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Influence of bacterial resistance on mortality in intensive care units: a registry study from 2000 to 2013 (IICU Study)☆

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SUMMARY

Background: Bacterial resistance to antibiotics is a daily concern in intensive care units. However, few data are available concerning the clinical consequences of in-vitro-defined resistance.

Aim: To compare the mortality of patients with nosocomial infections according to bacterial resistance profiles.

Methods: The prospective surveillance registry in 29 French intensive care units (ICUs) participating during the years 2000–2013 was retrospectively analysed. All patients presenting with a nosocomial infection in ICU were included.

Findings: The registry contained 88,000 eligible patients, including 10,001 patients with a nosocomial infection. Among them, 3092 (36.7%) were related to resistant microorganisms. Gram-negative bacilli exhibited the highest rate of resistance compared to Gram-positive cocci (52.8% vs 48.1%; $P < 0.001$). In-hospital mortality was higher in cases of patients with antibiotic-resistant infectious agents (51.9% vs 45.5%; $P < 0.001$), and critical care length of stay was longer (33 ± 26 vs 29 ± 22 days; $P < 0.001$). These results remained significant after SAPS II matching ($P < 0.001$) and in the Gram-negative bacilli and Gram-positive cocci subgroups. No difference in mortality was found with respect to origin prior to admission.

Conclusion: Patients with bacterial resistance had higher ICU mortality and increased length of stay, regardless of the bacterial species or origin of the patient.

☆ This work is dedicated to the late Dr Nadine Garreau.

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Introduction

As a cause of multi-organ failure in septic shock, or a precipitating event over the course of severe illness, infection is an independent risk factor of mortality in intensive care units (ICUs) and thus a daily concern. Furthermore, healthcare-associated infections have substantial effects on morbidity and length of hospital stay and represent a major public health issue [1–4]. Consequently, wide international prevention programmes have been implemented to specifically target these infections [5]. However, despite these efforts, the nosocomial infection incidence seems to be rising [1,6].

The problem is compounded by bacterial resistance to antibiotics, leading to delays in appropriate antibiotic therapy and raising the question of a possible overmortality [1,7]. Indeed, ICU patients are not only extremely vulnerable but also the most prone to infections related to resistant bacteria as a result of antibiotic misuse or overuse, long hospitalizations, and the rapid spread of resistant strains from abroad [8–12]. Improvements in infection management tend to focus on antibiotic resistance, as reflected by recent national campaigns in many countries [13,14].

Thus, surveillance and control networks have been implemented worldwide, such as the US Centers for Disease Control and Prevention or the Centres de Coordination de la Lutte contre les Infections Nosocomiales (CCLIN) in France. The latter prospectively includes demographic, bacteriological, and clinical data from a wide representative sample of ICUs.

However, only sparse data are available concerning the role of bacterial resistance, and conflicting evidence exists concerning its impact on mortality: a recent literature review reported studies in which resistant bacterial strains were associated with increased mortality and many others in which mortality was independent of antibiotic resistance [15–17].

Consequently, the aim of this study was to compare the mortality of hospital-acquired infections with respect to bacterial resistance to antibiotics over an extended period of 13 years in 29 French ICUs in the CCLIN Network. We hypothesized that patients with infections with resistant bacteria in ICU are associated with increased mortality rate and longer hospital stays than those with susceptible strains.

Methods

Ethics, consent, and permissions

Following institutional review board agreement (Ethics Committee for Research in Anesthesiology and Intensive Care, French Society of Anesthesiology and Intensive Care, 74 rue Raynouard, 75016 Paris, France; Ref. IRB 00010254-2016-119), prospective data were collected from 2000 to 2013 from a database involving 29 French ICUs included in a specific network aimed at studying hospital-acquired infections (Centres de Coordination de la Lutte contre les Infections Nosocomiales Ouest: CCLIN Ouest) [18]. Declaration of healthcare-associated infections has been mandatory in France since 2001. A national network, divided into five regional subsets, was created to provide both global overview and local feedback and to ensure uniformity in the definitions and diagnosis of nosocomial infections. Participation in this network is systematically offered to every ICU in France, public or not. In the West subset, participation increased from 5.6% in 2004 to 56.2% of available intensive care beds in 2014. A local co-ordinator was appointed in each participating centre and was responsible for inclusions and exhaustiveness assessment (checked by comparison between the number of inclusions and the number of eligible patients).

