EDITORIAL

Infection, Antibiotics, and Patient Outcomes in the Intensive Care Unit

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Infection is a major cause of admissions and prolonged stays in intensive care units (ICUs). Epidemiological information on the underlying source of infections, associated microorganisms, treatment, and eventual outcomes is essential for identifying gaps and opportunities to optimize patient management. Systematic and harmonized data collection across institutions allows for geographical comparisons and tracking of temporal trends and also enhances the generalizability of findings. However, such large-scale patient-level data are scarce, likely due to the immense logistical demands for coordinating such a study.

Related article

Building on previous work (the European Prevalence of Infection in Intensive Care [EPIC I] study in 1992 and the Extended Prevalence of Infection in Intensive Care [EPIC II] study in 2007),[1,2] and as reported in the Extended Study on Prevalence of Infection in Intensive Care III (EPIC III) in this issue of *JAMA*, Vincent and colleagues[3] collected comprehensive data on the global epidemiology of infections in ICUs from point prevalence surveys at 1150 centers in 88 countries spanning 6 continents. All cause in-hospital mortality within 2 months was also recorded. The majority of the ICUs were from academic medical centers in upper-middle to high-income countries. Among 15 165 patients with infection data, 8135 (54%) patients had suspected or proven infection and 10 640 (70%) received at least 1 antibiotic. Gram-negative bacteria were the predominant microorganisms isolated in those with positive cultures (3540/5259 [67%]). The in-hospital mortality was 30% among patients with suspected or proven infection.

The most striking finding of EPIC III is how little has changed in terms of the prevalence of infection and the associated mortality over 3 decades. The EPIC I study[1] was based on data from 1992 and reported that 45% of the participants had infections. The EPIC II study[2] was based on data from 2007 and reported that 51% of the participants had infections with an in-hospital mortality rate of 33%. These estimates are close to those from other similar studies performed during the past decade.[4] Although it could be argued that these studies vary in case definitions and durations of follow-up, and it may not be possible to draw conclusions based on direct comparisons, it is disappointing that mortality remains so high despite the focus on the early recognition and management of sepsis over the years. This could raise concerns about possible stagnation in investments by governments and pharmaceutical companies in antibacterial therapeutics and diagnostics, especially with multidrug-resistant bacteria becoming more common.

In the current report by Vincent et al,[3] the high prevalence of gram-negative bacteria among the positive microbiological cultures, especially among patients with hospital- and ICU-acquired infections, likely reflects the overall microbial ecosystem in the participating ICU units and is a cause for concern. This is because of the ability of gram-negative pathogens to acquire antibiotic-resistance genes, especially in the presence of antibiotic selection pressure.[5] This global trend has been recognized as a major challenge with a limited range of therapeutic options available. Two recent reports commissioned by the World Health Organization highlight the limited pipeline for antibiotic agents. The 60 potential therapeutics in development consist of 50 antibiotics and 10 biologics and provide little benefit over existing treatments because only a few target the most concerning multidrug-resistant gram-negative bacteria.[6]

Another important finding of this study is the persistently high rate of antibiotic use relative to the prevalence of infections, which is similar to that reported in 2007 by the EPIC II study.[2] Although appropriateness for the use of antibiotics was not assessed in the 15 165 patients, the data reveal that a substantial proportion of antibiotic use was either for prophylaxis (28%; n = 4217) or empirically prescribed (51%; n = 7723) and only 35% (n = 5259) had positive microbiological cultures. Antibiotic use is likely to be even higher in ICUs in low- to middle-income countries, with an increasing trend mirroring the economic resources available in these countries.[7] Given the emphasis on antibiotic stewardship programs in recent years, persistently high antibiotic consumption in the ICU highlights the challenges in implementing effective stewardship interventions in this setting.

Imprecise clinical and microbiological diagnostics are often slow or inadequate to explain the rapid changes in the physiological status of patients, contributing to the physicians' hesitancy to de-escalate or discontinue antibiotics in this high-stakes patient population.[8] Recent efforts to discontinue antibiotics have focused on procalcitonin use, diagnostic stewardship, and computerized decision support systems among others. However, these types of efforts have not been shown to have a lasting effect on antibiotic use or antibiotic resistance among patients in the ICU.[8] Even though major infectious disease societies and international expert groups have published recommendations and checklists for general antimicrobial stewardship programs,[9,10] there is a lack of guidance for both the utility and implementation of antimicrobial stewardship specific to the ICU. There is a need for novel approaches to optimize antibiotic use in these critically ill patients to enable better outcomes while minimizing the collateral harms associated with antimicrobial resistance.

It is encouraging to observe continued expansion of the EPIC I study since 1992, with increasing representation from

various geographical and resource settings. This reflects the unprecedented connectivity that the medical and scientific communities now exploit to form global networks. To improve participation from low- to middle-income countries, active support can be offered for specialized research tasks such as ethics applications and data collection. Capacity building through research can potentially promote successful collaborations and bring about sustained benefits to the local health care system. Another advantage of a wide collaborative network is the opportunity to engage local investigators in survey design to prioritize information for data collection and to enhance applicability of data and analysis with the aims of strengthening monitoring systems and designing interventions to improve patient care.

A limitation in the interpretation of EPIC III,[3] especially when considered together with other similar point prevalence surveys conducted in ICUs, is the inconsistent method of data collection. The ambiguity in diagnosing and treating infections, compounded by the diverse underlying pathologies among ICU patients, contribute to uncertainties around the identification of infections and classification of their sources. Compared with sepsis, which is usually identified by standardized criteria according to international consensus,[11] diagnosis of infections is more nuanced. In addition, nonsterile sites such as the respiratory tract and the urinary tract can potentially be overestimated as sources of infection because true infection cannot be confidently discriminated from colonization. These uncertainties threaten the reproducibility of the findings and limit the ability of these data to detect temporal trends. Carefully designed serial point prevalence surveys with core components to maintain comparability, and optional variables adapted for local interests, can better evaluate the clinical effects of developments in critical care and sepsis management.

The EPIC III study by Vincent et al[3] is an impressive report that highlights a high prevalence of infections and antibiotic use in ICUs globally. This will likely motivate further research to fill the gap in the design and implementation of antibiotic stewardship interventions specifically targeting ICU settings. Given that these 3 point prevalence studies spanning almost 30 years have consistently reported high and stable mortality rates,[1-3] it is imperative that continued development of novel diagnostics and therapeutics be encouraged. The infectious disease and critical care communities cannot remain complacent in the face of such high levels of infection-related ICU mortality.

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Prevalence and Outcomes of Infection Among Patients in Intensive Care Units in 2017

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IMPORTANCE Infection is frequent among patients in the intensive care unit (ICU). Contemporary information about the types of infections, causative pathogens, and outcomes can aid the development of policies for prevention, diagnosis, treatment, and resource allocation and may assist in the design of interventional studies.

OBJECTIVE To provide information about the prevalence and outcomes of infection and the available resources in ICUs worldwide.

DESIGN, SETTING, AND PARTICIPANTS Observational 24-hour point prevalence study with longitudinal follow-up at 1150 centers in 88 countries. All adult patients (aged ≥18 years) treated at a participating ICU during a 24-hour period commencing at 08:00 on September 13, 2017, were included. The final follow-up date was November 13, 2017.

EXPOSURES Infection diagnosis and receipt of antibiotics.

MAIN OUTCOMES AND MEASURES Prevalence of infection and antibiotic exposure (cross-sectional design) and all-cause in-hospital mortality (longitudinal design).

RESULTS Among 15 202 included patients (mean age, 61.1 years [SD, 17.3 years]; 9181 were men [60.4%]), infection data were available for 15 165 (99.8%); 8135 (54%) had suspected or proven infection, including 1760 (22%) with ICU-acquired infection. A total of 10 640 patients (70%) received at least 1 antibiotic. The proportion of patients with suspected or proven infection ranged from 43% (141/328) in Australasia to 60% (1892/3150) in Asia and the Middle East. Among the 8135 patients with suspected or proven infection, 5259 (65%) had at least 1 positive microbiological culture; gram-negative microorganisms were identified in 67% of these patients (n = 3540), gram-positive microorganisms in 37% (n = 1946), and fungal microorganisms in 16% (n = 864). The in-hospital mortality rate was 30% (2404/7936) in patients with suspected or proven infection. In a multilevel analysis, ICU-acquired infection was independently associated with higher risk of mortality compared with community-acquired infection (odds ratio [OR], 1.32 [95% CI, 1.10-1.60]; $P = .003$). Among antibiotic-resistant microorganisms, infection with vancomycin-resistant *Enterococcus* (OR, 2.41 [95% CI, 1.43-4.06]; $P = .001$), *Klebsiella* resistant to β-lactam antibiotics, including third-generation cephalosporins and carbapenems (OR, 1.29 [95% CI, 1.02-1.63]; $P = .03$), or carbapenem-resistant *Acinetobacter* species (OR, 1.40 [95% CI, 1.08-1.81]; $P = .01$) was independently associated with a higher risk of death vs infection with another microorganism.

CONCLUSIONS AND RELEVANCE In a worldwide sample of patients admitted to ICUs in September 2017, the prevalence of suspected or proven infection was high, with a substantial risk of in-hospital mortality.

Editorial

Supplemental content

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Infection is a common occurrence among patients in the intensive care unit (ICU) and a prerequisite to the development of sepsis.[1] Since 2009, several studies have provided national and international epidemiological data on sepsis,[2-6] but fewer studies have specifically concentrated on the underlying infections. Detailed data from around the world on types of infection, including causative microorganisms, as well as on the use and availability of diagnostic and treatment options are important because they can help increase and maintain awareness among clinicians, patients, and caregivers about the effects of infections; identify risk factors for infection; aid in the development of focused policies for diagnosis and treatment; facilitate adequate and appropriate resource allocation; assist in the design of interventional studies; and provide a baseline against which changes in patient characteristics and the effects of new treatments or management programs can be assessed over time.

In 1992, the European Prevalence of Infection in Intensive Care (EPIC I) study was conducted in western European ICUs.[7] On the study day, 45% of patients had suspected or proven infection and 62% were receiving antibiotics (prophylactic or therapeutic). In 2007, a study of similar design but extending inclusion to ICUs worldwide (Extended Prevalence of Infection in Intensive Care [EPIC II]) was conducted.[8] On the study day, 51% of the patients had suspected or proven infection and 71% were receiving prophylactic antibiotics, therapeutic antibiotics, or both types of antibiotics.

The current EPIC III study (Extended Study on Prevalence of Infection in Intensive Care III) was conducted in 2017 using a similar design to the earlier studies, but also included questions related to the availability of specific resources for the diagnosis and treatment of infection. It was hypothesized that the prevalence of infection and the associated outcomes would vary among geographic regions.

Key Points

Question What was the prevalence of infection and the hospital mortality rate in intensive care units (ICUs) worldwide in 2017?

Findings In a 24-hour point prevalence study conducted at 1150 centers in 88 countries on September 13, 2017, 54% of patients in the ICU had suspected or proven infection; 70% of all patients were receiving at least 1 antibiotic (prophylactic or therapeutic). Hospital mortality was 30% in patients with proven or suspected infection.

Meaning Among a worldwide sample of patients in ICUs in 2017, the prevalence of suspected or proven infection was 54%.

Methods

Study Design

This was an observational, cross-sectional, 24-hour point prevalence study that used a similar study design to that used in the previous EPIC studies.[7,8] An international steering committee was established with representatives from 5 continents who were selected for their acknowledged expertise in the field of intensive care infections (eAppendix 1 in the Supplement). With support from the World Federation of Societies of Intensive and Critical Care Medicine, emails were sent to members of national intensive care societies, to contacts of the steering committee members, and to more than 35 000 contacts held in the database of the International Symposium on Intensive Care and Emergency Medicine, informing them of the upcoming study. The initiative was also announced during various international meetings and shared on social media. Study participation was voluntary.

Participants

Physicians interested in participating registered their ICU on a secure website and received a login and password. All ICUs could participate except those caring only for neonates. The study protocol was approved by local ethics committees when required by local legislation or regulation. Most committees waived the need for informed consent due to the anonymous nature of the data collection. A few local ethics committees required written informed consent from the patient or their next of kin.

