Study of epidemiological features, antimicrobial resistance profile and clinical outcomes of healthcare-associated infections in intensive care units by Iranian Nosocomial Infection Surveillance System

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Abstract

Background: Healthcare-associated infections are a major cause of mortality worldwide, especially in intensive care units (ICUs) where severely ill patients are in a limited physical space.

Aims: To investigate the incidence rate, microbial etiology, antimicrobial resistance profile, and mortality rate of healthcare-associated infections in ICUs.

Methods: This observational study retrospectively reviewed the medical records of 1722 ICU patients with confirmed healthcare-associated infections at hospitals affiliated with Mashhad University of Medical Sciences in 2017–2019. The patient data collected included age, sex, comorbidities, device use, causative agents, infection type, antimicrobial resistance profile, length of stay, and mortality.

Results: In total, 4077 pathogens were isolated, yielding a healthcare-associated infection incidence rate of 22.1%. The most common microorganisms were *Acinetobacter* spp. (25.0%), *Klebsiella* spp. (15.1%), *Staphylococcus* spp. (14.0%), and *Candida* spp.(12.3%). Ventilator-associated events (39.5%), urinary tract infections (22.7%), and bloodstream infections (14.8%) were the main types of infection. Comorbidities, skin and soft tissue infections, and infections with *Acinetobacter* spp., *Klebsiella* spp., *Pseudomonas* spp., and *Candida* spp. were significantly associated with higher mortality among ICU patients. Gram-positive bacteria were most resistant to ciprofloxacin (49.2%), clindamycin (38.0%), and erythromycin (37.1%). Gram-negative bacteria were most resistant to ceftazidime (71.0%), ciprofloxacin (65.2%), and cefotaxime (60.5%). The overall mortality rate was 45.2%.

Conclusion: Healthcare-associated infections in nearly half of ICU patients were fatal, especially when caused by *Acinetobacter* spp., *Klebsiella* spp., *Pseudomonas* spp., or *Candida*

spp. Therefore, effective strategies must be implemented to combat antibiotic-resistant bacteria, along with stricter adherence to infection control programmes.

Keywords: healthcare-associated infection, intensive care unit, incidence, risk factor, drug resistance

Citation: Rimaz S, Tajzadeh P, Bahrami M, Nooghabi MJ, Eshrati B, Effati S et al. Study of epidemiological features, antimicrobial resistance profile and clinical outcomes of healthcare-associated infections in intensive care units by Iranian Nosocomial Infection Surveillance System. East Mediterr Health J. 2023;29(5):xxx-xxx http://doi.org/10.26719/emhj.23.043

Received: 05/08/22; accepted: 22/12/22

Introduction

Healthcare-associated infections arise 48 hours after hospital admission, and are a major cause of morbidity and mortality worldwide, accounting for ~2 million infections and 100 000 deaths annually (*1*, *2*). In addition to prolonging hospital stay, healthcare-associated infections carry a huge financial burden, estimated at US$4.5 billion annually(*3*, *4*). According to a World Health Organization (WHO) report, out of every 100 patients, 7 in high-income countries and 15 in low- and middle-income countries develop healthcare-associated infections during their stay at acute-care hospitals (*5*). The intensive care units (ICUs), in particular, are hotbeds for developing

infections (*5*). Even though they account for < 10% of all hospital beds, 20–50% of all healthcare-associated infections are contracted in ICUs (*6*). Immunocompromise, use of invasive devices, severe underlying illnesses, and indiscriminate use of antibiotics are all factors that place ICU patients at increased risk of healthcare-associated infections (*7*). Therefore, managing infection risk in ICUs should be a priority for all health care professionals.

The prevention of healthcare-associated infections in ICUs requires rigorous control measures. To achieve infection control, WHO recommends a multimodal hand hygiene improvement strategy consisting of 5 critical elements: (1) providing clinical staff with the materials and equipment they need to perform hand hygiene at the point of care, such as alcohol-based hand rub, clean water, soap, and single-use towels; (2) training and education of health workers, patients, and visitors about the importance of hand hygiene; (3) regular evaluation of hand hygiene infrastructure, and monitoring compliance with hand hygiene programmes; (4) continually reminding health workers about the importance of maintaining hand hygiene, verbally or by visual prompts such as posters, stickers, or banners; and (5) prioritizing compliance with hand hygiene at institutional and individual levels to achieve patient and health worker safety (*8*). The WHO multimodal hand hygiene improvement strategy promises to prevent up to 50% of healthcare-associated infections and save 16 times the cost of implementation (*8*).

