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MAJOR ARTICLE

Sepsis in Intensive Care Unit Patients: Worldwide Data From the Intensive Care over Nations Audit

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Background. There is a need to better define the epidemiology of sepsis in intensive care units (ICUs) around the globe.

Methods. The Intensive Care over Nations (ICON) audit prospectively collected data on all adult (>16 years) patients admitted to the ICU between May 8 and May 18, 2012, except those admitted for less than 24 hours for routine postoperative surveillance. Data were collected daily for a maximum of 28 days in the ICU, and patients were followed up for outcome data until death, hospital discharge, or for 60 days. Participation was entirely voluntary.

Results. The audit included 10 069 patients from Europe (54.1%), Asia (19.2%), America (17.1%), and other continents (9.6%). Sepsis, defined as infection with associated organ failure, was identified during the ICU stay in 2973 (29.5%) patients, including in 1808 (18.0%) already at ICU admission. Occurrence rates of sepsis varied from 13.6% to 39.3% in the different regions. Overall ICU and hospital mortality rates were 25.8% and 35.3%, respectively, in patients with sepsis, but it varied from 11.9% and 19.3% (Oceania) to 39.5% and 47.2% (Africa), respectively. After adjustment for possible confounders in a multilevel analysis, independent risk factors for in-hospital death included older age, higher simplified acute physiology II score, comorbid cancer, chronic heart failure (New York Heart Association Classification III/IV), cirrhosis, use of mechanical ventilation or renal replacement therapy, and infection with *Acinetobacter* spp.

Conclusions. Sepsis remains a major health problem in ICU patients worldwide and is associated with high mortality rates. However, there is wide variability in the sepsis rate and outcomes in ICU patients around the globe.

Keywords. critically ill; international; mortality; septic shock.

Sepsis is a major cause of morbidity and mortality in modern intensive care units (ICUs). Although several studies have provided epidemiological data on sepsis in ICU patients in the developed world [1–6], there is limited information on the global burden of sepsis worldwide [7, 8]. Yet, such data are crucially important to (1) increase awareness of the global impact of sepsis, (2) highlight the need for continued research into potential preventive and therapeutic interventions, and (3) help guide resource allocation [9]. Information on patterns of sepsis around the globe is also of interest, including causative microorganisms, primary source of infection, and associated outcomes.

In 2012, the World Federation of Societies of Intensive and Critical Care Medicine conducted a worldwide audit of data from ICUs around the world, providing a large database from which to extract information. We used these data to explore the characteristics of patients with sepsis around the world, including international differences in occurrence rates, causative microorganisms, and outcomes. We also evaluated some factors associated with in-hospital mortality in these patients.

METHODS

The worldwide Intensive Care over Nations (ICON) audit recruited ICUs by open invitation, through national scientific societies, national and international meetings, e-mail lists, and individual contacts. Participation was entirely voluntary, with no financial incentive. Ethics committee approval was obtained by the participating institutions according to local ethical regulations. Informed consent was not required for this

Received 17 October 2018; editorial decision 13 November 2018; accepted 16 November 2018.

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DOI: 10.1093/ofid/ofy313

observational and anonymous audit. Of the 730 ICUs contributing to the study from 84 countries (see the participants list in Appendix 1), 419 (57.4%) were in university/academic hospitals. The organizational characteristics of these centers have been described previously [10].

Each ICU was asked to prospectively collect data on all adult (>16 years) patients admitted to their ICU between May 8 and May 18, 2012, except those who stayed in the ICU for <24 hours for routine postoperative surveillance. Readmissions of previously included patients were not included. Data were collected daily for a maximum of 28 days in the ICU. Outcome data were collected at the time of ICU and hospital discharge or at 60 days. Data were entered anonymously using electronic case report forms via a secured internet-based website. Data collection on admission included demographic data and comorbidities. Clinical and laboratory data for simplified acute physiology (SAPS) II [11] and Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II [12] scores were reported as the worst values within the first 24 hours after admission. A daily evaluation of organ function was performed according to the sequential organ failure assessment (SOFA) score [13]; organ failure was defined as a SOFA subscore >2 for the organ in question. Clinical and microbiologic infections were reported daily as well as antimicrobial therapy.

Infection was defined according to the criteria of the International Sepsis Forum [14]. Sepsis was defined as the presence of infection with associated organ failure [15]. Septic shock was defined as sepsis associated with cardiovascular failure requiring vasopressor support (SOFA cardiovascular of 3 or 4). Intensive care unit-acquired infection was defined as infection identified at least 48 hours after ICU admission. Non-ICU acquired infection was defined as infection present on admission or within the first 48 hours after ICU admission. Only the first episode of infection was considered in the analysis.