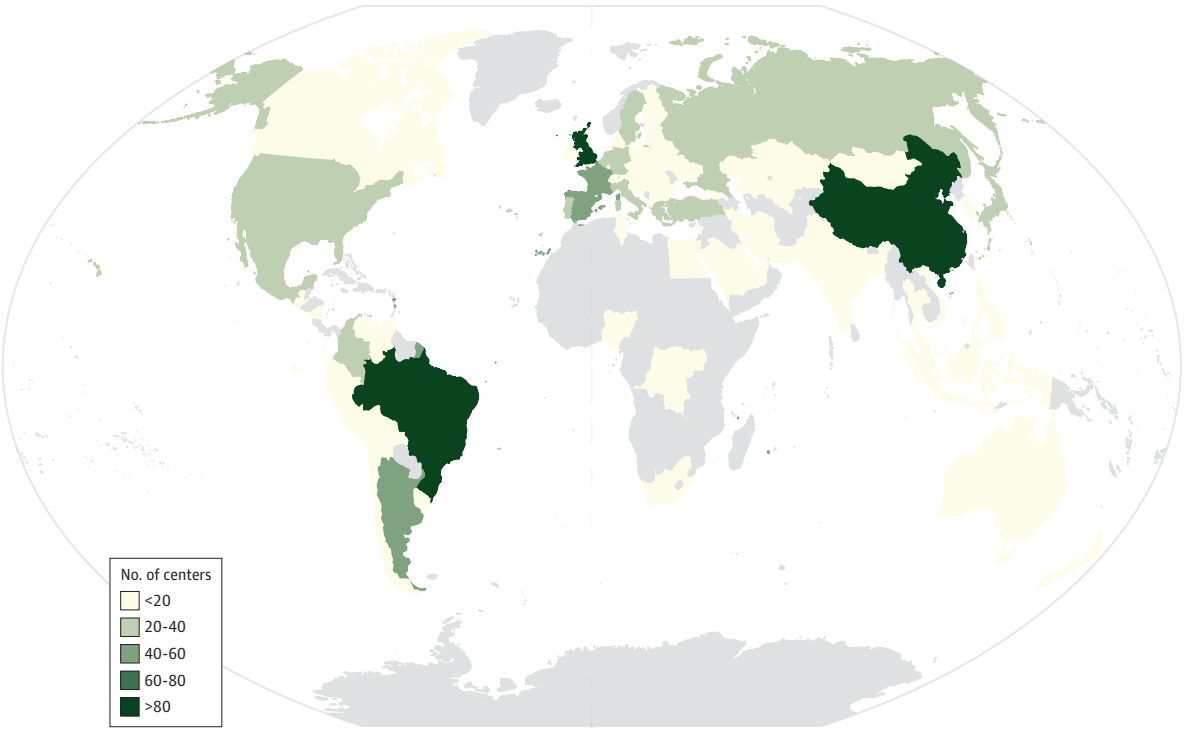
Data Collection and Exposures

Physicians participating in the study (or their delegate such as a trained research nurse or coordinator) were asked to record data for all patients treated at their ICU during the 24-hour period commencing at 08:00 (local time) on September 13, 2017. There were no exclusion criteria. Data were collected on preprinted case report forms by the attending intensivist or delegate (other physician or a trained research nurse or coordinator) and then entered electronically by the local investigators. Centers with limited internet access were able to send the completed paper forms to the coordinating center for data entry.

The case report form included 4 sections: (1) center demographics (characteristics of the hospital and the ICU and the availability of certain diagnostic, monitoring, and therapeutic techniques and interventions); (2) individual patient demographics (age, sex, height, weight, date of hospital and ICU admission, source of admission, and primary and comorbid diagnoses); (3) study day variables (interventions and variables measured or occurring only during the 24-hour study day, including 24-hour minimum and maximum hemodynamic, respiratory, and laboratory parameters, therapeutic interventions, presence of infection [as determined by the treating physician], type of infection, isolated microorganisms [these could be added later when the culture results related to any infections the patient had on the study day became available], antibiotics received, and presence of a documented decision in the patient's notes not to resuscitate or to withhold or withdraw life-sustaining measures); and (4) follow-up data on November 13, 2017 (date of ICU and hospital discharge [if no longer hospitalized] and date of ICU or hospital death).

The study definitions were provided in the case report form and appear in the Supplement. Closed ICUs were defined as those in which only ICU physicians could write orders. Volume in the ICU was defined as the number of admissions during the year prior to inclusion in the study (ie, 2016). If an infection was considered present, investigators were asked to indicate whether it was definite, probable, or possible per definitions from the International Sepsis Forum,[9] and its mode of

Figure 1. World Map Showing the Countries That Participated in EPIC III



The gray areas indicate no participating centers. EPIC III indicates Extended Study on Prevalence of Infection in Intensive Care III.

acquisition (in the community, at the hospital or health care-associated, or in the ICU). Antibiotics received on the study day (prophylactic and therapeutic) were recorded.

Because source data verification was not practical in this global study, the following steps were taken to optimize data quality: (1) the case report forms were built based on the forms used in the earlier EPIC studies; (2) the case report forms were discussed at several investigator meetings; (3) plausible maximum and minimum limits were set for each variable on the electronic forms to prevent erroneous values being entered and investigators were contacted regarding outliers or excessive numbers of missing values; and (4) the central coordinating center was available to all participants by email or telephone to answer any queries prior to and during data collection and follow-up.

Outcomes

The main outcome measure was prevalence of infection. Additional outcome measures were antibiotic exposure, all-cause mortality at hospital discharge censored at 60 days, ICU mortality, and ICU and hospital lengths of stay.

Statistical Analysis

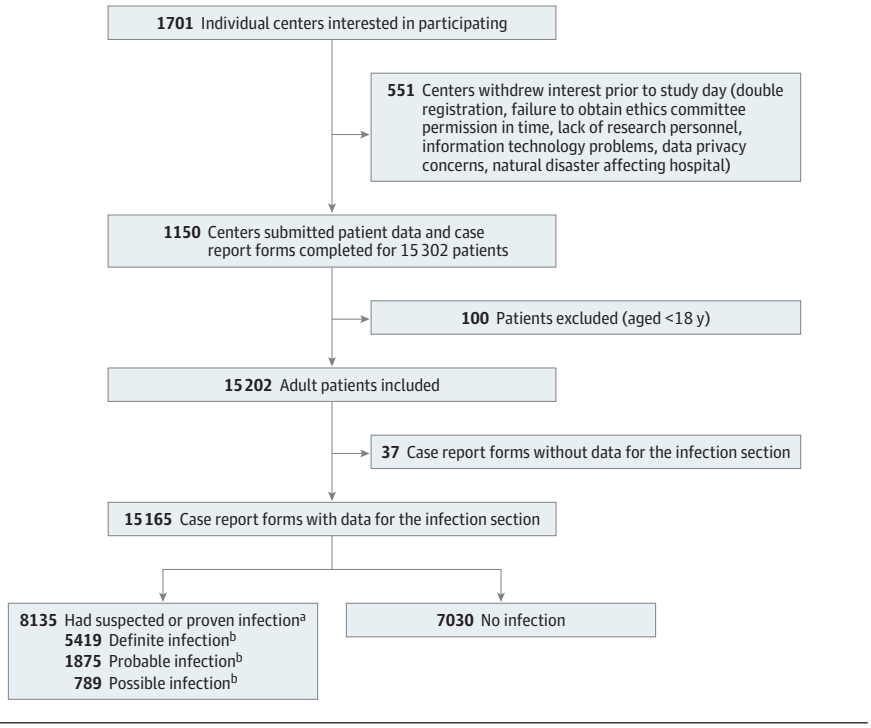
Clinical characteristics were summarized as mean and SD, mean and 95% CI, and median and interquartile range (IQR) as appropriate or number and percentage for categorical factors. Missing data represented less than 5% of collected data. Imputation of missing data was not performed. For the descriptive statistics, valid percentages (ie, not including missing data) were used.

The world was divided into 7 geographical regions: North America, Central and South America, Western Europe, Eastern Europe, Asia and the Middle East, Australasia, and Africa as in the EPIC II study.[8] Individual countries were classified into 3 income groups according to the 2017 gross national income per capita using thresholds defined by the World Bank atlas method[10]: low to lower-middle gross national income: $3895 or less; upper-middle income: $3896 to $12 055; and high income: greater than $12 055.

To estimate associations of patient characteristics, ICU organizational factors, and gross national income per capita with infection and in-hospital death, we used a 3-level technique with the structure of a patient (level 1) admitted to a hospital (level 2) within a country (level 3). Thus, patients were nested within hospitals within countries. The random-effects model included hospital and country units to express the concept that patients from the same country and treated at the same hospital share a common environment.

The dependency between patients treated at a hospital within a country was captured through the use of the random intercepts. Three such analyses were conducted in (1) all patients (with suspected or proven infection as the dependent variable); (2) patients with suspected or proven infection and positive cultures (with hospital mortality as the dependent variable and all microorganisms as independent variables); and (3) patients with suspected or proven infection and positive cultures (with hospital mortality as the dependent variable and antibiotic-resistant microorganisms as independent variables).

Figure 2. Diagram Showing the Numbers of Centers That Contributed Patient Data and the Number of Patients With Infection



[a] The division into definite, probable, or possible was not provided by the investigators for 52 patients (missing data).

[b] Categorization was made by local investigators according to definitions from the International Sepsis Forum.[9]

The explanatory variables considered in the models were (1) patient level (age, sex, Simplified Acute Physiology Score [SAPS] II [calculated from the study day variables], type of admission [surgical, medical, or trauma], source of admission [operating room or recovery, emergency department or ambulance, other hospital or hospital floor], duration of ICU stay prior to the study day, treatment with mechanical ventilation or kidney replacement therapy, any comorbidity, Sequential Organ Failure Assessment score on the study day, mode of acquisition of infection [in the community, at the hospital or health care-associated, or in the ICU], and microorganisms), (2) center level (type of hospital [university or nonuniversity] and ICU volume); and (3) country level (gross national income per capita). Missing cases for the included variables were analyzed using the missing-value indicator method.

For the multilevel analyses, only microorganisms that had a *P* value <.20 in the bivariable analysis were introduced in the final model. Collinearity between variables was checked by inspection of the correlation between them and by looking at the correlation matrix of the estimated parameters. The results of the fixed-effects model are given as odds ratios (ORs) and 95% CIs and also with the 80% interval OR for the constant within-cluster fixed effects. Random-effects measures included the variance, its SE, and the median OR. The restricted maximum likelihood procedure, which gives unbiased estimates of the model parameters, was used. The statistical significance of covariates was calculated using the likelihood ratio test.

The statistical analysis was performed by the coordinating center (Erasme Hospital, Brussels, Belgium) using SPSS version 24.0 (IBM) and R version 3.2.3 (R Foundation for Statistical Computing). All reported *P* values are 2-sided and a *P* value <.05 was considered to indicate statistical significance.

Results

Patients

A total of 1150 centers participated from 88 countries (**Figure 1** and eAppendix 2 in the Supplement) and 15 302 patients were included (median, 10 patients [IQR, 6-18 patients] per center). For the analysis, we only included the data obtained from the 15 202 adult patients (aged ≥18 years; **Figure 2**). The mean age was 61.1 years (SD, 17.3 years), 9181 were men (60.4%), and 8302 of 15 189 patients were medical admissions (55%). Admission to the ICU occurred through the emergency department for 5002 of 15 179 patients (33%). On the study day, 6658 of 14 991 patients (44%) required invasive mechanical ventilation, 4234 of 15 202 (28%) required vasopressor therapy, and 1669 of of 14 917 (11%) required kidney replacement therapy. The median length of ICU stay before the study day was 3 days (IQR, 1-10 days) and the total median length of ICU stay was 10 days (IQR, 3-28 days).

Participating Centers

Most of the centers (645 [56%]) were in countries with high gross national income per capita (**Table 1**). The countries that included the most patients were China (11%), the UK (11%), and Brazil (9%). Sixty-five percent of the ICUs (n = 750) were within university hospitals. The median number of ICU beds was 12 (IQR, 8-20 beds). Most ICUs (922 [80%]) were closed units.

Table 1. Number of Centers and Patients With Listed Characteristics

Characteristic	No. (%)[a] Centers (n = 1150)	Patients (n = 15 302)
Region[b]		
Western Europe	479 (41.7)	6293 (41.1)
Central and South America	226 (19.7)	2569 (16.8)
Asia and the Middle East	217 (18.9)	3195 (20.9)
Eastern Europe	133 (11.6)	1361 (8.9)
North America	45 (3.9)	1229 (8.0)
Africa	35 (3.0)	324 (2.1)
Australasia	15 (1.3)	331 (2.2)
Gross national income per capita for 2017		
Low to lower middle (≤$3895)	73 (6.3)	679 (4.4)
Upper middle ($3896-$12 055)	432 (37.6)	5557 (36.3)
High (>$12 055)	645 (56.1)	9066 (59.2)
Type of hospital		
University or academic	750 (65.2)	10 898 (71.2)
Nonuniversity	400 (34.8)	4404 (28.8)
Type of ICU		
Closed	922 (80.2)	12 245 (80.0)
Open	228 (19.8)	3057 (20.0)
High dependency unit within the hospital[c]	469 (40.8)	NA
Beds, median (IQR)	8 (6-16)	NA
ICU specialty		
Mixed medical-surgical	852 (74.1)	11 821 (77.3)
Surgical	160 (13.9)	1993 (13.0)
Medical	127 (11.0)	1446 (9.4)
Other[d]	11 (1.0)	42 (0.3)
ICU, median (IQR)		
Beds	12 (8-20)	NA
Admissions in 2016	723 (430-1226)	NA

Abbreviations: ICU, intensive care unit; IQR, interquartile range; NA, not applicable.

[a] Unless otherwise indicated.