Even though many healthcare-associated infections can be avoided with proper infection control, it is impossible to eradicate them entirely, and antibiotics are still frequently prescribed for ICU patients (*9*). With abundant use of antibiotics in a limited space, ICUs are the ideal setting for the emergence and transmission of antibiotic-resistant bacteria (*10*). In this situation, clinicians may face a lack of effective treatment options as bacteria withstand the effects of

antibiotics, leading to the emergence of multidrug-resistant, extensively drug-resistant, and pandrug-resistant strains (*11*). In 2019, antimicrobial resistance was estimated to be responsible for 1.27 million deaths worldwide (*12*). If we do not take prompt action now, antimicrobial resistance is estimated to cause 10 million deaths annually by 2050 (*13*).

The distribution of nosocomial infections and antibiotic resistance patterns vary geographically; therefore, each medical centre should devise its own specific antimicrobial treatment policy (*14*). This is the only way to reduce the incidence, mortality rate, and treatment cost of healthcare-associated infections. In this study, we attempted to investigate the incidence, microbial etiology, antimicrobial resistance profile, and clinical outcomes of healthcare-associated infections in ICUs in north-eastern Islamic Republic of Iran.

Methods

Study design

This observational study retrospectively reviewed the medical records of patients who acquired healthcare-associated infections in ICUs at 4 hospitals affiliated with Mashhad University of Medical Sciences, Islamic Republic of Iran between April 2017 and September 2019. Inclusion was restricted to patients who had been in an ICU for ≥ 48 hours and had developed healthcare-associated infections. Those with incomplete medical records were excluded from the data analysis. The infections were diagnosed according to criteria established by the US Centers for Disease Control and Prevention and the Iranian National Nosocomial Infections Surveillance Guideline (*15*, *16*). Apart from clinical manifestations and physical examination, microbiological tests were undertaken to confirm the diagnosis of healthcare-associated infections. Antibiotic

therapy was initiated in all patients after the antimicrobial sensitivity of bacterial isolates was determined.

Definitions

Healthcare-associated infection was defined as an adverse reaction to an infectious agent or its toxins 48 hours after hospital admission. Bloodstream infection was diagnosed if a pathogen was identified in 1 or more blood culture samples from a patient who had accompanying symptoms such as fever, chills, or hypotension. Pneumonia was diagnosed when a patient showed newly developed or progressive infiltrates, cavitation, consolidation, or pleural effusion; had new onset of purulent sputum or a change in the character of the sputum; or a pathogen was cultured from blood, tracheal aspirate, bronchoalveolar lavage, bronchial brushing, or biopsy. If pneumonia was caused by mechanical ventilation, the patient was diagnosed with ventilator-associated infection. Skin and soft tissue infection was defined as purulent pustules, vesicles, or boils, or having at least 2 of the following symptoms with no other recognized cause: pain or tenderness, localized swelling, redness, or heat. Surgical site infection was defined as an infection arising 30 days after surgery, from which a microorganism was isolated, or the site had a purulent discharge. Urinary tract infection was diagnosed when a patient had a urinary catheter placed for ≥ 2 consecutive days and showed ≥ 1 of the following symptoms: fever, urgency, frequency, dysuria, suprapubic tenderness, or costovertebral angle pain/tenderness.

Data collection

We obtained details of hospitalization of patients with healthcare-associated infection from their medical records in the Iranian Nosocomial Infection Surveillance System. The data collected

included age, sex, comorbidities, invasive device use, type of infection, causative agents, antimicrobial resistance profile, length of stay, and mortality. Patients who experienced multiple healthcare-associated infections during their stay in hospital were counted separately for analysis of the type of microorganisms and site of infection.