Patients

Every patient admitted for more than two days to one of the participating French ICUs was eligible for inclusion. Data prospectively collected on a standardized form in participating ICUs were as follows: demographic data, patient-related risk factors (immunosuppression, antibiotic treatment at admission, Simplified Acute Physiology Score (SAPS) II score, diagnostic category at admission), origin before admission in ICU (patient coming from home, long-term hospitalization, conventional unit, or ICU), exposure to invasive devices (orotracheal intubation, central venous catheter, urinary catheter) and diagnosed healthcare-associated infections.

Outcomes

The primary outcome was ICU mortality according to the bacterial resistance level.

Secondary outcomes were ICU length of stay (LOS), mortality according to the type of pathogen, patient origin, diagnostic category at admission, and site of infection.

Definitions

Only infectious events occurring >48 h after admission to the healthcare facility were considered nosocomial infections.

Pneumonia, urinary tract infection, bacteraemia, and catheter-related infections were defined according to international recommendations [19–21].

Catheter-related infection was defined by a quantitative culture $>10^3$ colony-forming units (cfu) associated with local or general symptoms [19]. Bacteraemia was defined by at least one positive blood culture with clinical and biological sepsis criteria [20]. One positive sample defined bloodstream infection except in case of multiple bacteria or coagulase-negative staphylococci, *Bacillus* spp. (except *B. anthracis*), *Corynebacterium* spp., *Propionibacterium* spp., *Micrococcus* spp., or other commensal or saprophytic micro-organism. In these cases, two positive blood samples with the same pathogens, obtained separately at two different times, within 48 h, were required to diagnose a bloodstream infection.

A diagnosis of pneumonia required compatible imaging (chest X-ray or computed tomography) associated with clinical evidence of infection (temperature >38°C without other causes and/or white blood cell count $<4000/mm^3$ or $>12{,}000/mm^3$) and at least one of the following symptoms: purulence or modification of sputum, cough, dyspnea, tachypnea, evocative auscultation, worsening of blood gas sample analysis, increased oxygen requirements or ventilatory support [21]. Microbiological evidence of pneumonia was defined by the following thresholds: 10^6 cfu for tracheal aspirations, 10^4 cfu for bronchoalveolar lavage, 10^3 cfu for protected specimen brush, and 10^3 cfu for plugged telescoping catheter.

Sputum culture has a very low specificity concerning the diagnosis of infection, as well as non-quantitative culture of

endo-bronchial sample. Thus, those two examinations were not taken into account in the study.

Antibiotic treatment at admission excluded prophylactic and local treatments.

Definitions from the SAPS II score [22] were used to determine diagnosis category upon admission (medical, elective surgery, or urgent surgery). Immunosuppression was defined as a polymorphonuclear neutrophil count <500 mm^3 or according to the Acute Physiological And Chronic Health Evaluation (APACHE) II definition of induced immunodepression [23]. Antibiotic susceptibility tests were performed and thus resistances were defined according to the latest guidelines of the Committee for Antimicrobial Testing of the French Society of Microbiology and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines susceptibility breakpoints at the time of inclusion [24]. An intermediate phenotype for antibiotic sensitivity was considered 'resistant'. Resistance profiles were divided into three categories for Gram-positive cocci (susceptible; ampicillin- or meticillin-resistant; vancomycin-resistant) and four categories for Gram-negative bacilli (susceptible; ceftazidime-resistant; imipenem-resistant or extended-spectrum β-lactamase producing; ceftazidime- and imipenem-resistant).

Statistical analysis

Variable distributions were tested by the Anderson–Darling test. Mortality and patient characteristics were compared between groups using Fisher's exact test for qualitative variables and Student's *t*-test or Mann–Whitney *U*-test for quantitative variables, depending on their distribution. Subgroup analysis was performed by one-way analysis of variance. In the case of significant inter-group difference, a Tukey post-hoc test was used to compare groups.