[b] The world was divided into these geographical regions as in the Extended Prevalence of Infection in Intensive Care (EPIC II) study.[8]

[c] Patients need more care than on a normal ward, but less than in an ICU.

[d] Included infectious diseases, pediatric, and obstetric.

Seventy-four percent of the ICUs were mixed medical-surgical units (n = 852).

Among 1144 ICUs, an infectious disease specialist or a clinical microbiologist was available 24 hours per day and 7 days per week in 673 (59%) but was never available in 114 (10%) (**Table 2**). A pharmacist (full-time or part-time) was assigned to the ICU at 627 of 1143 centers (55%). Of 1142 ICUs, 1096 (96%) were often or always able to perform blood cultures within 1 hour of ICU admission. Of 1143 ICUs, 1057 (93%) were often or always able to perform qualitative respiratory cultures and 881 (77%) were often or always able to perform quantitative respiratory cultures. Therapeutic drug monitoring was performed often or always for vancomycin in 797 of 1142 ICUs (70%) and for voriconazole in 180 of 1140 ICUs (16%).

Prevalence and Characteristics of Infections

The infection section of the case report form was completed for 15 165 patients (99%). Of these patients, 10 640 (70%) were receiving at least 1 antibiotic on the study day (4217 of 15 165 patients [28%] were receiving prophylactic antibiotics and 7723 of 15 165 patients [51%] were receiving therapeutic antibiotics). The most frequently used prophylactic antibiotics were cephalosporins (2144/4217 [51%]) and the most frequently used therapeutic antibiotics were penicillins (2751/7723 [36%]) (eTable 1 in the Supplement). Of the 15 165 patients, 8135 (54%) had at least 1 suspected or proven infection on the study day (**Table 3**) and 1921 (24%) of these patients had more than 1 suspected or proven infection.

The proportion of patients with suspected or proven infection on the study day ranged from 43% (141/328) in Australasia to 60% (1892/3150) in Asia and the Middle East (eTable 2 in the Supplement). The prevalence rates for infection were 58% (385/666) among patients from countries with low to lower-middle gross national income per capita, 59% (3232/5498) among patients from countries with upper-middle gross national income per capita, and 50% (4518/9001) among patients from countries with high gross national income per capita (eTable 2 in the Supplement).

When recorded, infection was considered definite in 5419 patients (67%), probable in 1875 (23%), and possible in 789 (10%) (Table 3). In the 7904 patients for whom it was recorded, infection was considered as acquired in the community by 3474 patients (44%), at the hospital or health care–associated by 2724 (35%), and in the ICU by 1706 (22%) (Table 3). The site of infection was the respiratory tract in 60% of patients (n = 4893), the abdomen in 18% (n = 1490), and in the bloodstream in 15% (n = 1239) (Table 3); these percentages varied across geographical regions (eTable 3 in the Supplement).

Table 2. Available Resources in the Participating Intensive Care Units (ICUs)

Resource	No. (%) by gross national income per capita[a]		
	Low to lower middle (n = 73)	Upper middle (n = 432)	High (n = 645)
Therapeutic and monitoring techniques			
High-flow nasal oxygen	39 (53.4)	275 (63.8)	557 (86.9)
Noninvasive mechanical ventilation	73 (100.0)	427 (99.1)	640 (100.0)
Invasive mechanical ventilation	72 (98.6)	429 (99.5)	638 (99.5)
Echocardiography by ICU team	48 (65.8)	276 (64.2)	554 (86.4)
Invasive monitoring (including central venous catheter and arterial lines)	67 (91.8)	399 (92.6)	634 (98.9)
Intermittent kidney replacement therapy (dialysis)	60 (82.2)	369 (86.0)	503 (78.6)
Continuous kidney replacement therapy	36 (49.3)	280 (65.0)	590 (92.2)
Extracorporeal membrane oxygenation (venovenous, venoarterial, or both)	15 (20.5)	130 (30.2)	243 (38.0)
Availability of infectious diseases specialist or clinical microbiologist			
At all times	30 (41.1)	203 (47.1)	440 (68.8)
Just during the week	31 (42.5)	157 (36.4)	169 (26.4)
Never	12 (16.4)	71 (16.5)	31 (4.8)
Pharmacist (full-time or part-time) assigned to the ICU team	35 (47.9)	250 (58.0)	342 (53.5)
Often or always able to perform microbiological cultures			
Blood	66 (90.4)	419 (97.4)	611 (95.5)
Qualitative respiratory secretions	64 (87.7)	401 (93.3)	592 (92.5)
Quantitative respiratory secretions	50 (68.5)	349 (81.2)	482 (75.3)
Urine	68 (93.2)	407 (94.9)	613 (96.1)
Often or always able to perform task			
Blood gas analysis within 1 h of ICU admission	63 (87.5)	418 (97.4)	637 (99.7)
Blood lactate within 1 h of ICU admission	51 (69.9)	384 (89.5)	636 (99.4)
Any antibiograms	55 (75.3)	384 (89.7)	559 (87.6)
Antibiotics often or always available			
Piperacillin/tazobactam	59 (80.8)	383 (89.1)	633 (98.9)
Echinocandins	34 (46.6)	285 (66.3)	585 (91.5)
Tigecycline	49 (68.1)	300 (69.8)	516 (80.8)
Therapeutic monitoring often or always performed			
Vancomycin	22 (30.1)	188 (43.7)	587 (91.9)
Voriconazole	3 (4.1)	34 (7.9)	143 (22.4)
β-Lactam antibiotics	8 (11.0)	47 (11.0)	61 (9.6)
Echinocandins	3 (4.1)	25 (5.8)	51 (8.0)
Aminoglycosides	0	1 (0.2)	0

[a] The percentages were calculated using the actual number of available results as the denominator and not the total results (eg, if there were forms for 100 centers but only 97 had the section in question completed, the denominator for calculating the percentages would be 97 and not 100).

Among the 8135 patients with suspected or proven infection, 5259 (65%) had at least 1 positive microbiological culture and 44% of these patients had more than 1 positive culture (eTable 4 in the Supplement). Among the patients with positive microbiological cultures, 3540 (67%) had a gram-negative microorganism, 1946 (37%) had a gram-positive microorganism, and 864 (16%) had a fungal microorganism.

Gram-negative microorganisms were isolated in 57% (1118/1972) of patients with culture-positive infections acquired in the community, 71% (1281/1813) of patients with culture-positive infections acquired at the hospital or health care-associated, and 78% (1074/1379) of patients with culture-positive infections acquired in the ICU (eTable 5 in the Supplement). Gram-negative microorganisms were most prominent in Eastern Europe (418 of 537 patients [78%]), in Africa (93 of 120 patients [78%]), and in Asia and the Middle East (922 of 1207 patients [76%]) (eTable 4 in the Supplement). Among the 3540 patients who had gram-negative microorganisms identified on culture, the most common were *Klebsiella* species (973 patients [27%]), *Escherichia coli* (902 patients [25%]), *Pseudomonas* species (850 patients [24%]), and *Acinetobacter* species (602 patients [17%]) (eTable 4 in the Supplement).

Gram-positive microorganisms were isolated in 42% (831/1972) of patients with culture-positive infections acquired in the community, 37% (663/1813) of patients with infections acquired at the hospital or health care-associated, and 31% (432/1379) of patients with infections acquired in the ICU (eTable 5 in the Supplement). Gram-positive microorganisms were most prominent in North America (182 of 396 patients [46%]). Of

Table 3. Characteristics and Outcomes According to the Type of Infection and the Isolated Microorganism

	Patients, No. (%)[a]	SAPS II, mean (SD)[b]	Median (IQR)			Mortality rates, No. (%)[a]	
			SOFA score[c]	Length of stay, d			
				ICU	Hospital	ICU	Hospital
Suspected or proven infection	8135	40.9 (18.8)	7 (4-11)	15 (6-35)	30 (15-56)	1870 (23.6)	2404 (30.3)
Type of infection[d]							
Definite	5419 (66.6)	41.2 (18.9)	7 (4-11)	18 (8-40)	33 (17-59)	1292 (24.4)	1666 (31.5)
Probable	1875 (23.1)	40.9 (18.8)	7 (4-11)	12 (5-27)	24 (13-47)	416 (22.9)	522 (28.7)
Possible	789 (9.7)	39.4 (18.8)	7 (4-11)	9 (4-23)	22 (10-41)	153 (19.6)	206 (26.4)
Mode of acquisition[e]							
In the community	3474 (44.0)	40.7 (19.0)	7 (4-11)	10 (4-23)	21 (11-40)	697 (20.6)	908 (26.8)
At the hospital or health care–associated	2724 (34.5)	41.7 (19.0)	7 (4-11)	15 (7-35)	34 (19-60)	661 (24.9)	867 (32.6)
In the ICU	1706 (21.6)	40.0 (18.3)	7 (4-10)	31 (17-62)	46 (26-73)	461 (27.6)	564 (33.7)
Patients with ≥1 positive microorganism isolate[f]	5259 (64.6)						
Gram-positive bacteria	1946 (37.0)	41.0 (19.0)	7 (4-11)	18 (9-38)	34 (19-59)	457 (24.0)	585 (30.7)
Gram-negative bacteria	3540 (67.3)	42.0 (19.0)	7 (4-11)	23 (10-48)	38 (20-65)	891 (25.8)	1139 (33.0)
Anaerobes	183 (3.5)	40.0 (20.0)	7 (3-11)	17 (7-30)	36 (21-56)	43 (23.6)	51 (28.0)
Other bacteria	92 (1.7)	45.0 (19.0)	8 (5-12)	12 (8-25)	27 (16-42)	22 (25.0)	27 (30.7)
Fungi	864 (16.4)	45.0 (20.0)	8 (5-13)	26 (13-51)	42 (23-69)	276 (32.4)	325 (38.2)
Viruses	196 (3.7)	43.0 (20.0)	7 (4-12)	18 (9-37)	30 (15-56)	52 (26.7)	60 (30.8)
Parasites	43 (0.8)	45.0 (21.0)	7 (4-12)	14 (10-25)	28 (15-50)	12 (27.9)	14 (32.6)
Mixed flora	90 (1.7)	41.0 (17.0)	7 (4-10)	13 (6-23)	22 (13-45)	25 (28.1)	30 (33.7)
Site of infection[f]							
Respiratory tract	4893 (60.1)	42.3 (18.7)	7 (4-11)	18 (8-39)	31 (16-58)	1179 (24.8)	1519 (31.9)
Abdomen	1490 (18.3)	41.0 (19.6)	7 (4-12)	13 (6-31)	30 (15-54)	376 (25.7)	467 (32.0)
Bloodstream	1239 (15.2)	43.7 (20.2)	9 (5-13)	20 (9-44)	36 (19-63)	381 (31.4)	462 (38.1)
Kidney	263 (3.2)	42.7 (18.7)	8 (5-11)	11 (5-36)	25 (13-60)	55 (21.5)	68 (26.6)
Skin	518 (6.4)	37.3 (18.4)	6 (4-10)	14 (6-36)	33 (16-61)	114 (22.6)	139 (27.5)
Related to catheter	255 (3.1)	43.7 (19.5)	8 (5-13)	28 (12-61)	47 (26-74)	79 (31.3)	99 (39.3)
Genitourinary	875 (10.8)	40.0 (18.6)	7 (4-10)	14 (5-41)	30 (14-61)	189 (22.3)	251 (29.6)
Central nervous system	314 (3.9)	40.4 (18.5)	6 (4-9)	16 (8-38)	31 (16-57)	66 (21.8)	88 (29.0)
Another site	529 (6.5)	37.9 (18.8)	7 (4-11)	17 (6-36)	33 (18-59)	110 (21.1)	142 (27.2)

Abbreviations: ICU, intensive care unit; IQR, interquartile range; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment.

[a] The percentages were calculated using the actual number of available results as the denominator and not the total results (eg, if there were forms for 100 patients but only 97 had the section in question completed, the denominator for calculating the percentages would be 97 and not 100).

[b] The range is from 0 to 163; higher values imply more severe disease and are associated with a higher risk of death. The estimated in-hospital mortality is between 19.6% and 34.8% when the SAPS II is between 37 and 45.[11]

[c] The range is from 0 to 24; higher values imply more severe disease and are associated with a higher risk of death. The estimated ICU mortality is between 21.5% and 33.3% when the SOFA score is between 6 and 9.[12]

[d] As determined by the investigator based on the International Sepsis Forum definitions.[9] The division into definite, probable, or possible was not provided by the investigators for 52 patients (missing data).

[e] As determined by the investigator based on definitions provided in the Supplement.

[f] Patients may have had more than 1 infection.

5259 patients with positive cultures, methicillin-resistant *Staphylococcus aureus* was isolated in 240 patients (5%); the highest rates were in North America (40 of 396 patients [10%]) and the lowest rates were in Western Europe (49 of 2148 patients [2%]) (eTable 4 in the Supplement). Patterns of isolated microorganisms by site of infection appear in eTable 6 in the Supplement.