Detailed instructions and definitions were available through a secured website for all participants before starting data collection and throughout the study period. Any additional queries were answered on a per case basis. Validity checks were made at the time of electronic data entry, including plausibility checks within each variable and between variables. Data were further reviewed by the coordinating center for completeness and plausibility, and any doubts were clarified with the participating center. There was no on-site monitoring. We did not attempt to verify the pathogenicity of the microorganisms, including the relevance of *Staphylococcus epidermidis* or the distinction between colonization and infection.

For the purposes of this audit, we divided the world into 8 geographic regions: North America, South America, Western Europe, Eastern Europe, South Asia, East and Southeast Asia, Oceania, and Africa. Individual countries were also classified into 3 income groups according to the 2011 gross national income (GNI) per capita, calculated using the World Bank Atlas method [16]: GNI <$4035 = low and lower middle income; GNI $4036–12 475 = upper middle income; and GNI >$12 476 = high income.

Statistical Analysis

Data are shown as means with standard deviation (SD), mean and 95% confidence intervals (CIs), medians and interquartile ranges (IQRs), numbers, and percentages. Differences between groups in distribution of variables were assessed using analysis of variance, Kruskal-Wallis test, Student's *t* test, Mann-Whitney test, χ^2 test, or Fisher's exact test as appropriate.

To identify the risk factors associated with in-hospital mortality in septic patients, we used a 3-level multilevel technique with the structure of an individual patient (level 1) admitted to a hospital (level 2) within a country (level 3). The explanatory variables considered in the model were as follows:

- Individual-level factors: age, sex, SAPS II score, type of admission, source of admission, mechanical ventilation or renal replacement therapy at any time during the ICU stay, comorbidities, onset of infection, site of infection, and the most common microorganisms
- Hospital-level factors: type of hospital; ICU specialty; total number of ICU patients in 2011; number of staffed ICU beds
- Country-level factors: GNI

Individual-level variables to be included in the final model were selected on the basis of a multilevel model including country-level and hospital-level factors and each of the individual-level factors; variables with $P < .2$ were considered in the final model. Collinearity between variables was checked by inspection of the correlation between them, by looking at the correlation matrix of the estimated parameters, and by looking at the change of parameter estimates and at their estimated standard errors (SEs) [17]. Q-Q plots were drawn to check for normality in the residuals. The results of fixed effects (measures of association) are given as odds ratios (ORs) with their 95% CIs and the 80% interval OR. Random effects (measures of variation) measures included the variance (var) and its SE and the median OR. The statistical significance of covariates was calculated using the Wald test.

Data were analyzed using IBM SPSS Statistics software, version 22 for Windows and R software, version 2.0.1 (CRAN project). All reported *P* values are 2-sided, and $P < .05$ was considered to indicate statistical significance. The results of fixed effects are given as OR with 95% CIs.

RESULTS

Characteristics of the Study Group

A total of 10 069 patients were included in the audit; 2973 patients (29.5%) had sepsis, including 1808 (18.0%) with sepsis at admission to the ICU (Figure 1). In the whole cohort, antimicrobials were given to 5975 (59.3%) patients during their ICU stay. Patients