Logistic regression was performed with mortality as the dependent variable for the population with documented infection. Variables were selected for logistic regression for $P < 0.10$ in univariate analysis. Model performance was evaluated by the Nagelkerke adjusted R^2 statistic, the *c*-index (discrimination), and the Cessie–van Houwelingen goodness-of-fit test (calibration).

The logit predicting probability of mortality was used to match patients according to resistance profiles using a 'greedy'-matching algorithm to match subjects using calipers that were defined by a maximum width of 0.1 standard deviations of the logit of the estimated propensity score.

Subsequently, univariate and multivariate analyses were performed on the matched population with mortality as the dependent variable.

All the tests were bilateral, and $P < 0.05$ was considered statistically significant. Statistical analyses were performed using R Statistical Software (Foundation for Statistical Computing, Vienna, Austria).

Results

Entire cohort

From 2000 to 2013, data from 87,931 patients were collected, including 10,001 with a hospital-acquired infection. There were 8428 cases with an identified pathogen, 1121 cases without a pathogen being detected, and 428 cases with missing data). The primary patient demographics and characteristics are reported in Table I. Multivariate analysis on the entire

Table I
Patient characteristics of the overall population and according to survival outcomes

Characteristic	Overall population	Survivors	Non-survivors	*P*-value
	N = 87,931	*n* = 53,431 (60.7%)	*n* = 34,500 (39.3%)	
Age (years)	61 (18)	60 (18)	63 (17)	<0.001
Male	55,018 (62.6%)	33,121 (62.0%)	21,897 (63.5%)	<0.001
LOS (days)	6 (4–12)	6 (4–12)	7 (4–13)	<0.001
SAPS II	47 (72)	44 (72)	52 (73)	<0.001
MV duration (days)	5 (2–11)	4 (2–10)	6 (3–12)	<0.001
CVC length (days)	3 (0–9)	3 (0–8)	5 (0–11)	<0.001
UC duration (days)	6 (3–12)	6 (3–11)	6 (4–13)	<0.001
Infection	10,001 (11.4%)	5323 (10.0)	4678 (13.6%)	<0.001
Diagnostic category at admission				
Medical	56,277 (64.0%)	32,858 (61.5%)	23,419 (67.9%)	<0.001
Urgent surgery	16,477 (18.7%)	10,363 (19.4%)	6114 (17.7%)	<0.001
Elective surgery	14,137 (16.1%)	9604 (18.0%)	4533 (13.1%)	<0.001
Origin				
Home	45,056 (51.2%)	27,524 (51.5%)	17,532 (50.8%)	0.044
Long-term care	3940 (4.5%)	2367 (4.4%)	1573 (4.6%)	0.37
Hospital	33,794 (38.4%)	20,190 (37.8%)	13,604 (39.4%)	<0.001
ICU	4164 (4.7%)	2694 (5.0%)	1470 (4.3%)	<0.001
Immunodepression	9153 (10.4%)	5069 (9.5%)	4084 (11.8%)	<0.001
Trauma	8032 (9.1%)	4972 (9.3%)	3060 (8.9%)	<0.001

LOS, length-of-stay; SAPS II, Simplified Acute Physiology Score; MV, mechanical ventilation; CVC, central venous catheter; UC, urinary catheterization; ICU, intensive care unit.
Values are expressed as no. (%), mean (standard deviation) or median (interquartile range).
P-values are given for the comparison between survivors and non-survivors.

population identified SAPS II score (odds ratio: 1.24, 95% confidence interval (CI): 1.20–1.29), immunodepression (1.14; 1.05–1.23), trauma (0.89; 0.85–0.95), patient origin prior to ICU admission (1.47; 1.336–1.58), and healthcare-associated infection (1.37; 1.32–1.42) as independent risk factors for mortality. Thus, patients exhibiting an infection had a higher mortality rate (46.8% (95% CI: 45.8–47.8) vs 38.3% (95% CI: 38.0–38.6); $P < 0.001$) and longer ICU length of stay (median: 24 days (range: 15–38) vs 6 (4–10); $P < 0.001$).