In a multilevel analysis with suspected or proven infection as the dependent variable, male sex, comorbid conditions (chronic obstructive pulmonary disease, cancer, diabetes, chronic kidney failure, HIV infection, and immunosuppression), and longer ICU stay prior to the study day were independently associated with a higher risk of infection (eTable 7 in the Supplement). The hospital within-country variance was 0.40 (SE, 0.04) for the occurrence of infection, which was statistically significant ($P < .001$), indicating that the occurrence of infection was influenced by between-hospital factors after adjustment for patient-related factors (eTable 7 in the Supplement).

Clinical Outcomes

Of the 7936 patients with suspected or proven infection and available outcome data, 2404 died (30%) at the hospital (eTable 1 in the Supplement). Hospital mortality rates were 32% (1666/5290) in patients with definite infection, 29% (522/1817) in patients with probable infection, and 26% (206/779) in patients with possible infection (Table 3). The findings for ICU mortality and ICU and hospital lengths of stay appear in Table 3.

In a multilevel analysis of patients with positive cultures for infection (with hospital death as the dependent variable) and including all microorganisms (as independent variables), ICU-acquired infection was independently associated with higher risk of in-hospital mortality compared with community-acquired infection (OR, 1.32 [95% CI, 1.10-1.60]; $P = .003$). In addition, older age; having a higher SAPS II on the study day; having metastatic cancer, heart failure (New York Heart Association class III-IV), HIV infection, or cirrhosis; requiring mechanical ventilation or kidney replacement therapy on the study day; and referral from the hospital ward compared with the operating room were also independently associated with a higher risk of in-hospital death (eTable 8 in the Supplement). Infections due to *Streptococcus pneumoniae* were associated with a lower risk of in-hospital death (OR, 0.46 [95% CI, 0.28-0.76]; $P = .002$).

In a multilevel analysis of patients with positive cultures for infection and with hospital death as the dependent variable and antibiotic-resistant microorganisms as the independent variables (eTable 9 in the Supplement), infection with a vancomycin-resistant *Enterococcus* (OR, 2.41 [95% CI, 1.43-4.06]; $P = .001$), a *Klebsiella* species resistant to β-lactam antibiotics, including third-generation cephalosporins and carbapenems (OR, 1.29 [95% CI, 1.02-1.63]; $P = .03$), or a carbapenem-resistant *Acinetobacter* species (OR, 1.40 [95% CI, 1.08-1.81]; $P = .01$) was associated with a higher risk of in-hospital death compared with infection with another microorganism. The hospital within-country and country-to-country variations in the risk of death were statistically significant after adjustment for other possible confounders (eTables 8 and 9 in the Supplement).

Discussion

In this 24-hour point prevalence study conducted at 1150 participating centers in 88 countries on September 13, 2017, the overall rate of suspected or proven infection was 54%, which was higher than in previous EPIC studies (45% for EPIC I [measured in 1992][7] and 51% for EPIC II [measured in 2007][8]). The effect of increased detection rates due to changes in protocols and improved technology cannot be ruled out, although the proportion of patients with positive microbiological cultures was lower than in the EPIC II study (65% vs 70%). The proportion of patients with ICU-acquired infection was similar to the 21% reported in the EPIC I study.[7]

The present data indicate that the proportions of patients in the ICU with infection continued to vary considerably across geographic regions. Although most of the participating centers were in Europe, the rest of the world was well represented with large numbers of centers in China and South America; however, countries with low to lower-middle gross national income per capita contributed just 6% of the centers and less than 5% of the patients. The variation in prevalence of infection was associated with patient-specific and disease-specific factors and with process of care factors across centers. Such factors may include different ICU admission criteria, lower availability of resources to adjudicate or exclude a diagnosis of infection, low nurse-to-patient ratios, and differences in infection control and antimicrobial stewardship policies. The independent effects of each of these factors could not be determined from this study, but process of care differences across centers and their relationship to the prevalence of infection should be considered when planning and interpreting the results of clinical trials.

Gram-negative microorganisms were identified more frequently than gram-positive microorganisms on culture. No specific microorganism was independently and significantly associated with a higher risk of death when considering all patients with an infection. Older age, higher SAPS II, and comorbid metastatic cancer, HIV infection, and heart failure were independently associated with a higher risk of death. This variation was associated with patient-specific and disease-specific factors and with process of care and country-to-country differences. In an extended analysis of data from the EPIC II study, the importance of hospital and ICU organizational factors on outcomes was also demonstrated.[13]

In terms of country-to-country variation, differences in health care (both primary care and hospital-based) expenditure, access to ICU facilities, and bed availability may play a role. Other country-related factors may include local variations in living conditions, nutritional status, vaccine availability, antibiotic availability and consumption, and poor sanitation.[14] It is not possible to determine the relevant importance of each of these aspects from the present data but these are important considerations when assessing the global burden of infection.

When considering only antibiotic-resistant microorganisms, infections with vancomycin-resistant *Enterococcus*, *Klebsiella* resistant to β-lactam antibiotics (including third-generation cephalosporins and carbapenems), and

carbapenem-resistant *Acinetobacter* species were independently associated with an increased risk of death, highlighting the association of antibiotic resistance with mortality and the importance of good antibiotic stewardship. Carbapenem-resistant *Acinetobacter baumannii* and carbapenem-resistant or third-generation cephalosporin-resistant *Enterobacteriaceae* have been listed as critical pathogens on the World Health Organization priority list of antibiotic-resistant bacteria for effective drug development, and vancomycin-resistant *Enterococcus* as high priority.[15] These infections are associated with high morbidity and mortality and contribute to prolonged hospital stays and high hospital costs.[16-19]

Limitations

The study has several limitations. First, participation was entirely voluntary, with no financial incentive, so that monitoring of data input and accuracy could only be performed centrally. Voluntary participation may also lead to participation bias.

Second, due to the study design, it was not possible to establish the time of infection onset and no information on infection resolution, appropriateness of treatment selection, or effectiveness of antibiotic choices was collected. Moreover, because this was a 24-hour point prevalence study conducted during autumn in the northern hemisphere and during spring in the southern hemisphere, it is possible that seasonal factors may account for some of the geographical differences. Differences in climate within and between countries may also potentially influence the types of causative microorganisms.[20] Point prevalence studies are also biased by patient length of stay, potentially resulting in an oversampling of patients with longer ICU lengths of stay and influencing assessments of risk for mortality.

Third, even though a large number of centers participated, the representation of each country may be heterogeneous in terms of the proportions of ICUs that participated, resulting in a patchwork picture rather than complete global coverage, and there may be important differences in availability and quality of health care within some of the geographical regions, limiting interpretation of some of the results. In addition, because of the small numbers of centers in some regions, particularly regions with low to lower-middle gross national income per capita, differences in infection rates by region and the true association with mortality are difficult to evaluate because of the multiple local variations in living conditions, access to medical care, local infrastructure, and facilities, including for microbiological cultures.

The effect of fundamental contributors to the burden of infection in these countries with low to lower-middle gross national income per capita, including poverty, political instability, poorly resourced health care systems, and antibiotic availability and consumption, on the present results cannot be determined.[14] Although there was between-hospital variation in risk of infection and outcomes, it was not possible to identify which aspects of the process of care or ICU organization were responsible. In addition, the gross national income per capita was used to compare countries and not a specific, detailed economic model.

Fourth, participants were asked to categorize infection into definite, probable, or possible categories based on the International Sepsis Forum definitions,[9] but these decisions can be subjective so should be interpreted with caution.

Fifth, despite improved communication capabilities, which helped to spread the news of the study, and more widespread access to the internet, which enabled easy and secure data input, many centers were unable to participate. Various reasons for this were cited, including increasingly strict administrative and legislative requirements, concerns about data privacy despite the anonymous data collection, and the need for informed consent from patients despite the observational, noninterventional nature of the study. These factors are likely to represent a continuing challenge for such studies in the future, making them difficult to conduct even with financial support.

Conclusions

In a worldwide sample of patients admitted to ICUs in September 2017, the prevalence of suspected or proven infection was high, with a substantial risk of in-hospital mortality.

ARTICLE INFORMATION

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Group Information: The EPIC III Investigators are listed in eAppendix 2 in the Supplement.

Author Contributions: Drs Vincent and Sakr had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
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Conflict of Interest Disclosures: Dr Marshall reported receiving personal fees from AKPA Pharma and serving on their data and safety monitoring board; receiving personal fees from Baxter and serving on their advisory board; receiving nonfinancial support from Sphingotec and serving on their advisory board; and receiving personal fees from AM Pharma and serving as chair on their data and safety monitoring board. Dr Brazzi reported receiving personal fees from Medtronic. Dr Timsit reported receiving grants and personal fees from Merck, Pfizer, and Biomerieux and serving on their advisory boards; receiving personal fees from Paratek, Nabriva, and Medimune and serving on their advisory boards; and receiving a grant from 3M. Dr Gorordo-Delsol reported receiving personal fees from Pfizer SA CV (México). Dr De Waele reported serving as consultant to Merck Sharp & Dohme and Pfizer; and serving on speaker's bureaus for Accelerate and Grifols (all honorariums paid to his institution). Dr Kollef reported receiving personal fees from Merck. Dr Angus reported receiving personal fees and serving as a consultant to Bristol-Myers Squibb, Bayer AG, and Ferring Pharmaceuticals Inc; owning stock in Alung Technologies Inc; having a patent pending with Ferring Pharmaceuticals Inc for Selepressin (compounds, compositions, and methods for treating sepsis); and having a patent pending with the University of Pittsburgh for proteomic biomarkers of sepsis in elderly patients. No other disclosures were reported.

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Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

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Definitions supplied to investigators

Type of ICU
- Open: non-ICU doctors can write orders
- Closed: only ICU doctors can write orders

Type of admission

- Surgical - defined as having surgery in the week preceding ICU admission. Elective surgery is defined as surgery scheduled > 24 hours in advance and emergency surgery as that scheduled within 24 hours of operation.
- Trauma - defined as an ICU admission directly related to, or as a complication of, a traumatic event in the 30 days preceding ICU admission. "Trauma" *and* "surgical" should be selected as type of admission if a trauma patient has undergone surgery.
- Medical - all other types of admission

Comorbidities

- Metastatic cancer - metastases proven by surgery, computed tomography or magnetic resonance scan, or any other method.
- Hematologic cancer - including but not limited to lymphoma, acute leukemia, multiple myeloma.
- HIV infection - HIV positive patients with clinical complications such as *Pneumocystis carinii* pneumonia, Kaposi's sarcoma, lymphoma, tuberculosis, or toxoplasma infection.
- Chronic kidney failure - defined as either chronic dialysis dependent kidney failure or history of chronic kidney 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 immunohumoral or cellular immune deficiency state.
- Chemotherapy/radiotherapy - in the 6 months prior to ICU admission.

Mode of acquisition of infection

- Hospital-acquired - infections evident at least 48 hours after hospitalization.
- Health-care-associated - infections in a patient who meets any of the following criteria: 1. Received intravenous therapy at home; received wound care or specialized nursing care through a health care agency, family, or friends in the 30 days prior to hospital admission patients whose only home therapy was oxygen use were not included), 2) Attended a hospital or hemodialysis clinic or received intravenous chemotherapy in the 30 days prior to hospital admission, 3) Had been admitted to an acute care hospital for 2 or more days in the 90 days prior to hospital admission, 4) Resided in a nursing home or a long-term care facility.
- ICU-acquired - infections occurring at least 24 hours following admission to the ICU.

eTable 1. Characteristics of the patients according to the presence or absence of infection

Characteristic	All patients with infection case report form completed n=15165	No Infection n=7030 (46.4%)	Infection n=8135 (53.6%)
Male, n (%)	9160 (60.4)	4176 (59.4)	4984 (61.3)
Age, mean ± SD	61.1±17.3	60.7±17.3	61.4±17.3
Type of admission, n (%)			
Medical	8279 (54.6)	3115 (44.3)	5164 (63.5)
Elective surgery	3178 (21.0)	2331 (33.2)	847 (10.4)
Emergency surgery	2549 (16.8)	963 (13.7)	1586 (19.5)
Trauma	1147 (7.6)	616 (8.8)	531 (6.5)
Admission source, n (%)			
ED/ambulance	4992 (33.0)	2252 (32.1)	2740 (33.7)
Hospital floor	4023 (26.6)	1458 (20.8)	2565 (31.6)
OR/recovery	3848 (25.4)	2448 (34.9)	1400 (17.2)
Other hospital	2099 (13.9)	745 (10.6)	1354 (16.7)
Other	181 (1.2)	114 (1.6)	67 (0.8)
Reason for admission, n (%)			
Cardiovascular	3338 (22.4)	1569 (22.8)	1769 (22.0)
Respiratory	3236 (21.7)	832 (12.1)	2404 (29.9)
Neurological	2520 (16.9)	1272 (18.5)	1248 (15.5)
Surveillance/monitoring	1822 (12.2)	1419 (20.7)	403 (5.0)
Digestive/liver	1574 (10.6)	588 (8.6)	986 (12.3)
Trauma	1343 (9.0)	699 (10.2)	644 (8.0)
Renal	479 (3.2)	182 (2.6)	297 (3.7)
Metabolic	279 (1.9)	140 (2.0)	139 (1.7)
Hematological	199 (1.3)	97 (1.4)	102 (1.3)
Ob/gyn	114 (0.8)	73 (1.1)	41 (0.5)
Comorbidities, n (%)			
Cancer (all)	2534 (16.7)	1173 (16.7)	1361 (16.7)
Solid cancer	2052 (13.5)	1029 (14.6)	1023 (12.6)
Non-metastatic cancer	448 (3.0)	209 (3.0)	239 (2.9)
Hematologic cancer	425 (2.8)	117 (1.7)	308 (3.8)
Non-insulin-dependent diabetes	2034 (13.4)	884 (12.6)	1150 (14.1)
Insulin-dependent diabetes	1142 (7.5)	461 (6.6)	681 (8.4)
COPD	1996 (13.2)	777 (11.1)	1219 (15.0)
Heart failure (NYHC III-IV)	1673 (11.0)	728 (10.4)	945 (11.6)
Chronic kidney failure	1576 (10.4)	637 (9.1)	939 (11.5)
Immunosuppression	971 (6.4)	306 (4.4)	665 (8.2)
Chemotherapy/radiotherapy	939 (6.2)	383 (5.4)	556 (6.8)
Cirrhosis	480 (3.2)	185 (2.6)	295 (3.6)
HIV	125 (0.8)	19 (0.3)	106 (1.3)