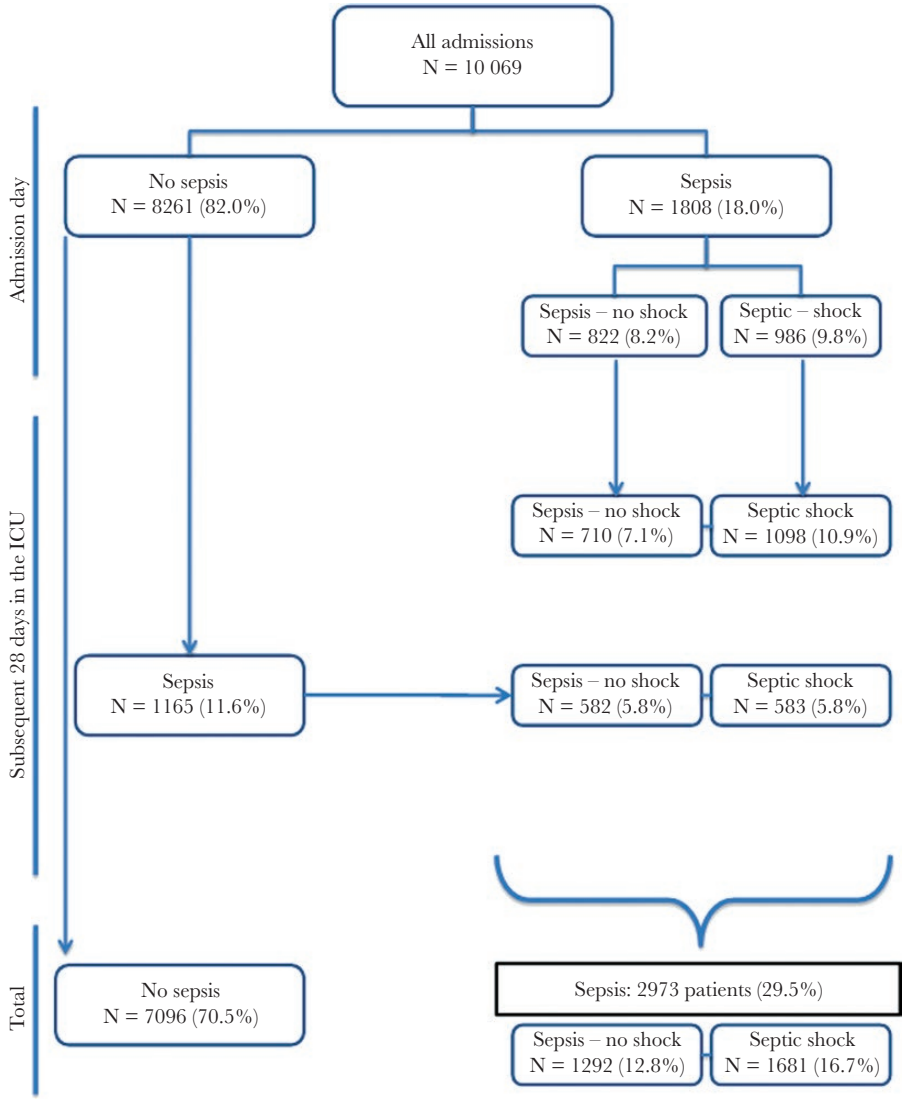

Figure 1. Distribution of patients according to the presence or absence of sepsis on admission and during the intensive care unit (ICU) stay.

with sepsis were older, had higher severity scores on admission to the ICU, had more comorbidities, and were more commonly receiving mechanical ventilation and renal replacement therapy on admission to the ICU than patients without sepsis (Table 1). Patients with sepsis also had more organ failures than the other patients (median [IQ]: 3 [1–4] vs 1 [0–2] organs; $P < .001$).

Patterns of Infections

The most common source of sepsis was the respiratory tract (67.4%) followed by the abdomen (21.8%) (Supplementary Table E1). Positive isolates were retrieved in 69.6% (n = 2069) of patients with sepsis; two thirds of these patients had Gram-negative microorganisms isolated and half had Gram-positive microorganisms; 1068 (51.6%) of the sepsis patients with positive isolates had more than 1 microorganism isolated (Table 2). Patients with urinary tract (82.6% vs 43.9%), abdominal (77.1% vs 50.8%), and respiratory tract (70.0% vs 51.4%) infections were more likely to have Gram-negative than Gram-positive isolates (Supplementary Table E1). Microbiological patterns varied around the globe (Table 2), with Gram-positive isolates being much less frequent (21.4%) in South Asia than in other regions. Methicillin-resistant *Staphylococcus aureus* (MRSA) was more common in the Middle East (14.4%) and North America (12.8%) than in Western Europe (6.1%). *Klebsiella* spp isolates were most commonly reported in Africa (31.3%), Eastern Europe (28.5%), and South America (24.7%), and *Pseudomonas* spp was most frequent in Eastern Europe (21.1%) and South America (20.4%). Fungal organisms contributed to 14.5% and 14.8% of isolates in Western and Eastern Europe, respectively, but to only 5.1% of isolates in North America.

Patients with ICU-acquired infections (n = 764) were younger, more likely to be surgical admissions, and had lower

Table 1. Characteristics of the Study Cohort on Admission to the ICU According to the Presence of Sepsis[a]