Patients exhibiting a documented infection

Gram-negative bacilli were identified in 54.7% (95% CI: 53.6–54.8) of cases, and Gram-positive cocci were identified in 30.0% (24.4–26.2) of cases. The most frequent pathogens are reported in Table II. Among the 8428 (84.3% (83.6–85.0)) documented infections, 3092 (36.7% (35.7–36.7)) were caused by resistant pathogens. The antibiotic resistance profile is presented in Figure 1.

Characteristics of patients with documented infections are reported in Table III. Multivariate analysis identified SAPS II score, patient origin prior to ICU admission, trauma, infection site and antibiotic resistance as independent risk factors for mortality. A logistic regression model using these factors poorly estimated mortality (Nagelkerke $R^2 = 0.04$); thus, no further analysis was performed using this model. The observed differences persisted after 2:1 matching using the SAPS II score (Supplementary Table S1; $P < 0.001$).

Table II
Frequently isolated pathogens (2000–2013)

Pathogen	Incidence (95% CI)	Resistance (95% CI)
Staphylococcus aureus	19.9% (19.0–20.8)	30.7% (28.5–32.9)
Pseudomonas aeruginosa	15.7% (14.9–16.5)	43.9% (41.2–46.6)
Enterobacter spp.	7.2% (6.6–7.8)	72.6% (69.0–76.2)
Klebsiella pneumoniae	3.1% (2.7–3.5)	64.9% (59.1–70.7)
Enterococcus faecalis	2.2% (1.9–2.5)	8.6% (4.6–12.6)
Acinetobacter baumannii	1.1% (0.9–1.3)	70.5% (61.3–79.7)
Enterococcus faecium	0.6% (0.4–0.8)	49.0% (35.0–63.0)

Pathogen resistance profiles

Mortality was higher in the case of patients with bacterial resistance (51.9% (95% CI 50.1–53.7) vs 45.5% (44.2–46.8); $P < 0.001$), as was hospital LOS in the survivor group (33±26 vs 29±23 days; $P < 0.001$).

Resistance profiles according to pathogen, infection site, and patient origin are presented in Supplementary Table S2. Pathogens were considered resistant in 39.3% vs 33.5% ($P < 0.01$) cases for patients coming from conventional units versus long-term care; and only the first grade of resistance reached a significant difference (26.4% in hospital vs 21.8% in long-term care, $P = 0.04$). Mortality was 44±3% in cases of meticillin-susceptible *S. aureus* infection, compared with 52±7% and 55±12% in cases of meticillin- and vancomycin-resistant strains, respectively. Mortality in *Pseudomonas aeruginosa* infections was 47±3% if the strain was susceptible, 55±5% if the strain was ceftazidime resistant, 55±12% in cases of imipenem resistance, and 53±18% if the strain was resistant to both ceftazidime and imipenem. No significant difference was detected when comparing the different centres.

Identified pathogens

Comparing the different pathogens, mortality ranged from 42.6% (95% CI: 28.5–56.7) for Gram-positive cocci to 55.6% (42.3–68.9) for anaerobes. Gram-negative bacilli were responsible for a higher mortality than Gram-positive cocci