Characteristic	All patients with infection case report form completed	No Infection	Infection
Number of comorbidities, n (%)			
0	6879 (45.4)	3480 (49.5)	3399 (41.8)
1	4524 (29.8)	2025 (28.8)	2499 (30.7)
2	2403 (15.8)	1015 (14.4)	1388 (17.1)
3	988 (6.5)	385 (5.5)	603 (7.4)
4+	371 (2.4)	125 (1.8)	246 (3.0)
Severity scores on study day			
SAPS II, mean ± SD	35.8±18.8	29.9±16.8	40.9±18.8
SOFA, median [IQR]	6 [3-9]	4 [2-7]	7 [4-11]
Procedures on the study day, n (%)			
Renal replacement therapy	1668 (11.2)	415 (6.0)	1253 (15.7)
Mechanical ventilation			
Non-invasive	1544 (10.3)	593 (8.6)	951 (11.9)
Invasive	6654 (44.4)	2277 (32.8)	4377 (54.4)
Vasopressor use	4232 (27.9)	1356 (19.3)	2876 (35.4)
Antibiotic use	10640 (70.2)	2758 (39.2)	7882 (96.9)
Prophylactic	4217 (27.8)	2758 (39.2)	1459 (17.9)
Cephalosporins	2144 (14.1)	1627 (23.1)	517 (6.4)
Penicillins	1046 (6.9)	671 (9.5)	375 (4.6)
Carbapenems	394 (2.6)	150 (2.1)	244 (3.0)
Other beta lactams	48 (0.3)	36 (0.5)	12 (0.1)
Aminoglycosides	147 (1.0)	75 (1.1)	72 (0.9)
Quinolones	248 (1.6)	139 (2.0)	109 (1.3)
Glycopeptides	378 (2.5)	209 (3.0)	169 (2.1)
Macrolides	89 (0.6)	43 (0.6)	46 (0.6)
Other antibiotics	778 (5.1)	440 (6.3)	338 (4.2)
Antifungal	229 (1.5)	82 (1.2)	147 (1.8)
Antiviral	180 (1.2)	55 (0.8)	125 (1.5)
Therapeutic	7723 (50.9)	0 (0.0)	7723 (94.9)
Cephalosporins	1784 (11.8)		1784 (21.9)
Penicillins	2751 (18.1)		2751 (33.8)
Carbapenems	2422 (16.0)		2422 (29.8)
Other beta lactams	114 (0.8)		114 (1.4)
Aminoglycosides	649 (4.3)		649 (8.0)
Quinolones	868 (5.7)		868 (10.7)
Glycopeptides	1472 (9.7)		1472 (18.1)
Macrolides	395 (2.6)		395 (4.9)
Other antibiotics	2130 (14.0)		2130 (26.2)
Antifungal	1173 (7.7)		1173 (14.4)

Characteristic	All patients with infection case report form completed	No Infection	Infection
End-of-life decisions[a], n (%)			
Do-not-resuscitate	1300 (8.6)	504 (7.2)	796 (9.8)
Withhold	977 (6.4)	365 (5.2)	612 (7.5)
Withdraw	324 (2.1)	122 (1.7)	202 (2.5)
Length of stay			
ICU, Median [IQR]	10 [3-28]	5 [2-17]	15 [6-35]
Survivors	9 [3-27]	5 [2-15]	15 [6-36]
Non-survivors	16 [7-33]	12 [5-28]	17 [8-34]
Hospital, Median [IQR]	23 [11-48]	16 [8-36]	30 [15-56]
Survivors	23 [11-49]	16 [8-35]	32 [17-60]
Non-survivors	23 [11-45]	19 [8-40]	24 [13-46]
Mortality, n (%)			
ICU	2534 (17.1)	664 (9.6)	1870 (23.6)
Hospital	3328 (22.5)	924 (13.4)	2404 (30.3)

SOFA: sequential organ failure assessment; IQR; interquartile range; ICU: intensive care unit; ED: emergency department; OR: operating room; COPD: chronic obstructive pulmonary disease; HIV: human immunodeficiency virus. [a]documented in the patient's notes on the day of the study. Percentages calculated taking into account missing values

eTable 2. Prevalence of and outcome from infection according to different factors

	Infection, number of patients (%)	SOFA score, median (IQR)		ICU LOS, median (IQR)		Hospital LOS, median (IQR)		ICU mortality, n (%)		Hospital mortality, n (%)	
		No infection	Infection	No infection	Infection	No infection	Infection	No infection	Infection	No infection	Infection
Geographic region											
Western Europe	3170 (50.7)	4 [2-8]	7 [4-11]	4 [2-14]	14 [6-31]	16 [8-33]	29 [16-51]	294 (9.7)	674 (21.5)	422 (13.9)	892 (28.4)
Central/South America	1470 (57.9)	3 [1-6]	7 [4-10]	6 [2-22]	17 [7-42]	15 [7-39]	32 [16-60]	118 (11.6)	417 (30.2)	158 (15.6)	508 (36.8)
Asia/Middle East	1892 (60.1)	5 [3-8]	8 [5-11]	7 [2-26]	17 [8-43]	19 [10-46]	31 [16-62]	102 (8.4)	384 (20.9)	144 (11.9)	506 (27.6)
Eastern Europe	737 (54.5)	5 [3-8]	7 [4-11]	6 [2-19]	18 [8-38]	18 [9-36]	30 [16-56]	91 (14.9)	206 (28.6)	114 (18.7)	264 (36.6)
North America	561 (45.7)	4 [2-7]	6 [4-10]	4 [2-11]	11 [4-24]	10 [5-24]	20 [10-39]	39 (5.8)	117 (20.9)	58 (8.7)	147 (26.2)
Australasia	141 (43.0)	5 [2-8]	8 [3-12]	3 [1-7]	9 [3-21]	13 [7-25]	21 [12-35]	8 (4.3)	24 (17.0)	15 (8.0)	33 (23.4)
Africa	164 (51.4)	4 [2-7]	8 [4-12]	47 [9-63]	31 [12-68]	59 [15-66]	42 [22-72]	12 (7.7)	48 (29.4)	13 (8.4)	54 (33.1)
Gross national income[a]											
Low and lower-middle	385 (57.8)	4 [2-7]	7 [4-11]	6 [2-13]	15 [8-43]	12 [7-26]	25 [13-54]	32 (12.1)	99 (28.0)	35 (13.2)	110 (31.1)
Upper-middle	3232 (58.8)	4 [2-7]	7 [4-11]	7 [2-28]	19 [8-44]	19 [9-45]	32 [16-62]	240 (11.0)	821 (26.4)	322 (14.8)	1019 (32.7)
High	4518 (50.2)	4 [2-7]	7 [4-11]	4 [2-13]	13 [6-30]	15 [8-32]	28 [15-51]	392 (8.8)	950 (21.3)	567 (12.8)	1275 (28.5)
Type of Hospital											
University/academic	5792 (53.6)	5 [2-8]	7 [4-11]	6 [2-18]	16 [7-36]	17 [9-38]	31 [16-57]	507 (10.2)	1309 (22.9)	685 (13.8)	1693 (29.7)
Non-university	2343 (53.7)	4 [2-6]	7 [4-10]	4 [2-13]	13 [6-32]	13 [7-29]	26 [13-51]	157 (8.2)	561 (25.2)	239 (12.4)	711 (31.9)
Type of admission											
Medical	5164 (62.4)	4 [2-7]	7 [4-11]	7 [3-24]	14 [6-35]	17 [8-44]	28 [14-55]	434 (14.3)	1303 (26.0)	606 (20.0)	1686 (33.6)
Surgical/elective	847 (26.7)	4 [2-7]	6 [3-10]	2 [1-6]	14 [6-34.5]	13 [7-24]	33 [19-59]	59 (2.6)	151 (18.1)	91 (4.0)	184 (22.1)
Surgical/emergency	1586 (62.2)	5 [3-8]	7 [4-11]	8 [2-22]	16 [7-33]	20 [10-39]	31 [17-53]	109 (11.5)	334 (21.4)	153 (16.2)	429 (27.5)
Trauma	531 (46.3)	4 [2-7]	6 [4-9]	10 [4-27]	26 [13-47]	22 [9-40]	37 [22-60]	62 (10.2)	79 (15.2)	74 (12.2)	101 (19.4)
Quartiles of SAPS II (calculated from study day variables)											
<22	1179 (31.7)	2 [1-4]	3 [1-4]	3 [1-9]	12 [4-30]	12 [6-26]	29 [15-55]	38 (1.5)	54 (4.7)	72 (2.9)	84 (7.3)
22-32	1867 (49.1)	4 [2-6]	4 [3-6]	5 [2-14.5]	13 [5-33]	17 [9-36]	29 [15-55]	92 (4.9)	161 (8.8)	139 (7.3)	268 (14.6)
33-47	2382 (62.3)	6 [5-9]	7 [5-10]	9 [3-27]	17 [7-38]	23 [11-48]	32 [17-58]	178 (12.6)	474 (20.4)	274 (19.4)	691 (29.7)
48+	2707 (70.8)	10 [8-13]	12 [9-15]	8 [3-24]	17 [8-37]	19 [9-41]	28 [14-54]	356 (32.4)	1181 (44.9)	439 (39.9)	1361 (51.7)
Duration of ICU stay pre-study day											
0-1	1861 (34.1)	4 [2-7]	7 [4-11]	2 [1-5]	4 [2-10]	11 [6-21]	16 [8-32]	235 (6.7)	379 (20.8)	335 (9.5)	495 (27.2)
2-7	2948 (59.6)	4 [2-7]	7 [4-11]	6 [3-11]	10 [6-19]	15 [9-29]	22 [13-40]	200 (10.2)	604 (21.0)	293 (15.0)	826 (28.7)
8-14	1447 (72.9)	5 [3-8]	7 [4-11]	16 [12-24]	19 [13-31]	29 [18-48]	32 [20-54]	88 (16.6)	350 (24.9)	115 (21.7)	442 (31.5)
>14	1879 (67.7)	4 [2-7]	7 [4-11]	49 [30-88]	47 [30-78]	65 [41-102]	62 [41-87]	141 (16.0)	537 (29.3)	181 (20.5)	641 (35.0)

a: gross national income per capita for 2017: <$3,895 = low and lower-middle income; $3896–12,055 = upper-middle income; and >$12,055 = high income; percentages calculated taking into account missing values

eTable 3. Mode of acquisition and site of infection according to geographic area and gross national income