Characteristics	All Patients N = 10069	No Sepsis N = 7096	Sepsis N = 2973	*P* Value
Age, years, mean ± SD	60.0 ± 18.0	59.4 ± 18.4	61.5 ± 17.0	<.001
Male, n (%)	5973 (60.1)	4177 (59.7)	1796 (61.0)	.21
Severity scores, mean ± SD				
SAPS II score	40.2 ± 18.2	36.4 ± 17.4	49.2 ± 16.6	<.001
SOFA score	5 [3–9]	4 [2–7]	8 [6–11]	<.001
Type of admission, n (%)				<.001
Surgical	3432 (36.0)	2475 (37.0)	957 (33.7)	
Medical	5382 (56.5)	3646 (54.6)	1736 (61.1)	
Trauma	643 (6.8)	512 (7.7)	131 (4.6)	
Other	66 (0.7)	49 (.7)	17 (.6)	
Source of admission, n (%)				<.001
ER/ambulance	3814 (37.9)	2780 (39.2)	1034 (34.8)	
Hospital floor	2625 (26.1)	1664 (23.4)	961 (32.3)	
OR/recovery	1811 (18.0)	1363 (19.2)	448 (15.1)	
Other hospital	981 (9.7)	652 (9.2)	329 (11.1)	
Other	838 (8.3)	637 (9.0)	201 (6.8)	
Comorbidities, n (%)				
COPD	1240 (12.3)	788 (11.1)	452 (15.2)	<.001
Cancer	1049 (10.4)	710 (10.0)	339 (11.4)	.04
Diabetes mellitus, insulin-dependent	972 (9.7)	664 (9.4)	308 (10.4)	.12
Heart failure, NYHA III/IV	921 (9.1)	588 (8.3)	333 (11.2)	<.001
Chronic renal failure	912 (9.1)	582 (8.2)	330 (11.1)	<.001
Cirrhosis	349 (3.5)	217 (3.1)	132 (4.4)	<.001
Immunosuppression	346 (3.4)	177 (2.5)	169 (5.7)	<.001
Metastatic cancer	332 (3.3)	221 (3.1)	111 (3.7)	.11
Haematologic cancer	212 (2.1)	99 (1.4)	113 (3.8)	<.001
HIV infection	71 (.7)	37 (.5)	34 (1.1)	<.001
Number of comorbidities, n (%)				<.001
None	5512 (54.7)	4145 (58.4)	1367 (46.0)	
1	2800 (27.8)	1880 (26.5)	920 (30.9)	
2	1207 (12.0)	740 (10.4)	467 (15.7)	
3	416 (4.1)	249 (3.5)	167 (5.6)	
≥4	134 (1.3)	82 (1.2)	52 (1.7)	
Procedures, n (%)				
Mechanical ventilation	4776 (47.4)	2755 (38.8)	2021 (68.0)	<.001
Renal replacement therapy	537 (5.3)	264 (3.7)	273 (9.2)	<.001
Antimicrobials, n (%)	5975 (59.3)	3002 (42.3)	2973 (100)	<.001
Antibiotic	5935 (58.9)	2979 (42.0)	2956 (99.4)	<.001
Antifungal	784 (7.8)	202 (2.8)	582 (19.6)	<.001
Antiviral	273 (2.7)	80 (1.1)	193 (6.5)	<.001

Abbreviations: COPD, chronic obstructive pulmonary disease; ER, emergency room; HIV, human immunodeficiency virus; ICU, intensive care unit; NYHA, New York Heart Association Classification; OR, operating room; SAPS, simplified acute physiology; SOFA, sequential organ assessment; SD, standard deviation.

[a]Valid percentages are given after exclusion of missing values (data missing from 546 patients for type of admission).

SAPS II and SOFA scores on admission to the ICU, compared with those who had infections within the first 48 hours on the ICU (Table 3 and Supplementary Table E2). Respiratory and catheter-associated infections were more frequent and abdominal infections less frequent in patients with ICU-acquired than in those with non-ICU-acquired infections (Supplementary Table E2). Patients with ICU-acquired infections were more likely to have positive isolates than patients with non-ICU-acquired infections (79.5% vs 66.2%, $P < .001$) (Supplementary Table E3).

Outcomes

Intensive care unit mortality rates were 25.8% in patients with sepsis and 12.1% in those without ($P < .001$); hospital mortality rates were 35.3% vs 16.7%, $P < .001$). Intensive care unit and hospital mortality rates varied from 11.9% and 19.3% (Oceania) to 39.5% and 47.2% (Africa), respectively (Table 2). Intensive care unit length of stay was longer (6 [3–13] vs 2 [1–4] days, $P < .001$) in patients with than in those without sepsis. As expected, there was a stepwise increase in ICU and hospital mortality rates according to the severity of sepsis (Table 3).

Table 2. Distribution of the Most Common Microorganisms in Patients With Positive Isolates and Mortality Rates According to Geographic Region