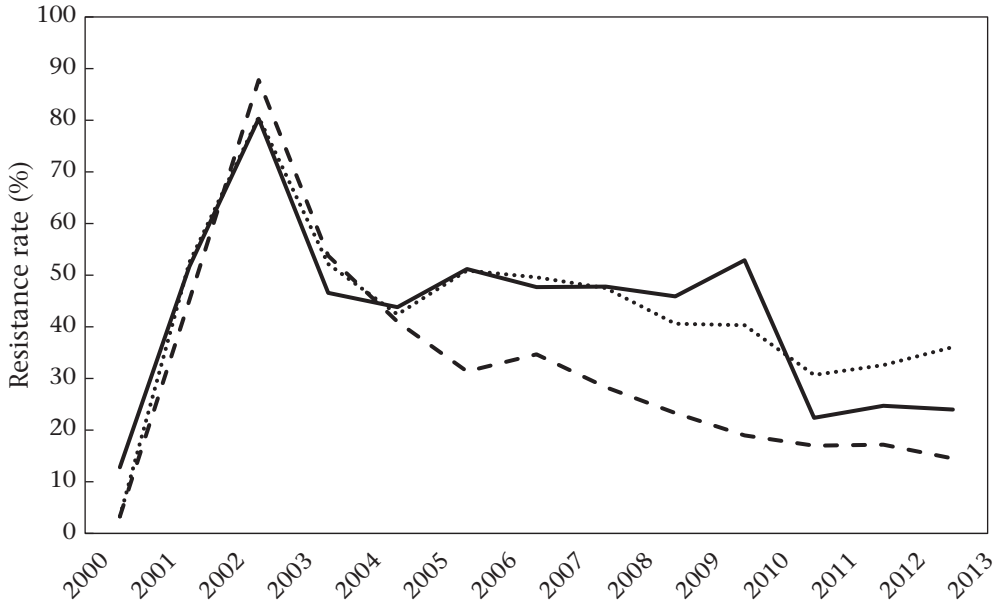

Figure 1. Evolution of resistance rates.

Table III
Infected population characteristics

Characteristic	Total	Survivors	Non-survivors	*P*
	N = 8428	*n* = 4395 (52.1%)	*n* = 4033 (47.9%)	
Age (years)	61 (±17)	59 (±17)	63 (±16)	<0.001
Male	5785 (68.6%)	3044 (69.3%)	2741 (68.0%)	0.20
LOS	31 (±24)	32 (±24)	30 (±25)	0.001
SAPS II	53 (±70)	51 (±71)	55 (±69)	0.015
MV duration	26 (±27)	26 (±27)	26 (±27)	0.994
CVC length	23 (±36)	23 (±46)	22 (±23)	0.61
UC duration	27 (±22)	27 (±21)	27 (±24)	0.53
Diagnostic category at admission				
Medical	4845 (57.5%)	2499 (56.9%)	2346 (58.2%)	0.22
Urgent surgery	2119 (25.1%)	1111 (25.3%)	1008 (25.0%)	0.76
Elective surgery	1330 (15.8%)	711 (16.2%)	619 (15.3%)	0.30
Origin				
Home	4179 (49.6%)	2310 (52.6%)	1869 (46.3%)	<0.001
Long-term care	394 (4.7%)	201 (4.6%)	193 (4.8%)	0.645
Hospitalization	3250 (38.6%)	1566 (35.6%)	1684 (41.8%)	<0.001
ICU	522 (6.2%)	280 (6.4%)	242 (6.0%)	0.48
Immunodepression	887 (10.5%)	482 (11.0%)	405 (10.0%)	0.31
Trauma	1194 (14.2%)	594 (13.5%)	600 (14.9%)	0.013
Antibiotic at admission	3632 (43.1%)	1930 (43.9%)	1702 (42.2%)	0.55
Bacterial resistance				
Resistant	3092 (36.7%)	1487 (33.8%)	1605 (39.8%)	<0.001
Infection site				
Lung	4529 (53.7%)	2188 (49.8%)	2341 (58.0%)	0.003
Bloodstream infection	1810 (21.5%)	842 (19.2%)	968 (24.0%)	0.002
CVC	924 (11.0%)	454 (10.3%)	470 (11.7%)	0.883
Urinary tract	2084 (24.7%)	1100 (25.0%)	984 (24.4%)	<0.001
Type of pathogen				
GPC	2531 (30.0%)	1375 (31.3%)	1156 (28.7%)	0.009
GNC	26 (0.3%)	12 (0.3%)	14 (0.3%)	0.54
GPB	47 (0.6%)	27 (0.6%)	20 (0.5%)	0.47
GNB	4613 (54.7%)	2390 (54.4%)	2223 (55.1%)	0.495
Enterobacteria	2693 (32.0%)	1401 (31.9%)	1292 (32.0%)	0.88
Non-enterobacterial GNB	1920 (22.8%)	989 (22.5%)	931 (23.1%)	0.53
Anaerobes	54 (0.6%)	24 (0.5%)	30 (0.7%)	0.26
Fungi	300 (3.6%)	136 (3.41%)	164 (4.1%)	0.017
Virus	4 (0.0%)	3 (0.1%)	1 (0.0%)	0.35