	TOTAL number of patients (%)	Geographic region							Gross national income[a]		
Mode of acquisition		Western Europe	Central/South America	Asia/Middle East	Eastern Europe	North America	Australasia	Africa	Upper	Upper-middle	Lower and lower-middle
Community-acquired	3474 (44)	1386 (44.7)	585 (41.5)	864 (47.4)	239 (33.1)	276 (50.4)	67 (48.2)	57 (35.6)	1967 (44.5)	1322 (42.5)	185 (49.5)
Hospital-acquired/healthcare-associated	2724 (34.5)	1020 (32.9)	495 (35.1)	646 (35.4)	270 (37.4)	204 (37.2)	56 (40.3)	33 (20.6)	1517 (34.3)	1092 (35.1)	115 (30.7)
ICU-acquired	1706 (21.6)	695 (22.4)	331 (23.5)	314 (17.2)	212 (29.4)	68 (12.4)	16 (11.5)	70 (43.8)	938 (21.2)	694 (22.3)	74 (19.8)
Site of infection											
Respiratory	4893 (60.1)	1782 (56.2)	847 (57.6)	1316 (69.6)	470 (63.8)	316 (56.3)	83 (58.9)	79 (48.2)	2576 (57)	2083 (64.4)	234 (60.8)
Abdominal	1490 (18.3)	679 (21.4)	230 (15.6)*	304 (16.1)	152 (20.6)	77 (13.7)	19 (13.5)	29 (17.7)	900 (19.9)	546 (16.9)	44 (11.4)
Blood	1239 (15.2)	486 (15.3)	165 (11.2)*	278 (14.7)	121 (16.4)	116 (20.7)	26 (18.4)	47 (28.7)	757 (16.8)	405 (12.5)	77 (20)
Renal	263 (3.2)	81 (2.6)	64 (4.4)*	46 (2.4)	43 (5.8)	20 (3.6)	1 (0.7)	8 (4.9)	130 (2.9)	110 (3.4)	23 (6)
Skin	518 (6.4)	192 (6.1)	103 (7)	104 (5.5)	64 (8.7)	36 (6.4)	9 (6.4)	10 (6.1)	288 (6.4)	205 (6.3)	25 (6.5)
Catheter-related	255 (3.1)	116 (3.7)	34 (2.3)	50 (2.6)	26 (3.5)	11 (2)	4 (2.8)	14 (8.5)	153 (3.4)	85 (2.6)	17 (4.4)
Genitourinary	875 (10.8)	268 (8.5)	192 (13.1)*	211 (11.2)	89 (12.1)	81 (14.4)	4 (2.8)	30 (18.3)	434 (9.6)	367 (11.4)	74 (19.2)
Central nervous system	314 (3.9)	107 (3.4)	66 (4.5)	80 (4.2)	24 (3.3)	22 (3.9)	4 (2.8)	11 (6.7)	155 (3.4)	140 (4.3)	19 (4.9)
Other site	529 (6.5)	243 (7.7)	79 (5.4)	90 (4.8)	48 (6.5)	50 (8.9)	11 (7.8)	8 (4.9)	356 (7.9)	150 (4.6)	23 (6)

a: gross national income per capita for 2017: <$3,895 = low and lower-middle income; $3896–12,055 = upper-middle income; and >$12,055 = high income;
ICU: intensive care unit; percentages calculated taking into account missing values

eTable 4. Number of infected patients with positive microbiological isolates and the isolated microorganisms according to geographic region and gross national income

	Number of patients (%) n=8135	Geographic region							Gross national income[a]		
		Western Europe n=3170	Central/South America n=1470	Asia/Middle East n=1892	Eastern Europe n=737	North America n=561	Australasia n=141	Africa n=164	Upper n=4518	Middle n=3232	Lower n=385
Culture positive infections	5259 (64.6)	2148 (67.8)	744 (50.6)	1207 (63.8)	537 (72.9)	396 (70.6)	107 (75.9)	120 (73.2)	3122 (69.1)	1854 (57.4)	283 (73.5)
>1 positive culture	2299 (43.7)	943 (43.9)	265 (35.6)	513 (42.5)	317 (59.0)	166 (41.9)	33 (30.8)	62 (51.7)	1394 (44.7)	782 (42.2)	123 (43.5)
Gram positive bacteria	1946 (37.0)	876 (40.8)	258 (34.7)	326 (27.0)	221 (41.2)	182 (46.0)	46 (43.0)	37 (30.8)	1301 (41.7)	559 (30.2)	86 (30.4)
MSSA	390 (7.4)	214 (10.0)	59 (7.9)	41 (3.4)	35 (6.5)	27 (6.8)	11 (10.3)	3 (2.5)	288 (9.2)	89 (4.8)	13 (4.6)
S. aureus resistant to methicillin, linezolid or vancomycin	245 (4.7)	51 (2.4)	53 (7.1)	60 (5.0)	31 (5.8)	40 (10.1)	4 (3.7)	6 (5.0)	124 (4.0)	109 (5.9)	12 (4.2)
MRSA	240 (4.6)	49 (2.3)	53 (7.1)	58 (4.8)	30 (5.6)	40 (10.1)	4 (3.7)	6 (5.0)	122 (3.9)	107 (5.8)	11 (3.9)
S. aureus, sensitivity unknown	143 (2.7)	58 (2.7)	18 (2.4)	23 (1.9)	17 (3.2)	23 (5.8)	3 (2.8)	1 (0.8)	86 (2.8)	41 (2.2)	16 (5.7)
Staph coag -ve, methicillin sensitive	131 (2.5)	55 (2.6)	19 (2.6)	26 (2.2)	27 (5.0)	2 (0.5)	2 (1.9)	0 (0.0)	78 (2.5)	46 (2.5)	7 (2.5)
Staph coag -ve, methicllin resistant	174 (3.3)	74 (3.4)	35 (4.7)	29 (2.4)	23 (4.3)	5 (1.3)	2 (1.9)	6 (5.0)	101 (3.2)	68 (3.7)	5 (1.8)
Staph coag -ve, sensitivity unknown	127 (2.4)	60 (2.8)	19 (2.6)	24 (2.0)	5 (0.9)	14 (3.5)	1 (0.9)	4 (3.3)	84 (2.7)	38 (2.0)	5 (1.8)
S. pneumoniae	144 (2.7)	66 (3.1)	17 (2.3)	23 (1.9)	15 (2.8)	10 (2.5)	6 (5.6)	7 (5.8)	97 (3.1)	34 (1.8)	13 (4.6)
S. pneumoniae resistant to macrolides	12 (0.2)	4 (0.2)	1 (0.1)	4 (0.3)	0 (0.0)	2 (0.5)	0 (0.0)	1 (0.8)	9 (0.3)	2 (0.1)	1 (0.4)
Other strep	228 (4.3)	115 (5.4)	19 (2.6)	39 (3.2)	19 (3.5)	27 (6.8)	8 (7.5)	1 (0.8)	169 (5.4)	46 (2.5)	13 (4.6)
Enterococcus	358 (6.8)	201 (9.4)	26 (3.5)	45 (3.7)	49 (9.1)	25 (6.3)	8 (7.5)	4 (3.3)	279 (8.9)	76 (4.1)	3 (1.1)
Enterococcus vancomycin-intermediate or resistant	80 (1.5)	44 (2.0)	7 (0.9)	3 (0.2)	15 (2.8)	8 (2.0)	3 (2.8)	0 (0.0)	62 (2.0)	17 (0.9)	1 (0.4)
Other Gram positive bacteria	228 (4.3)	102 (4.7)	15 (2.0)	48 (4.0)	17 (3.2)	37 (9.3)	2 (1.9)	7 (5.8)	164 (5.3)	60 (3.2)	4 (1.4)
Gram negative bacteria	3540 (67.3)	1310 (61.0)	537 (72.2)	922 (76.4)	418 (77.8)	213 (53.8)	47 (43.9)	93 (77.5)	1909 (61.1)	1433 (77.3)	198 (70.0)
Klebsiella	973 (18.5)	280 (13.0)	170 (22.8)	280 (23.2)	166 (30.9)	37 (9.3)	3 (2.8)	37 (30.8)	447 (14.3)	449 (24.2)	77 (27.2)
Klebsiella resistant to beta-lactams, including 3rd generation cephalosporins and carbapenems	497 (9.5)	103 (4.8)	112 (15.1)	154 (12.8)	98 (18.2)	8 (2.0)	0 (0.0)	22 (18.3)	176 (5.6)	267 (14.4)	54 (19.1)
E. coli	902 (17.2)	414 (19.3)	117 (15.7)	176 (14.6)	95 (17.7)	69 (17.4)	15 (14.0)	16 (13.3)	570 (18.3)	274 (14.8)	58 (20.5)
E. coli resistant to beta-lactams, including 3rd generation cephalosporins and carbapenems	239 (4.5)	81 (3.8)	37 (5.0)	69 (5.7)	28 (5.2)	18 (4.5)	2 (1.9)	4 (3.3)	120 (3.8)	94 (5.1)	25 (8.8)*
Pseudomonas	850 (16.2)	289 (13.5)	124 (16.7)	227 (18.8)	122 (22.7)	50 (12.6)	9 (8.4)	29 (24.2)	435 (13.9)	363 (19.6)	52 (18.4)
Pseudomonas resistant to beta-lactams, including 3rd generation cephalosporins and carbapenems	134 (2.5)	43 (2.0)	24 (3.2)	38 (3.1)	20 (3.7)	6 (1.5)	1 (0.9)	2 (1.7)	61 (2.0)	66 (3.6)	7 (2.5)
Acinetobacter	602 (11.4)	75 (3.5)	70 (9.4)	309 (25.6)	123 (22.9)	4 (1.0)	2 (1.9)	19 (15.8)	137 (4.4)	411 (22.2)	54 (19.1)
Acinetobacter resistant to carbapenems	423 (8.0)	46 (2.1)	45 (6.0)	230 (19.1)	88 (16.4)	0 (0.0)	1 (0.9)	13 (10.8)	81 (2.6)	306 (16.5)	36 (12.7)
Enterobacter	196 (3.7)	91 (4.2)	21 (2.8)	34 (2.8)	20 (3.7)	15 (3.8)	7 (6.5)	8 (6.7)	124 (4.0)	65 (3.5)	7 (2.5)

	Number of patients (%)	Geographic region							Gross national income		
		Western Europe	Central/South America	Asia/Middle East	Eastern Europe	North America	Australasia	Africa	Upper	Middle	Lower
Proteus	197 (3.7)	73 (3.4)	25 (3.4)	34 (2.8)	38 (7.1)	14 (3.5)	2 (1.9)	11 (9.2)	112 (3.6)	69 (3.7)	16 (5.7)
Stenotrophomonas	147 (2.8)	53 (2.5)	21 (2.8)	49 (4.1)	9 (1.7)	15 (3.8)	0 (0.0)	0 (0.0)	85 (2.7)	61 (3.3)	1 (0.4)
Serratia	139 (2.6)	73 (3.4)	16 (2.2)	19 (1.6)	11 (2.0)	11 (2.8)	1 (0.9)	8 (6.7)	101 (3.2)	33 (1.8)	5 (1.8)
Hemophilus	94 (1.8)	60 (2.8)	10 (1.3)	8 (0.7)	1 (0.2)	10 (2.5)	5 (4.7)	0 (0.0)	80 (2.6)	12 (0.6)	2 (0.7)
Citrobacter	68 (1.3)	43 (2.0)	10 (1.3)	6 (0.5)	4 (0.7)	3 (0.8)	1 (0.9)	1 (0.8)	54 (1.7)	12 (0.6)	2 (0.7)
Other Gram negative bacteria	661 (13.1)	317 (14.8)	80 (10.8)	132 (10.9)	74 (13.8)	47 (11.9)	14 (13.1)	27 (22.5)	455 (14.6)	207 (11.2)	29 (10.2)
Anaerobes	183 (3.5)	105 (4.9)	12 (1.6)	9 (0.7)	23 (4.3)	24 (6.1)	7 (6.5)	3 (2.5)	152 (4.9)	30 (1.6)	1 (0.4)
Other bacteria[b]	92 (1.7)	42 (2.0)	12 (1.6)	20 (1.7)	7 (1.3)	10 (2.5)	0 (0.0)	1 (0.8)	59 (1.9)	26 (1.4)	7 (2.5)
Fungi	864 (16.4)	398 (18.5)	69 (9.3)	205 (17.0)	89 (16.6)	59 (14.9)	17 (15.9)	27 (22.5)	554 (17.7)	256 (13.8)	54 (19.1)
Candida albicans.	512 (9.7)	238 (11.1)	41 (5.5)	107 (8.9)	69 (12.8)	27 (6.8)	11 (10.3)	19 (15.8)	329 (10.5)	147 (7.9)	36 (12.7)
Candida non albicans.	265 (5.0)	122 (5.7)	23 (3.1)	76 (6.3)	21 (3.9)	12 (3.0)	3 (2.8)	8 (6.7)	158 (5.1)	91 (4.9)	16 (5.7)
Candida (any species) resistant to azoles	58 (1.1)	23 (1.1)	7 (0.9)	13 (1.1)	7 (1.3)	4 (1.0)	0 (0.0)	4 (3.3)	33 (1.1)	24 (1.3)	1 (0.4)
Aspergillus	76 (1.4)	48 (2.2)	0 (0.0)	17 (1.4)	6 (1.1)	4 (1.0)	1 (0.9)	0 (0.0)	64 (2.0)	10 (0.5)	2 (0.7)
Other fungi	61 (1.2)	17 (0.8)	6 (0.8)	15 (1.2)	2 (0.4)	18 (4.5)	3 (2.8)	0 (0.0)	43 (1.4)	17 (0.9)	1 (0.4)
Viruses	196 (3.7)	82 (3.8)	16 (2.2)	52 (4.3)	6 (1.1)	16 (4.0)	20 (18.7)	4 (3.3)	130 (4.2)	42 (2.3)	24 (8.5)
Parasites	43 (0.8)	27 (1.3)	5 (0.7)	6 (0.5)	1 (0.2)	3 (0.8)	0 (0.0)	1 (0.8)	34 (1.1)	7 (0.4)	2 (0.7)
Mixed flora	90 (1.7)	44 (2.0)	12 (1.6)	12 (1.0)	5 (0.9)	13 (3.3)	3 (2.8)	1 (0.8)	64 (2.0)	24 (1.3)	2 (0.7)

a: gross national income per capita for 2017: <$3,895 = low and lower-middle income; $3896–12,055 = upper-middle income; and >$12,055 = high income; [b]i.e., mycobacteria, chlamydia, rickettsia, mycoplasma, legionella. MSSA: methicillin-sensitive *S. aureus*; MRSA: methicillin-resistant *S. aureus*; percentages calculated taking into account missing values

eTable 5. Distribution of isolated microorganisms according to mode of acquisition