Characteristic	All Patients	Western Europe	Eastern Europe	South America	North America	East and Southeast Asia	South Asia	Oceania	Middle East	Africa
Total number of patients, n	10 069	4335	1110	993	730	946	982	439	393	141
Patients with sepsis, n (%)	2973 (29.5)	1357 (31.3)	336 (30.3)	303 (30.5)	147 (20.1)	372 (39.3)	134 (13.6)	135 (30.8)	151 (38.4)	38 (27.0)
Patients with positive isolates, n (%)[a]	2069 (69.6)	947 (69.8)	256 (76.2)	186 (61.4)	117 (79.6)	240 (64.5)	84 (62.7)	105 (77.8)	118 (78.1)	16 (42.1)
Gram-positive, n (%)	1030 (49.8)	517 (54.6)	144 (56.3)	84 (45.2)	59 (50.4)	86 (35.8)	18 (21.4)	57 (54.3)	58 (49.2)	7 (43.8)
Methicillin-sensitive *Staphylococcus aureus*	257 (12.4)	120 (12.7)	37 (14.5)	29 (15.6)	14 (12.0)	25 (10.4)	6 (7.1)	14 (13.3)	10 (8.5)	2 (12.5)
Methicillin-resistant *S aureus*	151 (7.3)	58 (6.1)	20 (7.8)	15 (8.1)	15 (12.8)	14 (5.8)	2 (2.4)	9 (8.6)	17 (14.4)	1 (6.3)
Coagulase-negative *Staphylococcus*	500 (24.2)	269 (28.4)	79 (30.9)	39 (21.0)	25 (21.4)	25 (10.4)	11 (13.1)	19 (18.1)	27 (22.9)	6 (37.5)
Streptococcus, D group	84 (4.1)	52 (5.5)	10 (3.9)	5 (2.7)	5 (4.3)	3 (1.3)	-	6 (5.7)	3 (2.5)	-
Streptococcus, Others	222 (10.7)	109 (11.5)	25 (9.8)	12 (6.5)	15 (12.8)	27 (11.3)	1 (1.2)	15 (14.3)	16 (13.6)	2 (12.5)
Other Gram-positive cocci	46 (2.2)	19 (2.0)	11 (4.3)	-	3 (2.6)	7 (2.9)	-	4 (3.8)	2 (1.7)	-
Gram negative, n (%)	1389 (67.1)	610 (64.4)	189 (73.8)	140 (75.3)	65 (55.6)	159 (66.3)	67 (79.8)	66 (62.9)	84 (71.2)	9 (56.3)
Escherichia coli	470 (22.7)	236 (24.9)	57 (22.3)	51 (27.4)	22 (18.8)	35 (14.6)	22 (26.2)	25 (23.8)	19 (16.1)	3 (18.8)
Klebsiella spp	356 (17.2)	124 (13.1)	73 (28.5)	46 (24.7)	13 (11.1)	45 (18.8)	18 (21.4)	13 (12.4)	19 (16.1)	5 (31.3)
Pseudomonas spp	337 (16.3)	147 (15.5)	54 (21.1)	38 (20.4)	18 (15.4)	35 (14.6)	13 (15.5)	12 (11.4)	20 (16.9)	-
Acinetobacter spp	243 (11.7)	39 (4.1)	55 (21.5)	36 (19.4)	5 (4.3)	51 (21.3)	24 (28.6)	1 (1.0)	29 (24.6)	3 (18.8)
Enterobacter spp	188 (9.1)	91 (9.6)	45 (17.6)	13 (7.0)	3 (2.6)	11 (4.6)	10 (11.9)	8 (7.6)	5 (4.2)	2 (12.5)
Proteus spp	121 (5.8)	63 (6.7)	25 (9.8)	6 (3.2)	5 (4.3)	7 (2.9)	1 (1.2)	5 (4.8)	6 (5.1)	3 (18.8)
Gram-negative, others	320 (15.5)	174 (18.4)	35 (13.7)	20 (10.8)	14 (12.0)	32 (13.3)	4 (4.8)	17 (16.2)	22 (18.6)	2 (12.5)
Anaerobes, n (%)	79 (3.8)	45 (4.8)	12 (4.7)	3 (1.6)	8 (6.8)	4 (1.7)	-	4 (3.8)	2 (1.7)	1 (6.3)
Other bacteria, n (%)	18 (0.9)	4 (0.4)	2 (0.8)	2 (1.1)	1 (0.9)	5 (2.1)	1 (1.2)	2 (1.9)	1 (0.8)	-
Fungi, n (%)	266 (12.9)	137 (14.5)	38 (14.8)	18 (9.7)	6 (5.1)	31 (12.9)	8 (9.5)	10 (9.5)	16 (13.6)	2 (12.5)
Candida albicans	185 (8.9)	93 (9.8)	31 (12.1)	9 (4.8)	3 (2.6)	23 (9.6)	6 (7.1)	9 (8.6)	10 (8.5)	1 (6.3)
Candida non-*albicans*	89 (4.3)	47 (5.0)	8 (3.1)	8 (4.3)	2 (1.7)	11 (4.6)	4 (4.8)	4 (3.8)	4 (3.4)	1 (6.3)
Fungi, others	44 (2.1)	28 (3.0)	4 (1.6)	2 (1.1)	1 (0.9)	5 (2.1)	-	-	4 (3.4)	-
Viruses and parasites, n (%)	59 (2.9)	31 (3.3)	5 (2.0)	6 (3.2)	2 (1.7)	10 (4.2)	-	1 (1.0)	3 (2.5)	1 (6.3)
Mortality rates in patients with sepsis, n (%)										
Intensive care unit	753 (25.8)	309 (22.9)	118 (35.3)	102 (36.3)	27 (18.5)	76 (21.2)	37 (28.9)	16 (11.9)	53 (35.6)	15 (39.5)
Hospital	1004 (35.3)	439 (33.3)	146 (44.8)	119 (45.4)	37 (25.2)	108 (31)	44 (35.2)	26 (19.3)	68 (46.6)	17 (47.2)

[a]In patients with sepsis.