SAPS II, Simplified Acute Physiology Score; MV, mechanical ventilation; CVC, central venous catheter; UC, urinary catheterization; ICU, intensive care unit; GPC, Gram-positive cocci; GNC, Gram-negative cocci; GPB, Gram-positive bacilli; GNB, Gram-negative bacilli.
Values are expressed as no. (%) or as mean ± standard deviation.

(48.2% (46.8–49.6) vs 45.7% (43.8–47.6), respectively; $P = 0.044$). Fungi were responsible for the highest mortality (54.7% (49.1–60.3), $P = 0.029$ vs Gram-negative bacilli and $P = 0.003$ vs Gram-positive cocci). As seen by comparing periods 2000–2005 and 2006–2013, mortality decreased for Gram-negative bacilli (51.8% vs 47.4%; $P = 0.022$) and remained stable for every other pathogen.

Infections with Gram-negative bacilli were associated with longer hospital LOS than Gram-positive cocci infections (32 ± 24 days vs 30 ±23 days; $P = 0.033$). No difference in hospital LOS was observed between the periods 2000–2005 and 2006–2013.

There was a significant difference in the bacterial resistance among pathogens: Gram-negative bacilli exhibited the highest rate of resistance (46.5% (95% CI: 45.1–47.9)) compared with any other pathogens ($P < 0.001$). The resistance rates of frequently isolated pathogens are reported in Table II.

Infection sites

Subgroup analyses revealed that mortality was 51.7% (95% CI: 50.2–53.2) in cases of pulmonary infection, 53.4% (51.2–55.8) in cases of bacteraemia, 50.9% (47.7–54.1) in central venous catheter infections and 47.2% (45.1–49.3) in urinary tract infections (Table IV). Urinary tract infections were associated with shorter hospital LOS (25±18 days) than any other site ($P < 0.001$), whereas lung infections were associated with the longest LOS (33±26 days; $P < 0.001$). Supplementary Table S2 reports bacterial resistance profiles according to infection site, patient origin prior to ICU admission

Table IV
Mortality according to pathogen, infection site, patient origin, and diagnostic category

Characteristic	Mortality (%) (95% CI)	Length of stay (days) (±SD)
Pathogen		
Gram-positive cocci	45.7 (43.8–47.6)	29.7 (±23.4)
Gram-negative bacilli	48.2 (46.8–49.6)	31.5 (±24.1)
Infection site		
Lung	51.7 (50.2–53.2)	32.9 (±25.6)
Bloodstream infection	53.4 (51.2–55.8)	32.7 (±26.3)
CVC	50.9 (47.7–54.1)	30.9 (±23.8)
Urinary tract	47.2 (45.1–49.3)	25.2 (±18.3)
Patient origin		
Home	44.7 (43.2–46.2)	29.2 (±23.7)
Long-term care	49.0 (44.1–53.9)	32.3 (±26.8)
Conventional	51.8 (20.1–53.5)	30.4 (±25.4)
ICU	46.4 (42.1–50.7)	32.6 (±26.5)
Diagnostic category		
Medical	48.4 (47.0–49.8)	30.4 (±23.3)
Urgent surgery	47.6 (45.5–49.7)	31.4 (±25.4)
Elective surgery	46.5 (43.8–49.2)	31.9 (±26.1)

CI, confidence interval; SD, standard deviation; CVC, central venous catheter; ICU, intensive care unit.

and diagnostic category at admission. Central venous catheter infections were associated with the highest rate of resistance (75.0% (95% CI: 63.2–86.8) relative to pulmonary infections (48.2% (46.6–49.8); $P < 0.001$), bacteraemia (48.7% (45.3–52.1); $P = 0.009$), and urinary tract infections (40.8% (37.5–44.1); $P < 0.001$).

