.63 (0.45)	0.20 [0.08–0.47]	
Source control			0.0003
Achieved	Ref	1	
Not required	0.12 (0.15)	1.12 [0.83–1.52]	
Required, not achieved	1.77 (0.44)	5.86 [2.5–13.9]	
Co-variance parameters			
Country	0 (–)[e]		–
Centre	0.53 (0.16)		0.001

SE standard error, *OR* odds ratio, *95 %CI* 95 % confidence interval
MDR multidrug resistant, *XDR* extensively drug resistant, *PDR* pan-drug resistant (see Electronic Supplement for definitions). In patients with multiple organisms, the worst resistance status was considered

[a] Hierarchical logistic model with random effects for both country and centre

[b] SAPS II score at ICU admission

[c] SOFA score at the onset of hospital-acquired bloodstream infection

[d] The reference day if the day of collection of the first positive blood culture

[e] Co-variance parameter is zero

study. Third, the study data were abstracted and entered by investigators at each ICU, with more than 100 individuals entering data in all, raising the possibility of inconsistencies. However, we attempted to minimize inconsistencies through the use of standardised definitions and of direct data entry into a web-based server. In addition, three of us (A.T., D.K., J.-F.T.) reviewed each included case for inconsistencies.

This study provides contemporary information on HA-BSI outcomes in critically ill patients within the context of increasing rates of antimicrobial resistance, particularly among gram-negative pathogens. Both MDR pathogens and failure to administer adequate antimicrobials were associated with 28-day mortality. Furthermore, the results confirm the importance of source control in severe infections. Our data underline the importance of enhanced measures to prevent HA-BSI and to control the dissemination of resistant micro-organisms. They also indicate a need for developing new antimicrobial agents for MDR gram-negative infections. The high resistance rates found in our study should encourage health authorities to preserve one of our most important resources, namely antimicrobials [33].

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References

1. Garrouste-Orgeas M, Timsit JF, Tafflet M, Misset B, Zahar JR, Soufir L, Lazard T, Jamali S, Mourvillier B, Cohen Y, De Lassence A, Azoulay E, Cheval C, Descorps-Declere A, Adrie C, Costa de Beauregard MA, Carlet J (2006) Excess risk of death from intensive care unit-acquired nosocomial bloodstream infections: a reappraisal. Clin Infect Dis 42:1118–1126
2. Lambert ML, Suetens C, Savey A, Palomar M, Hiesmayr M, Morales I, Agodi A, Frank U, Mertens K, Schumacher M, Wolkewitz M (2011) Clinical outcomes of health-care-associated infections and antimicrobial resistance in patients admitted to European intensive-care units: a cohort study. Lancet Infect Dis 11:30–38
3. Prowle JR, Echeverri JE, Ligabo EV, Sherry N, Taori GC, Crozier TM, Hart GK, Korman TM, Mayall BC, Johnson PD, Bellomo R (2011) Acquired bloodstream infection in the intensive care unit: incidence and attributable mortality. Crit Care 15:R100
4. Valles J, Alvarez-Lerma F, Palomar M, Blanco A, Escoresca A, Armestar F, Sirvent JM, Balasini C, Zaragoza R, Marin M (2011) Health-care-associated bloodstream infections at admission to the ICU. Chest 139:810–815
5. Garrouste Orgeas M, Timsit JF, Soufir L, Tafflet M, Adrie C, Philippart F, Zahar JR, Clec'h C, Goldran-Toledano D, Jamali S, Dumenil AS, Azoulay E, Carlet J (2008) Impact of adverse events on outcomes in intensive care unit patients. Crit Care Med 36:2041–2047
6. Blot S, Vandewoude K, De Bacquer D, Colardyn F (2002) Nosocomial bacteremia caused by antibiotic-resistant gram-negative bacteria in critically ill patients: clinical outcome and length of hospitalization. Clin Infect Dis 34:1600–1606
7. Brun-Buisson C, Doyon F, Carlet J (1996) Bacteremia and severe sepsis in adults: a multicenter prospective survey in ICUs and wards of 24 hospitals. French Bacteremia-Sepsis Study Group. Am J Respir Crit Care Med 154:617–624
8. Laupland KB, Kirkpatrick AW, Church DL, Ross T, Gregson DB (2004) Intensive-care-unit-acquired bloodstream infections in a regional critically ill population. J Hosp Infect 58:137–145
9. Corona A, Bertolini G, Lipman J, Wilson AP, Singer M (2010) Antibiotic use and impact on outcome from bacteraemic critical illness: the BActeraemia Study in Intensive Care (BASIC). J Antimicrob Chemother 65:1276–1285
10. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP (2007) The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. PLoS Med 4:e296
11. Timsit JF, Fosse JP, Troche G, de Lassence A, Alberti C, Garrouste-Orgeat M, Bornstain C, Adrie C, Cheval C, Chevret S (2002) Calibration and discrimination of daily LOD score in predicting hospital mortality of critically ill patients, comparison with daily SOFA score. Crit Care Med 30:2003–2013