Ethical considerations

The protocol complied with the ethical principles specified in the 1964 Helsinki Declaration and was approved by the Ethics Committee of Mashhad University of Medical Sciences (registration number IR.MUMS.REC.1399.331)and Iran University of Medical Sciences (registration number IR.IUMS.REC.1398.1219)

Statistical analysis

SPSS for Windows version 11 (SPSS Inc., Chicago, IL, USA) was used for data analysis. The categorical variables were described using frequency and percentage, whereas continuous variables were defined by mean (standard deviation) with 95% confidence interval (CI) for precision. Logistic regression analysis using the stepwise forward method was applied to estimate crude odds ratio (OR) and adjusted OR (AOR) with 95% CI, and to identify univariate and multivariate predictors of healthcare-associated infection mortality. All statistics were subjected to an effect size analysis. Statistical significance was defined as $P < 0.05$.

Results

Clinical and demographic characteristics

Over the course of the study,18 382 patients were admitted to ICUs and 1722 contracted healthcare-associated infections: 901 male (52.3%) and 821 female (47.7%), with a mean age of 57.30 (24.24) years (Table 1). Most (55.2%) patients with healthcare-associated infections were aged > 60 years. Children aged < 2 years (4.8%) and adults aged 40–59 years (22.1%) had the highest rate of healthcare-associated infections. While most patients had no underlying medical condition (30.8%), cardiac (17.5%) and respiratory (12.5%) diseases accounted for most comorbidity at the time of ICU admission. The incidence of healthcare-associated infections in ICU patients steadily increased over a 2-year period, starting from 49 cases in April 2017 to a peak of 269 in September 2019 (Figure 1). The median length of hospital stay was 20 days (interquartile range, 11–33 days). During their stay, patients developed healthcare-associated infections at a median of 5 days from admission to the first episode of infection (interquartile range, 2–12 days). Unfortunately, 45.2% of patients eventually died from infections acquired in the ICU (Table 1).

Device use, infection sites and nosocomial pathogens

During the study period, 4077 pathogens were isolated from 1722 patients: 981 (24.0%) Gram-positive bacteria, 2591 (63.6%) Gram-negative bacteria, and 505 (12.4%) fungi, yielding a healthcare-associated infection incidence rate of 22.1% (Table 2). The most common microorganisms were *Acinetobacter* spp. (25.0%), *Klebsiella* spp. (15.1%), *Staphylococcus* spp. (14.0%), and *Candida* spp. (12.3%). Among Gram-negative strains, *Acinetobacter* spp. (39.3%) were the most frequently isolated, followed by *Klebsiella* spp. (23.9%), *Pseudomonas* spp. (15.5%), and *Escherichia coli* (14.1%). Among Gram-positive strains, *Staphylococcus* spp. (58.4%), especially *Staphylococcus aureus* (25.0%), and *Enterococcus* spp. (32.8%) were

responsible for most healthcare-associated infections in ICU patients. Endotracheal tubes (39.5%), urinary catheters (19.9%), central venous catheters (12.9%), and arterial catheters (0.3%) were the invasive devices mostly associated with healthcare-associated infections, and other devices were responsible for 31.0%. Ventilator-associated infection (39.5%), urinary tract infection (22.7%), and bloodstream infection (14.8%)were the 3 main types of infection in ICU patients (Table 2).

Independent predictors for mortality

Multivariate logistic regression analysis identified 6 independent predictors of mortality among ICU patients (Table 3). Patients with comorbidity had a significantly increased risk of death (P < 0.001, AOR: 1.46, 95% CI: 1.28–1.65). *Acinetobacter* spp. (P = 0.039, AOR: 1.40, 95% CI: 1.01–1.93), *Klebsiella* spp. (P = 0.013, AOR: 1.53, 95% CI: 1.09–2.15), *Pseudomonas* spp. (P < 0.0001, AOR: 1.93, 95% CI: 1.34–2.78), and *Candida* spp. (P < 0.0001, AOR: 1.99, 95% CI: 1.37–2.89) were independently associated with higher in-hospital mortality among ICU patients. Mortality associated with the isolated pathogens was: *Pseudomonas* spp. 59.9%, *Candida* spp. 59.5%, *Klebsiella* spp. 58.3%, *Acinetobacter* spp. 55.0%, *E. coli* 47.9%, *Staphylococcus* spp. (34.7%), *Enterococcus* spp. 47.8%, and *Streptococcus* spp. 38.4%. Among infection types, only skin and soft tissue infection had a significant mortality risk of 53.4% (P = 0.0391, AOR: 1.40, 95% CI: 1.01–1.93). Even though death from ventilator-associated, urinary tract, and bloodstream infections occurred in 57.2% (AOR: 0.75, 95% CI: 0.38–1.48), 51.6% (AOR: 0.48, 95% CI: 0.29–0.82), and 49.8% (AOR: 0.86, 95% CI: 0.56–1.31) of patients, respectively, logistic regression analysis did not establish a significant association with mortality. Death

eventually occurred in 36.1% of patients with surgical site infection and 43.9% of those with pneumonia.