Table 3. Severity Scores on Admission to the ICU, Maximum Number of Organ Failure, and Mortality Rates According to Sepsis Status

Category	n	Severity Scores, Mean ± SD		ICU LOS[a], Median [IQR]	No. of Organ Failures Median [IQR]	Mortality Rates, % (95% CI)	
		SAPS II	SOFA			ICU[b]	In-Hospital[c]
Onset of Sepsis							
Within the first 48 hours[d]	2209	50.5 ± 16.8	9.2 ± 3.9	5 [2–10]	3 [2–4]	26.0 (24.2–27.9)	35.8 (33.8–37.9)
Later	764	45.4 ± 15.5[e]	7.5 ± 3.8[e]	12 [6–19][e]	3 [2–4]	25.1 (22.0–28.3)	33.8 (30.3–37.2)
Severity of Sepsis on ICU Admission							
No sepsis[d]	8261	37.8 ± 17.5	5.3 ± 4.1	3 [1–5]	1 [0–2]	13.6 (12.9–14.4)	19.0 (18.1–19.9)
Sepsis without shock	822	46.2 ± 15.4[e]	7.4 ± 2.9[e]	5 [2–9][e]	2 [1–3][e]	20.1 (17.4–22.9)[e]	30.3 (27.1–33.6)[e]
Septic shock	986	55.1 ± 17.2[e]	11.3 ± 3.6[e]	5 [2–11][e]	3 [2–4][e]	33.7 (30.7–36.7)[e]	43.0 (39.9–46.2)[e]
Severity of Sepsis During ICU Stay							
No sepsis[d]	7096	36.4 ± 17.4	4.9 ± 4.0	2 [1–4]	1 [0–2]	12.1 (11.3–12.8)	16.7 (15.8–17.6)
Sepsis without shock	1292	44.6 ± 15.3[e]	7.0 ± 3.2[e]	6 [3–11][e]	2 [1–3][e]	14.3 (12.4–16.2)[f]	23.6 (21.3–26.0)[e]
Septic shock	1681	52.7 ± 16.7[e]	10.1 ± 3.9[e]	7 [3–14][e]	3 [2–4][e]	34.6 (32.3–36.9)[e]	44.2 (41.7–46.6)[e]

Abbreviations: CI, confidence interval; ICU, intensive care unit; IQR, interquartile; LOS, length of stay; SAPS, simplified acute physiology score; SD, standard deviation; SOFA, sequential organ failure assessment score.

Missing observations: [a]489, [b]401, [c]797.

[d]The reference group.

[e]$P < .01$ among groups.

[f]$P < .05$ among groups.

Although patients with ICU-acquired sepsis had longer ICU stays than those who had sepsis within 48 hours of admission to the ICU, they did not have higher mortality rates (Table 3).

The crude risk of in-hospital death was higher in patients with infections caused by *Pseudomonas* spp, *Acinetobacter* spp, and fungi (Table 4). In the multilevel analysis, independent risk factors for in-hospital death in patients with sepsis were older age, higher SAPS II score, cirrhosis, metastatic cancer, chronic heart failure (NYHA III/IV), use of mechanical ventilation or renal replacement therapy at any time during the ICU stay, and

Table 4. Outcome According to Isolated Microorganisms in Patients With Sepsis (n = 2973)

Risk Factor	ICU Mortality, n (%)	Hospital Mortality, n (%)	Crude Risk of In- Hospital Death OR (95% CI)	*P* Value
Gram-positive	267 (26.2)	360 (36.0)	1.05 (0.89–1.23)	.55
Staphylococcus aureus methicillin sensitive	71 (28.0)	89 (36.0)	1.04 (0.79–1.36)	.80
MRSA	36 (24.2)	51 (34.7)	0.97 (0.69–1.38)	.87
Staphylococcus, coagulase negative	129 (26.0)	184 (37.9)	1.14 (0.93–1.40)	.20
Streptococcus, D group	16 (19.3)	22 (27.5)	0.69 (0.42–1.13)	.14
Streptococcus, others	57 (26.1)	77 (35.8)	1.02 (0.77–1.37)	.87
Other Gram-positive cocci	9 (19.6)	13 (29.5)	0.77 (0.40–1.47)	.42
Gram negative	364 (26.6)	492 (37.0)	1.15 (0.99–1.34)	.07
Escherichia coli	114 (24.7)	162 (36.0)	1.04 (0.84–1.28)	.74
Enterobacter spp	45 (24.1)	67 (36.8)	1.07 (0.79–1.46)	.66
Klebsiella spp	92 (26.4)	128 (37.9)	1.13 (0.90–1.43)	.29
Acinetobacter spp	88 (37.0)	110 (48.0)	1.78 (1.36–2.33)	<.01
Proteus spp	28 (23.1)	40 (33.6)	0.92 (0.63–1.36)	.69
Pseudomonas spp	100 (30.1)	131 (40.4)	1.28 (1.01–1.62)	.04
Gram negative, others	82 (25.9)	110 (35.7)	1.02 (0.80–1.31)	.87
Anaerobes	23 (29.1)	31 (39.7)	1.22 (0.77–1.93)	.41
Other bacteria	6 (33.3)	7 (38.9)	1.17 (0.45–3.02)	.75
Fungi	77 (29.2)	107 (41.6)	1.34 (1.04–1.75)	.03
Candida albicans	49 (26.8)	71 (39.9)	1.23 (0.90–1.68)	.19
Candida non-*albicans*	26 (29.2)	38 (43.7)	1.44 (0.93–2.21)	.10
Fungi, others	16 (36.4)	20 (45.5)	1.54 (0.85–2.80)	.16
Viruses and parasites	16 (28.1)	21 (36.8)	1.07 (0.62–1.84)	.81