Discussion

The present study shows that patients with infections are associated with increased mortality in ICU. Among infected patients, Gram-negative bacilli were responsible for a higher mortality and longer survivor-LOS than were Gram-positive cocci. Patients with bacterial resistance were associated with increased mortality and longer ICU survivor-LOS.

Sepsis is a known risk factor for ICU mortality, yet the impact of antibiotic resistance on mortality has been debated [1,16,17]. Among previously reported studies on bacterial resistance, increased mortality was observed in all of the studies reporting more than 350 patients and in those focusing on only infections with Gram-negative bacilli [15]. It remains unclear whether this results from a lack of power among studies with small sample sizes or whether the difference in mortality is strain dependent. Indeed, the present study and previous publications suggest that infections with Gram-negative bacilli might be associated with poorer outcomes than other pathogens [1,25]. Nonetheless, the present work reports findings on 10,000 patients with infections and 8428 with identified organisms related to Gram-negative bacilli and other pathogens, and it supports the current hypothesis of increased mortality in cases of bacterial resistance. The only other wide-scale study on this specific topic included patients from 537 centres between 2005 and 2008, giving an excellent epidemiological overview of bacterial resistances, but it did not focus on a specific population [26].

It remains unclear whether the reason for the increased mortality is due to greater virulence in resistant strains or to the increased time necessary to adopt appropriate antibiotic therapy related to the resistance profiles. Although some studies have reported a biological cost of resistance acquisition, recent studies of bacterial genomes reported that increased virulence is associated with resistant strains of Gram-negative bacilli such as *P. aeruginosa*, *Escherichia coli*, *Acinetobacter baumannii*, and *Salmonella typhi* [27–33]. However, many studies of ICU patients with different nosocomial infections have repeatedly demonstrated that delays in appropriate antimicrobial therapy increase mortality, even when those delays are as short as a single hour [34–37]. The respective weight of these two hypotheses is impossible to assess, as genomic analysis is not routinely performed in ICUs and as huge cohorts would be required due to the vast numbers of strains involved and the multiple confounding factors. Another difficulty would be to precisely report the time before initiation of appropriate antibiotic therapy, which was not available in the present study.

The internal validity of the present study should be emphasized. First, all ICU patients admitted to any of the 29 centres were comprehensively included in the CCLIN Network. Second, the study case report form was standardized across the network in all participating ICUs based on international definitions and guidelines [19–24]. Finally, definitions used for bacterial resistance remained constant over the study period, decreasing inclusion bias.

This study has several limitations. First, the retrospective design limits its power, although data were collected prospectively through standardized forms. However, the large number of cases enrolled in the ICUs in northwestern France limited the heterogeneity of the antibiotic protocols as well as the bacterial ecology. Second, although the choice and timing of antibiotics, as well as individual patient histories and status, are known to influence infection outcomes, those data were not collected by the surveillance network. For example, an explanation for the decreased mortality for patients with Gram-negative bacilli infections, comparing periods 2000–2005 and 2006–2013, could not be clearly established. We might argue that there was not only an increase in the recognition of the importance of timely urgent source control, but also an expected benefit of the Surviving Sepsis Campaign, the combination of antimicrobial therapies based on an extended-spectrum β-lactam and either an aminoglycoside or a fluoroquinolone, an optimization of antibiotic regimens for ICU patients, or the evolution of minimally invasive means to achieve it such as computed tomography-guided drainage [38–40]. Third, only patients hospitalized in the ICU >48 h were included. Therefore, the most severe infections causing death within the first 48 h and the least severe infections that did not require >48 h of ICU hospitalization were not included. Finally, this study did not include data from other ICUs in France or Europe, which limited external validity but enabled the analysis of the long-term evolution of bacterial ecology and antibiotic resistance in a relatively homogeneous population.

In conclusion, patients with bacterial resistance to antibiotics are associated with increased ICU mortality and longer survivor ICU lengths of stay. Further studies are required to evaluate the respective weight of resistance-related virulence and delayed proper antibiotherapy.

Conflict of interest statement
None declared.

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None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhin.2019.01.011.

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