Antimicrobial resistance profile

Gram-positive and Gram-negative bacteria demonstrated varying levels of antimicrobial resistance. Gram-positive bacteria were most resistant to ciprofloxacin (49.2%), clindamycin (38.0%), erythromycin (37.1%), and cefoxitin (27.1%) (Table 4). *S. aureus*, *Staphylococcus epidermidis*, and other coagulase-negative staphylococci exhibited considerable resistance to ciprofloxacin (44.4%, 37.0%, and 50.2%), clindamycin (52.8%, 62.0%, and 56.8%), erythromycin (51.2%, 62.0%, and 53.3%), and cefoxitin (41.4%, 52.0%, and 42.2%). *Enterococcus* spp. were also highly resistant to ciprofloxacin (63.0%), vancomycin (63.0%), and ampicillin (47.2%). However, *Streptococcus* spp. were susceptible to most antibiotics, except for erythromycin and clindamycin, which recorded resistance of 36.9% and 30.7%, respectively. <body>Gram-negative bacteria exhibited strong resistance to ceftazidime (71.0%), ciprofloxacin (65.2%), cefotaxime (60.5%), gentamicin (55.2%), trimethoprim–sulfamethoxazole (51.2%), amikacin (46.6%), and imipenem (35.2%). Infections with *Acinetobacter* spp., *Klebsiella* spp., and *Pseudomonas* spp. were best treated with amoxicillin/clavulanic acid (99.4%, 99.4%, and 99.6% susceptibility), ampicillin (98.0%, 96.4%, and 97.1% susceptibility), levofloxacin (96.8%, 98.3%, and 98.6% susceptibility), and cefepime (81.7%, 81.7%, and 80.7% susceptibility). However, treatment with ceftazidime and ciprofloxacin was relatively ineffective because *Acinetobacter* spp., *Klebsiella* spp., and *Pseudomonas* spp. were resistant to ceftazidime (74.9%, 79.8%, and 62.0%) and ciprofloxacin (70.1%, 61.4%, and 69.6%). *E. coli* also demonstrated resistance to ceftazidime (50.1%), ciprofloxacin (47.9%), cefotaxime (43.8%), and

trimethoprim–sulfamethoxazole (36.7%), although to a lesser extent than the other Gram-negative bacteria.

Discussion

In this study, we found a high incidence (22.1%) of healthcare-associated infections in ICUs in north-eastern Islamic Republic of Iran. The most commonly isolated microorganisms were *Acinetobacter* spp., *Klebsiella* spp., *Staphylococcus* spp., and *Candida* spp. The main types of infection were ventilator-associated, urinary tract, and bloodstream infections. Comorbidities, skin and soft tissue infections, and infections with *Acinetobacter* spp., *Klebsiella* spp., *Pseudomonas* spp., and *Candida* spp. were associated with higher mortality among ICU patients. Gram-positive bacteria exhibited the strongest resistance to ciprofloxacin, clindamycin, and erythromycin, and Gram-negative bacteria were most resistant to ceftazidime, ciprofloxacin, and cefotaxime.