	Number of patients (%)	Mode of acquisition		
		Community acquired	Hospital-acquired	ICU-acquired
Culture positive infections, n (%)	5164 (65.3)	1972 (56.8)	1813 (66.6)	1379 (80.8)
>1 positive culture, n (%)	2269 (43.9)	793 (40.2)	842 (46.4)	634 (46.0)
Gram positive bacteria, n (%)	1926 (37.3)	831 (42.1)	663 (36.6)	432 (31.3)
MSSA	386 (7.5)	173 (8.8)	124 (6.8)	89 (6.5)
S. aureus resistant to methicillin, linezolid or vancomycin	242 (4.7)	94 (4.8)	91 (5.0)	57 (4.1)
MRSA	237 (4.6)	91 (4.6)	91 (5.0)	55 (4.0)
S. aureus, sensitivity unknown	141 (2.7)	79 (4.0)	36 (2.0)	26 (1.9)
Staph coag -ve, methicillin sensitive	130 (2.5)	40 (2.0)	51 (2.8)	39 (2.8)
Staph coag -ve, methicllin resistant	171 (3.3)	31 (1.6)	74 (4.1)	66 (4.8)
Staph coag -ve, sensitivity unknown	125 (2.4)	38 (1.9)	49 (2.7)	38 (2.8)
S. pneumoniae	143 (2.8)	110 (5.6)	17 (0.9)	16 (1.2)
S. pneumoniae resistant to macrolides	12 (0.2)	8 (0.4)	3 (0.2)	1 (0.1)
Other strep	228 (4.4)	150 (7.6)	61 (3.4)	17 (1.2)
Enterococcus	353 (6.8)	105 (5.3)	167 (9.2)	81 (5.9)
Enterococcus vancomycin-intermediate or resistant	79 (1.5)	18 (0.9)	42 (2.3)	19 (1.4)
Other Gram positive bacteria	227 (4.4)	102 (5.2)	76 (4.2)	49 (3.6)
Gram negative bacteria, n (%)	3473 (67.3)	1118 (56.7)	1281 (70.7)	1074 (77.9)
Klebsiella	964 (18.7)	285 (14.5)	367 (20.2)	312 (22.6)
Klebsiella resistant to beta-lactams, including 3rd generation cephalosporins and carbapenems	490 (9.5)	106 (5.4)	180 (9.9)	204 (14.8)
E. coli	883 (17.1)	393 (19.9)	325 (17.9)	165 (12.0)
E. coli resistant to beta-lactams, including 3rd generation cephalosporins and carbapenems	236 (4.6)	89 (4.5)	94 (5.2)	53 (3.8)
Pseudomonas	827 (16.0)	191 (9.7)	319 (17.6)	317 (23.0)
Pseudomonas resistant to beta-lactams, including 3rd generation cephalosporins and carbapenems	130 (2.5)	34 (1.7)	52 (2.9)	44 (3.2)
Acinetobacter	587 (11.4)	117 (5.9)	241 (13.3)	229 (16.6)
Acinetobacter resistant to carbapenems	415 (8.0)	75 (3.8)	166 (9.2)	174 (12.6)
Enterobacter	195 (3.8)	78 (4.0)	74 (4.1)	43 (3.1)
Proteus	194 (3.8)	62 (3.1)	74 (4.1)	58 (4.2)
Stenotrophomonas	144 (2.8)	43 (2.2)	56 (3.1)	45 (3.3)
Serratia	138 (2.7)	30 (1.5)	53 (2.9)	55 (4.0)
Hemophilus	93 (1.8)	49 (2.5)	23 (1.3)	21 (1.5)
Citrobacter	68 (1.3)	25 (1.3)	27 (1.5)	16 (1.2)
Other Gram negative bacteria	684 (12.2)	223 (11.3)	246 (13.6)	215 (15.6)
Anaerobes, n (%)	181 (3.5)	59 (3.0)	77 (4.2)	45 (3.3)
Other bacteria[b], n (%)	90 (1.7)	77 (3.9)	10 (0.6)	3 (0.2)
Fungi, n (%)	848 (16.4)	293 (14.9)	300 (16.5)	255 (18.5)
Candida albicans.	503 (9.7)	167 (8.5)	173 (9.5)	163 (11.8)
Candida non albicans.	259 (5.0)	80 (4.1)	103 (5.7)	76 (5.5)
Candida (any species) resistant to azoles	56 (1.1)	16 (0.8)	26 (1.4)	14 (1.0)
Aspergillus	75 (1.5)	33 (1.7)	30 (1.7)	12 (0.9)
Other fungi	60 (1.2)	35 (1.8)	15 (0.8)	10 (0.7)
Viruses, n (%)	193 (3.7)	131 (6.6)	46 (2.5)	16 (1.2)
Parasites, n (%)	41 (0.8)	33 (1.7)	8 (0.4)	0 (0.0)
Mixed flora, n (%)	88 (1.7)	44 (2.2)	34 (1.9)	10 (0.7)

[b]i.e., mycobacteria, chlamydia, rickettsia, mycoplasma, legionella. MSSA: methicillin-sensitive *S. aureus*; MRSA: methicillin-resistant *S. aureus*; percentages calculated taking into account missing values

eTable 6. Isolated microorganisms according to site of infection

	Site of infection								
	Respiratory	**Abdominal**	**Blood**	**Renal**	**Skin**	**Catheter-related**	**Genitourinary**	**Central nervous system**	**Other site**
Gram positive bacteria, n (%)	783 (14.9)	238 (4.5)	494 (9.4)	23 (0.4)	190 (3.6)	92 (1.7)	89 (1.7)	65 (1.2)	151 (2.9)
MSSA	205 (3.9)	16 (0.3)	98 (1.9)	1 (0.0)	42 (0.8)	12 (0.2)	8 (0.2)	5 (0.1)	34 (0.6)
S. aureus resistant to methicillin, linezolid or vancomycin	147 (2.8)	6 (0.1)	54 (1.0)	1 (0.0)	30 (0.6)	3 (0.1)	4 (0.1)	2 (0.0)	16 (0.3)
MRSA	143 (2.7)	6 (0.1)	54 (1.0)	1 (0.0)	30 (0.6)	3 (0.1)	4 (0.1)	2 (0.0)	15 (0.3)
S. aureus, sensitivity unknown	78 (1.5)	7 (0.1)	28 (0.5)	0 (0.0)	14 (0.3)	4 (0.1)	3 (0.1)	2 (0.0)	11 (0.2)
Staph coag -ve, methicillin sensitive	32 (0.6)	4 (0.1)	52 (1.0)	1 (0.0)	7 (0.1)	21 (0.4)	2 (0.0)	4 (0.1)	9 (0.2)
Staph coag -ve, methiclin resistant	23 (0.4)	16 (0.3)	73 (1.4)	0 (0.0)	11 (0.2)	31 (0.6)	1 (0.0)	8 (0.2)	14 (0.3)
Staph coag -ve, sensitivity unknown	34 (0.6)	8 (0.2)	57 (1.1)	2 (0.0)	11 (0.2)	8 (0.2)	0 (0.0)	2 (0.0)	10 (0.2)
S. pneumoniae	110 (2.1)	2 (0.0)	11 (0.2)	0 (0.0)	1 (0.0)	0 (0.0)	3 (0.1)	20 (0.4)	3 (0.1)
S. pneumoniae resistant to macrolides	6 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	4 (0.1)	0 (0.0)
Other strep	185 (3.5)	37 (0.7)	58 (1.1)	4 (0.1)	37 (0.7)	2 (0.0)	6 (0.1)	26 (0.5)	28 (0.5)
Enterococcus	55 (1.0)	134 (2.5)	58 (1.1)	8 (0.2)	38 (0.7)	9 (0.2)	43 (0.8)	4 (0.1)	25 (0.5)
Enterococcus vancomycin-intermediate or resistant	14 (0.3)	29 (0.6)	11 (0.2)	2 (0.0)	4 (0.1)	2 (0.0)	7 (0.1)	3 (0.1)	11 (0.2)
Other Gram-positive bacteria	78 (1.5)	33 (0.6)	40 (0.8)	6 (0.1)	24 (0.5)	3 (0.1)	23 (0.4)	12 (0.2)	14 (0.3)
Gram-negative bacteria, n (%)	2089 (39.7)	497 (9.5)	515 (9.8)	157 (3.0)	176 (3.3)	107 (2.0)	469 (8.9)	42 (0.8)	131 (2.5)
Klebsiella	565 (10.7)	125 (2.4)	144 (2.7)	31 (0.6)	46 (0.9)	25 (0.5)	114 (2.2)	7 (0.1)	29 (0.6)
Klebsiella resistant to beta-lactams, including 3rd generation cephalosporins and carbapenems	281 (5.3)	55 (1.0)	86 (1.6)	14 (0.3)	31 (0.6)	20 (0.4)	60 (1.1)	5 (0.1)	15 (0.3)
E. coli	239 (4.5)	224 (4.3)	116 (2.2)	87 (1.7)	33 (0.6)	9 (0.2)	227 (4.3)	6 (0.1)	33 (0.6)

	Site of infection								
	Respiratory	**Abdominal**	**Blood**	**Renal**	**Skin**	**Catheter-related**	**Genitourinary**	**Central nervous system**	**Other site**
E. coli resistant to beta-lactams, including 3rd generation cephalosporins and carbapenems	63 (1.2)	43 (0.8)	32 (0.6)	19 (0.4)	10 (0.2)	5 (0.1)	66 (1.3)	4 (0.1)	11 (0.2)
Pseudomonas	604 (11.5)	74 (1.4)	67 (1.3)	13 (0.2)	36 (0.7)	27 (0.5)	56 (1.1)	9 (0.2)	30 (0.6)
Pseudomonas resistant to beta-lactams, including 3rd generation cephalosporins and carbapenems	100 (1.9)	8 (0.2)	10 (0.2)	1 (0.0)	4 (0.1)	2 (0.0)	11 (0.2)	0 (0.0)	2 (0.0)
Acinetobacter	458 (8.7)	33 (0.6)	68 (1.3)	4 (0.1)	22 (0.4)	21 (0.4)	19 (0.4)	11 (0.2)	16 (0.3)
Acinetobacter resistant to carbapenems	318 (6.0)	22 (0.4)	53 (1.0)	4 (0.1)	17 (0.3)	17 (0.3)	12 (0.2)	8 (0.2)	9 (0.2)
Enterobacter	1692 (32.2)	260 (4.9)	323 (6.1)	59 (1.1)	127 (2.4)	81 (1.5)	222 (4.2)	28 (0.5)	85 (1.6)
Proteus	76 (1.4)	26 (0.5)	17 (0.3)	9 (0.2)	24 (0.5)	4 (0.1)	34 (0.6)	2 (0.0)	11 (0.2)
Stenotrophomonas	115 (2.2)	9 (0.2)	14 (0.3)	1 (0.0)	4 (0.1)	6 (0.1)	1 (0.0)	0 (0.0)	5 (0.1)
Serratia	93 (1.8)	6 (0.1)	25 (0.5)	1 (0.0)	8 (0.2)	7 (0.1)	4 (0.1)	2 (0.0)	4 (0.1)
Hemophilus	89 (1.7)	1 (0.0)	3 (0.1)	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Citrobacter	30 (0.6)	17 (0.3)	4 (0.1)	3 (0.1)	7 (0.1)	1 (0.0)	7 (0.1)	0 (0.0)	3 (0.1)
Other Gram-negative bacteria	322 (6.1)	118 (2.2)	114 (2.2)	19 (0.4)	40 (0.8)	23 (0.4)	51 (1.0)	9 (0.2)	29 (0.6)
Anaerobes, n (%)	16 (0.3)	104 (2.0)	19 (0.4)	0 (0.0)	14 (0.3)	1 (0.0)	4 (0.1)	3 (0.1)	28 (0.5)
Other bacteria[b], n (%)	74 (1.4)	3 (0.1)	5 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	7 (0.1)	4 (0.1)
Fungi, n (%)	384 (7.3)	149 (2.8)	126 (2.4)	30 (0.6)	20 (0.4)	40 (0.8)	145 (2.8)	10 (0.2)	30 (0.6)
Candida albicans.	216 (4.1)	97 (1.8)	71 (1.4)	21 (0.4)	10 (0.2)	21 (0.4)	91 (1.7)	1 (0.0)	16 (0.3)
Candida non albicans.	99 (1.9)	49 (0.9)	53 (1.0)	6 (0.1)	7 (0.1)	17 (0.3)	44 (0.8)	3 (0.1)	9 (0.2)
Candida (any species) resistant to azoles	15 (0.3)	19 (0.4)	10 (0.2)	2 (0.0)	1 (0.0)	3 (0.1)	12 (0.2)	1 (0.0)	2 (0.0)
Aspergillus	66 (1.3)	3 (0.1)	3 (0.1)	0 (0.0)	3 (0.1)	0 (0.0)	0 (0.0)	2 (0.0)	3 (0.1)
Other fungi	31 (0.6)	4 (0.1)	4 (0.1)	4 (0.1)	1 (0.0)	2 (0.0)	11 (0.2)	4 (0.1)	3 (0.1)
Viruses, n (%)	120 (2.3)	9 (0.2)	29 (0.6)	1 (0.0)	8 (0.2)	0 (0.0)	5 (0.1)	17 (0.3)	16 (0.3)
Parasites, n (%)	30 (0.6)	2 (0.0)	3 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.1)	3 (0.1)
Mixed flora, n (%)	48 (0.9)	19 (0.4)	2 (0.0)	4 (0.1)	9 (0.2)	0 (0.0)	6 (0.1)	1 (0.0)	3 (0.1)