12. Charlson ME, Pompei P, Ales KL, MacKenzie CR (1987) A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 40:373–383
13. Knaus WA, Draper EA, Wagner DP, Zimmerman JE (1985) APACHE II: a severity of disease classification system. Crit Care Med 13:818–829
14. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, Harbarth S, Hindler JF, Kahlmeter G, Olsson-Liljequist B, Paterson DL, Rice LB, Stelling J, Struelens MJ, Vatopoulos A, Weber JT, Monnet DL (2011) Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect. doi:101111/j.1469-069120 1103570x
15. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance, 2011. Available from http://www.ecdc.europa.eu/en/activities/diseaseprogrammes/ARHAI/Pages/public_consultation_clinical_microbiology_infection_article.aspx
16. Blakely TA, Woodward AJ (2000) Ecological effects in multi-level studies. J Epidemiol Community Health 54:367–374
17. Valles J, Leon C, Alvarez-Lerma F (1997) Nosocomial bacteremia in critically ill patients: a multicenter study evaluating epidemiology and prognosis. Spanish Collaborative Group for Infections in Intensive Care Units of Sociedad Espanola de Medicina Intensiva y Unidades Coronarias (SEMIUC). Clin Infect Dis 24:387–395
18. Souli M, Galani I, Giamarellou H (2008) Emergence of extensively drug-resistant and pandrug-resistant Gram-negative bacilli in Europe. Euro Surveill 13(47):pii:19045
19. Rogers BA, Aminzadeh Z, Hayashi Y, Paterson DL (2011) Country-to-country transfer of patients and the risk of multi-resistant bacterial infection. Clin Infect Dis 53:49–56
20. Schweizer ML, Furuno JP, Harris AD, Johnson JK, Shardell MD, McGregor JC, Thom KA, Sakoulas G, Perencevich EN (2010) Empiric antibiotic therapy for *Staphylococcus aureus* bacteremia may not reduce in-hospital mortality: a retrospective cohort study. PLoS ONE 5:e11432
21. Thom KA, Schweizer ML, Osih RB, McGregor JC, Furuno JP, Perencevich EN, Harris AD (2008) Impact of empiric antimicrobial therapy on outcomes in patients with *Escherichia coli* and *Klebsiella pneumoniae* bacteremia: a cohort study. BMC Infect Dis 8:116
22. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, Reinhart K, Angus DC, Brun-Buisson C, Beale R, Calandra T, Dhainaut JF, Gerlach H, Harvey M, Marini JJ, Marshall J, Ranieri M, Ramsay G, Sevransky J, Thompson BT, Townsend S, Vender JS, Zimmerman JL (2008) Vincent JL (2008) Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock. Intensive Care Med 34:17–60
23. Micek ST, Lloyd AE, Ritchie DJ, Reichley RM, Fraser VJ, Kollef MH (2005) *Pseudomonas aeruginosa* bloodstream infection: importance of appropriate initial antimicrobial treatment. Antimicrob Agents Chemother 49:1306–1311
24. Vogelaers D, De Bels D, Foret F, Cran S, Gilbert E, Schoonheydt K, Blot S (2010) Patterns of antimicrobial therapy in severe nosocomial infections: empiric choices, proportion of appropriate therapy, and adaptation rates—a multicentre, observational survey in critically ill patients. Int J Antimicrob Agents 35:375–381
25. de Kraker ME, Davey PG, Grundmann H (2011) Mortality and hospital stay associated with resistant *Staphylococcus aureus* and *Escherichia coli* Bacteremia: estimating the burden of antibiotic resistance in Europe. PLoS Med 8:e1001104
26. Kang CI, Kim SH, Park WB, Lee KD, Kim HB, Kim EC, Oh MD, Choe KW (2005) Bloodstream infections caused by antibiotic-resistant gram-negative bacilli: risk factors for mortality and impact of inappropriate initial antimicrobial therapy on outcome. Antimicrob Agents Chemother 49:760–766
27. Zahar JR, Timsit JF, Garrouste-Orgeas M, Francais A, Vesin A, Descorps-Declere A, Dubois Y, Souweine B, Haouache H, Goldgran-Toledano D, Allaouchiche B, Azoulay E, Adrie C (2011) Outcomes in severe sepsis and patients with septic shock: pathogen species and infection sites are not associated with mortality. Crit Care Med 39:1886–1895
28. Linares JF, Lopez JA, Camafeita E, Albar JP, Rojo F, Martinez JL (2005) Overexpression of the multidrug efflux pumps MexCD-OprJ and MexEF-OprN is associated with a reduction of type III secretion in *Pseudomonas aeruginosa*. J Bacteriol 187:1384–1391
29. Deptula A, Gospodarek E (2010) Reduced expression of virulence factors in multidrug-resistant *Pseudomonas aeruginosa* strains. Arch Microbiol 192:79–84
30. Boyer A, Vargas F, Coste F, Saubusse E, Castaing Y, Gbikpi-Benissan G, Hilbert G, Gruson D (2009) Influence of surgical treatment timing on mortality from necrotizing soft tissue infections requiring intensive care management. Intensive Care Med 35:847–853
31. De Waele JJ, Hoste EA, Blot SI (2008) Blood stream infections of abdominal origin in the intensive care unit: characteristics and determinants of death. Surg Infect (Larchmt) 9:171–177
32. George P, Morris AM (2010) Pro/con debate: should antimicrobial stewardship programs be adopted universally in the intensive care unit? Crit Care 14:205
33. Carlet J, Collignon P, Goldmann D, Goossens H, Gyssens IC, Harbarth S, Jarlier V, Levy SB, N'Doye B, Pittet D, Richtmann R, Seto WH, van der Meer JW, Voss A (2011) Society's failure to protect a precious resource: antibiotics. Lancet 378:369–371