Abbreviations: CI, confidence interval; ICU, intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus*; OR, odds ratio.

infection with *Acinetobacter* spp (Supplementary Table E4). The use of mechanical ventilation and presence of comorbid cirrhosis more than doubled the risk of death. The relative risk of death was higher in patients admitted to ICUs in countries with upper middle GNI than in those with high GNI (1.77 [1.31–2.39], $P < .001$). However, although the model suggested significant between-hospital variation (var = 0.28, $P = .001$) in the individual risk of in-hospital death, the between-country variation was not significant.

DISCUSSION

The present audit confirms the considerable burden that sepsis presents in modern ICUs. This large study, including more than 10 000 patients from 730 ICUs, indicates that approximately 30% of all ICU patients have sepsis, as defined by the presence of infection and organ dysfunction. This percentage is identical to that (29.5%) reported in the earlier Sepsis Occurrence in Acutely Ill Patients (SOAP) study [1], a large European study that used the same methodology, and in a recent analysis of a large United Kingdom database [18], but somewhat higher than in some other large studies [4, 5, 19, 20]. In addition to possible differences associated with different definitions of sepsis used in the various studies, 2 other major elements may account for these apparent inconsistencies. First, we did not include all patients admitted to the ICU, but only critically ill patients, excluding patients admitted to the ICU for postoperative surveillance without complications. Second, some studies focused on admission data [20]; if we consider only the patients who had sepsis on admission in our study, the rate of sepsis was 18%. More importantly, the percentage of ICU patients with sepsis varied around the globe, with particularly high rates in East and Southeast Asia, confirming the high disease burden in this area [21, 22]. Although these data were collected in 2012, we believe they are still relevant, especially given the general lack of global data in this regard.

A strength of the present study compared with studies assessing only sepsis on admission or prevalence studies (eg, EPIC II [2]) is that patients were followed throughout the ICU course, enabling evaluation of sepsis that developed during the ICU stay as well as sepsis present on admission. It is interesting to note that patients with ICU-acquired sepsis had similar outcomes to those of patients with sepsis on admission, and ICU-acquired sepsis was not independently associated with a higher risk of mortality after adjusting for confounders in the multilevel analysis. Although we were unable to assess this specifically, van Vught et al [23] recently reported a low attributable mortality of ICU-acquired infections. Shankar-Hari et al [24] reported that the inferred causal link between sepsis and long-term mortality was significantly confounded by age, comorbidity, and preacute illness trajectory. More importantly, in our multivariable regression analysis, all the above-mentioned factors were found to be significant determinants of mortality, suggesting that ICU-acquired sepsis may not on its own be a causative factor for mortality. Nevertheless, nosocomial infections are responsible for prolonged stays in the ICU and increased costs [25, 26].

Positive isolates were obtained in 70% of the patients with sepsis, a similar finding to that reported in other studies [1, 19, 27, 28]. Two thirds of these patients had Gram-negative organisms isolated and one half had Gram-positive organisms isolated. The most common Gram-negative microorganisms recovered were *E coli*, *Klebsiella* spp, *Pseudomonas* spp, and *Acinetobacter* spp, as in previous studies [1, 27, 28]. It is interesting to note that Gram-positive organisms were more common in North America than in other parts of the world; MRSA was also more common in North America than in other parts of the world except the Middle East. These findings are important when using guidelines for management of infection and sepsis, because guidelines developed in one part of the world, for example North America, may not be relevant to other areas. The results also underline the ongoing importance of fungal infections, which were involved in 13% of cases of sepsis overall, although the frequency was lower in the United States (5%), perhaps because more stringent criteria are used to characterize fungal infections in the United States. Finally it is noteworthy that approximately 42% of patients without sepsis received antimicrobial agents. The reasons for this are unclear, but antimicrobials may still be prescribed despite sepsis resolution or exclusion. In a retrospective analysis of 269 patients who were diagnosed with suspected sepsis in the emergency department and started on antibiotic therapy, 29% of the patients were found not to have bacterial disease, but the median duration of antibiotics in these patients was still 7 days (IQR, 4–10) [29].