[b] i.e., mycobacteria, chlamydia, rickettsia, mycoplasma, legionella. MSSA: methicillin-sensitive *S. aureus*; MRSA: methicillin-resistant *S. aureus*; percentages calculated taking into account missing values

eTable 7. Multilevel analysis in the whole cohort with infection as the dependent variable

Variables	OR (95%CI)	p value	IOR-80
Fixed-effects, varying within clusters			
Age	1.00 (1.00-1.00)	0.158	
Male	1.11 (1.03-1.20)	0.01	
Type of admission (%)			
Surgical	Ref	na	
Medical	2.78 (2.44-3.18)	<0.001	
Trauma	3.37 (2.95-3.84)	<0.001	
Other	1.61 (1.34-1.94)	<0.001	
Source of admission			
OR/recovery	Ref	na	
Other hospital	1.63 (1.40-1.90)	<0.001	
ED/ambulance	1.18 (1.03-1.35)	0.02	
Hospital floor	1.77 (1.56-2.02)	<0.001	
Other	0.56 (0.39-0.81)	0.002	
Comorbidities			
COPD	1.39 (1.24-1.56)	<0.001	
Metastatic cancer	1.09 (0.86-1.39)	0.47	
Hematologic cancer	1.64 (1.27-2.12)	<0.001	
Solid cancer	1.14 (1.01-1.30)	0.04	
Insulin-dependent diabetes mellitus	1.29 (1.11-1.49)	0.001	
Non-insulin-dependent diabetes mellitus	1.15 (1.03-1.29)	0.01	
Heart failure, NYHA III/IV	0.93 (0.82-1.06)	0.26	
Chronic kidney failure	1.14 (1.01-1.30)	0.04	
HIV infection	4.69 (2.74-8.03)	<0.001	
Cirrhosis	1.20 (0.97-1.48)	0.09	
Immunosuppression	1.39 (1.21-1.60)	<0.001	
Duration of ICU stay prior to study day, days			
0-1	Ref	na	
2-7	2.45 (2.24-2.68)	<0.001	
8-14	4.20 (3.71-4.77)	<0.001	
>14	3.17 (2.83-3.54)	<0.001	
Fixed-effects, constant within clusters			
Type of hospital			
Non university	Ref	na	
University/Academic	0.98 (0.87-1.12)	0.78	(0.3-3.1)
ICU admissions, 2016			
<250	Ref	na	
250-499	0.83 (0.62-1.10)	0.19	(0.3-2.6)
500-749	0.58 (0.43-0.77)	<0.001	(0.2-1.8)
750+	0.54 (0.42-0.71)	<0.001	(0.2-1.7)
Gross national income			
Low and lower-middle	Ref	na	
Upper-middle	0.87 (0.62-1.20)	0.39	(0.6-1.2)

Variables	OR (95%CI)	p value	IOR-80
High	0.65 (0.47-0.89)	0.01	(0.5-0.9)
Random-effects			
Country			
Variance (se)	0.04 (0.02)		
p value	0.05		
MOR	1.21		
Hospital within country			
Variance (se)	0.40 (0.04)		
p value	<0.001		
MOR	1.82		

COPD: chronic obstructive pulmonary disease; ED: emergency department; HIV: human immunodeficiency virus; ICU: intensive care unit; NYHA: New York Heart Association; OR: operating room; MOR: median odds ratio

eTable 8. Multilevel analysis in infected patients with positive isolates with hospital mortality as the dependent variable and all microorganisms as independent variables

Variables	OR (95%CI)	p value	IOR-80
Fixed-effects, varying within clusters			
Age	1.01 (1.00-1.01)	0.002	
Male	0.93 (0.80-1.07)	0.29	
SAPS II[b]	1.05 (1.04-1.05)	<0.001	
Type of admission (%)			
Surgical	Ref	na	
Medical	1.18 (0.90-1.55)	0.23	
Trauma	0.88 (0.67-1.17)	0.38	
Other	0.88 (0.59-1.32)	0.55	
Source of admission			
OR/recovery	Ref	na	
Otherhospital	0.92 (0.70-1.20)	0.53	
ED/ambulance	0.93 (0.72-1.21)	0.59	
Hospital floor	1.30 (1.02-1.65)	0.04	
Other	0.86 (0.41-1.80)	0.68	
Comorbidities			
COPD	0.99 (0.82-1.20)	0.90	
Metastatic cancer	1.66 (1.11-2.49)	0.01	
Hematologic cancer	1.26 (0.87-1.83)	0.23	
Solid	1.16 (0.93-1.46)	0.18	
Insulin-dependent diabetes mellitus	0.95 (0.74-1.21)	0.67	
Non-insulin-dependent diabetes mellitus	0.98 (0.80-1.19)	0.80	
Heart failure, NYHA III/IV	1.49 (1.21-1.84)	<0.001	
Chronic kidney failure	1.05 (0.85-1.31)	0.66	
HIV infection	0.45 (0.24-0.83)	0.01	
Cirrhosis	1.60 (1.13-2.25)	0.01	
Immunosuppression	1.16 (0.93-1.44)	0.19	
Acquisition mode			
Community-acquired	Ref	na	
Hospital-acquired/healthcare-associated	1.03 (0.87-1.22)	0.77	
ICU acquired	1.32 (1.10-1.60)	0.003	
Mircoorganisms[a]			
S. aureus, MSSA	1.20 (0.93-1.57)	0.17	
S. aureus, MRSA	1.06 (0.77-1.48)	0.71	
S. epidermidis, methicillin sensitive	0.80 (0.52-1.24)	0.32	
S. epidermidis, methicllin resistant	1.04 (0.71-1.51)	0.85	
Enterococcus	1.31 (1.00-1.73)	0.05	
S. pneumoniae	0.46 (0.28-0.76)	0.002	
Pseudomonas	0.89 (0.74-1.07)	0.22	
E coli	1.00 (0.83-1.20)	0.97	
Klebsiella	1.13 (0.94-1.36)	0.18	
Acinetobacter	1.24 (0.99-1.56)	0.07	
Enterobacter	0.98 (0.67-1.43)	0.92	

Variables	OR (95%CI)	p value	IOR-80
Candida	1.19 (0.98-1.44)	0.08	
Aspergillus	1.51 (0.88-2.60)	0.14	
Procedures			
Mechanical ventilation	1.28 (1.08-1.51)	0.004	
Renal replacement therapy	1.50 (1.24-1.81)	<0.001	
Fixed-effects, constant within clusters			
Type of hospital			
Non university	Ref	na	
University/Academic	0.88 (0.74-1.06)	0.19	(0.4-2.0)
ICU admissions, 2016			
<250	Ref	na	
250-499	0.79 (0.54-1.16)	0.23	(0.3-1.8)
500-749	0.86 (0.59-1.26)	0.45	(0.4-2.0)
750+	0.88 (0.62-1.25)	0.48	(0.4-2.0)
Income			
Low and lower-middle	Ref	na	
Upper-middle	1.05 (0.68-1.62)	0.84	(0.6-1.7)
High	0.74 (0.48-1.13)	0.16	(0.5-1.2)
Random-effects			
Country			
Variance (se)	0.07 (0.03)		
P value	0.03		
MOR	1.29		
Hospital within country			
Variance (se)	0.21 (0.06)		
P value	<0.001		
MOR	1.55		

COPD: chronic obstructive pulmonary disease; ED: emergency department; HIV: human immunodeficiency virus; ICU: intensive care unit; NYHA: New York Heart Association; OR: operating room; MOR: median odds ratio. [a]only microorganisms with a p value < 0.2 in the univariate analysis were introduced in the final model; [b]calculated from study day variables

eTable 9. Multilevel analysis in infected patients with positive isolates with hospital mortality as the dependent variable and resistant microorganisms as independent variables

Variables	OR (95%CI)	P value	IOR-80
Fixed-effects, varying within clusters			
Age	1.01 (1.00-1.01)	0.001	
Male	0.92 (0.80-1.06)	0.24	
SAPS II[h]	1.05 (1.04-1.05)	<0.001	
Type of admission (%)			
Surgical	Ref	na	
Medical	1.21 (0.92-1.59)	0.18	
Trauma	0.91 (0.69-1.21)	0.52	
Other	0.92 (0.62-1.38)	0.69	
Source of admission			
OR/recovery	Ref	na	
Other hospital	0.91 (0.69-1.19)	0.47	
ED/ambulance	0.91 (0.70-1.18)	0.47	
Hospital floor	1.27 (1.00-1.62)	0.05	
Other	0.83 (0.40-1.75)	0.63	
Comorbidities			
COPD	0.99 (0.82-1.20)	0.95	
Metastatic cancer	1.70 (1.14-2.56)	0.01	
Hematologic cancer	1.25 (0.86-1.81)	0.25	
Solid	1.17 (0.93-1.46)	0.18	
Insulin-dependent diabetes mellitus	0.95 (0.75-1.22)	0.70	
Non-insulin-dependent diabetes mellitus	0.97 (0.79-1.18)	0.74	
Heart failure, NYHA III/IV	1.48 (1.20-1.82)	<0.001	
Chronic kidney failure	1.05 (0.84-1.30)	0.69	
HIV infection	0.47 (0.25-0.86)	0.02	
Cirrhosis	1.61 (1.14-2.27)	0.006	
Immunosuppression	1.16 (0.93-1.44)	0.20	
Acquisition mode			
Community-acquired	Ref	na	
Hospital-acquired/healthcare-associated	1.03 (0.87-1.22)	0.70	
ICU-acquired	1.30 (1.08-1.57)	0.005	
Resistant microorganisms			
S. aureus[a]	1.04 (0.76-1.44)	0.80	
S. coagulase neg[b]	1.02 (0.70-1.49)	0.91	
Enterococcus[c]	2.41 (1.43-4.06)	0.001	
S. pneumoniae[d]	0.53 (0.10-2.69)	0.44	
E. coli[e]	1.08 (0.78-1.49)	0.64	
Klebsiella[e]	1.29 (1.02-1.63)	0.03	
Pseudomonas[e]	1.16 (0.76-1.78)	0.49	
Acinetobacter[f]	1.40 (1.08-1.81)	0.01	
Candida[g]	1.40 (0.76-2.57)	0.28	

Variables	OR (95%CI)	P value	IOR-80
Procedures			
Mechanical ventilation	1.29 (1.09-1.52)	0.003	
Renal replacement therapy	1.51 (1.25-1.82)	<0.001	
Fixed-effects, constant within clusters			
Type of hospital			
Non university	Ref	na	
University/Academic	0.88 (0.73-1.06)	0.17	(0.4-2.0)
ICU admissions, 2016			
<250	Ref	na	
250-499	0.80 (0.55-1.17)	0.25	(0.4-1.8)
500-749	0.86 (0.59-1.27)	0.45	(0.4-2.0)
750+	0.89 (0.63-1.27)	0.53	(0.4-2.0)
Income			
Low and lower-middle	Ref	na	
Upper-middle	1.05 (0.68-1.62)	0.82	(0.7-1.6)
High	0.78 (0.51-1.18)	0.23	(0.5-1.2)
Random-effects			
Country			
Variance (se)	0.06 (0.03)		
P value	0.03		
MOR	1.26		
Hospital within country			
Variance (se)	0.21 (0.06)		
P value	<0.001		
MOR	1.55		

COPD: chronic obstructive pulmonary disease; ED: emergency department; HIV: human immunodeficiency virus; ICU: intensive care unit; NYHA: New York Heart Association; OR: operating room; SAPS: Simplified Acute Physiology Score; MOR: median odds ratio; a: resistant to methicillin, linezolid, or vancomycin; b: resistant to methicillin; c: resistant to vancomycin; d: resistant to macrolides; e: resistant to beta lactams or just carpapenems; f: resistant to carbapenems; g: resistant to azoles; h: calculated from study day variables