Intensive care unit mortality rates in patients with sepsis were approximately 26% and were twice as high as those in nonseptic patients. This percentage is lower than the 32% observed in the SOAP study (using their "severe sepsis" definition that is equivalent to our current definition of sepsis) [1] and in other studies [1, 19, 27, 28]. Intensive care unit mortality rates in patients with septic shock were approximately 35%, a percentage that is also lower than that reported in earlier studies [1, 5]. Increased awareness of sepsis diagnosis and improved early management may have contributed to improved outcomes over time. Mortality rates varied around the globe, but in multivariable analysis, the between-country variation was not significant. These findings are in contrast to those from the International Multicenter Prevalence Study on Sepsis (IMPreSS) study of 1794 patients with sepsis from 62 countries, in which mortality rates were higher in East Europe and Central/South America compared with North America after adjustment for adjusted for ICU admission, sepsis status, location of diagnosis, origin of sepsis, APACHE II score, and country [30].

As expected, nonsurvivors were older and had more comorbidities. As in previous ICU studies [1, 2], *Pseudomonas* and fungal infections were associated with worse outcomes,

although only *Acinetobacter* infection was an independent predictor for hospital death in the multilevel analysis. More importantly, our data do not infer a cause-effect relationship, and the presence of *Acinetobacter* may simply be a marker of severity. In a systematic review of 6 matched case-control and cohort studies, Falagas et al [31] reported that *Acinetobacter* infection was associated with increased attributable mortality, although others have suggested no independent link between *Acinetobacter* infection and increased risk of death [32].

Mechanical ventilation at any time during the ICU stay and pre-existing liver cirrhosis were also important prognostic factors, more than doubling the risk of death. Use of renal replacement therapy at any time during the ICU stay was also associated with increased mortality. We also identified significant between-center variation, suggesting that differences in local ICU organization may have an impact on outcomes of patients with sepsis. Some of the potential factors associated with between-center outcomes differences have been identified in the literature. In an international cohort of 13 796 ICU patients, Sakr et al [33] reported that a high nurse/patient ratio was independently associated with a lower risk of in-hospital death. Gaieski et al [34] reported that sepsis outcomes were improved in centers with higher sepsis case volumes. In a multicenter study in Canada, Yergens et al [35] reported that ICU occupancy >90% was associated with an increase in hospital mortality in patients with sepsis admitted from the emergency department. We are unable to identify which particular organizational factors may have influenced outcomes from our data, and this is an area that needs further study.

Our database was very large, including considerable data on demographics, organ function, and outcomes. Nevertheless, to successfully collect a large amount of data in many ICUs requires some limitations in the level of detail of the collected data; therefore, we did not collect precise information on all subtypes of microorganisms or their resistance patterns or on the appropriateness of antimicrobial coverage. Moreover, data were collected by ICU doctors or research nurses who may not have specific expertise in infectious diseases, although the significance of this is uncertain. Our study has other limitations. First, although the audit included a large number of ICUs, the purely voluntary nature of the participation may have an impact on the representativeness of the data. Second, data collection was not monitored so small errors could not be corrected; only obvious incongruous data were verified. Third, in some countries, identification of microorganisms may have been incomplete because of the limited availability of microbiological testing. Moreover, the quality of the antimicrobials used in the treatment of infection has also been questioned in low-resource countries [36]. Fourth, there was no means of differentiating between colonization and infection for some organisms, including *Acinetobacter* and coagulase-negative staphylococci. Therefore, microorganisms were weighted equally in the multilevel analysis. The absence of comparative large epidemiologic data that address this issue makes it difficult to judge whether the estimates of microorganisms provided in our study overestimate the frequency of these infections. Fifth, data were collected for the same period in all regions and therefore do not take into account any possible influence of seasonal variation. Sixth, we did not use the exact recent Sepsis-3 definitions [37], which were published after our study, partly because we had no data on the evolution of SOFA scores before ICU admission and blood lactate levels were not available in all patients. Nevertheless, we used a definition based on the presence of organ dysfunction, a key feature of Sepsis-3. Finally, despite adjusting for a large number of variables that may influence outcome, the results of the multilevel analysis could not take into account other unmeasured variables that may have been of potential significance.

CONCLUSIONS

Sepsis, as defined by infection with organ dysfunction, remains a major health problem in ICU patients worldwide, associated with high mortality. There is wide variation in sepsis rates, causative microorganisms, and outcome in ICU patients around the world. A history of liver cirrhosis or metastatic cancer, use of mechanical ventilation or renal replacement therapy, and *Acinetobacter* infection were independently associated with an increased risk of in-hospital death. Global epidemiological data such as these help increase awareness of sepsis and provide crucial information for future healthcare planning. Further studies in this field should be done on a regular basis with standardized methodology to ensure the comparability of the results.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Acknowledgments

We thank Dr. Hassane Njimi (Department of Intensive Care, Erasme University Hospital, Brussels, Belgium) for help with the statistical analyses.

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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