ICUs are breeding grounds for healthcare-associated infections (*5*). In ICUs, physicians and nurses can act as vehicles for transferring resident pathogens between wards (*17*). ICU patients undergo invasive medical procedures and are in a debilitated condition; therefore, they have a 5–10 times higher risk of developing healthcare-associated infections than patients in general medical wards (*18*). This is why despite representing < 10% of hospital beds, ICUs account for 20–50% of all healthcare-associated infections (*6*). In 2017, the global incidence of healthcare-associated infections in ICUs was as high as 54% (*19*), whereas in Europe, the incidence was only 8.3% (*20*). In our study, healthcare-associated infections occurred in 22.1% of the study population, which was higher than the 9.6–12% documented in previous studies (*21*, *22*).This rate is of concern because it has been steadily increasing from 2017 to 2019. A study in northern

Islamic Republic of Iran revealed that compliance with WHO hand hygiene guidelines was as low as 43.4% (*23*). More disturbingly, another study found that only 56.6% of health care workers had good knowledge of hand hygiene (*24*). It is now evident that serious action is required to lower the incidence of healthcare-associated infections in Iranian hospitals. We hope to take a critical step toward helping hospitals optimize their infection control programmes and minimize cross-infection risk by identifying the root causes of healthcare-associated infections as well as their microbial etiology and patterns of antimicrobial resistance.

The present study indicated that *Acinetobacter* spp. (25.0%), *Klebsiella* spp. (15.1%), *Staphylococcus* spp.(14.0%), and *Candida* spp. (12.3%) were the most common microorganisms responsible for healthcare-associated infections in ICUs in northeast Islamic Republic of Iran. Infections with *Acinetobacter* spp., *Klebsiella* spp., *Pseudomonas* spp., and *Candida* spp. were independently associated with higher in-hospital mortality among ICU patients. In a national study with a similar design, Etemad et al. discovered that *Acinetobacter* spp. (16.52%), *E. coli* (12.01%), and *Klebsiella* spp. (9.93%) were the major microorganisms isolated from ICU patients in the Islamic Republic of Iran. They also found that *Acinetobacter* spp., *Enterococcus* spp., *Enterobacter* spp., and *Candida* spp. were associated with an increased risk of in-hospital mortality (*25*). Similarly, in a multicentre study by Jahani-Sherafat et al., *Acinetobacter baumannii* (33.3%), *S. aureus* (14.4%), and *Pseudomonas aeruginosa* (14.4%) were the most prevalent pathogens causing healthcare-associated infections in ICUs, followed by *Klebsiella pneumoniae* (10.9%) and *Enterococcus* spp. (8.7%) (*26*). The prevalence and distribution of microorganisms that cause healthcare-associated infections vary by hospital, geographic area, and patient status (*27*). It is, therefore, reasonable to expect differences from previous studies regarding microbial etiology.

In our study, endotracheal tubes, urinary catheters, and central venous catheters were the invasive devices most frequently associated with healthcare-associated infections. As demonstrated by the US National Nosocomial Infection Surveillance System, mechanical ventilators, urinary catheters, and central venous catheters contributed to 83% of nosocomial pneumonia, 97% of urinary tract infections, and 87% of bloodstream infections in ICUs (*28*). The most common types of infection among our ICU patients were ventilator-associated, urinary tract, and bloodstream infections, in accordance with previous regional studies (*29*, *30*). However, none of these infections were associated with an increased risk of death, as also found by Boncagni et al. (*31*). The only type of infection that was independently associated with increased mortality risk was skin and soft tissue infection. In contrast, Rosenthal et al. conducted a multicentre cohort study of 786 ICUs worldwide and found that ventilator-associated, urinary tract, and bloodstream infections were independent risk factors for mortality (*32*). This was supported by Bonnet et al. who reported that lung, urinary tract, and bloodstream infections were the most prevalent among ICU patients and were all closely associated with higher mortality (*33*). The currently available data are inconclusive; therefore, this issue warrants further research.

In our study, treatment of ICU patients was largely interrupted because the bacteria were resistant to the antibiotics. Ceftazidime, cefotaxime, and ciprofloxacin achieved little clinical success against *Acinetobacter* spp., *Klebsiella* spp., and *Pseudomonas* spp. Isolates of *Staphylococcus* spp. showed resistance to ciprofloxacin, clindamycin, and erythromycin, and *Enterococcus* spp. were resistant to ciprofloxacin, vancomycin, and ampicillin. Similar patterns of resistance were observed in ICUs in Tehran, where Amimi et al. reported high resistance to ciprofloxacin, cefotaxime, ceftazidime, and ampicillin among *A. baumannii*, *E. coli*, *P.*

aeruginosa, *and K. pneumoniae* isolates (*34*). Likewise, in Qazvin, Bagherian et al. demonstrated that most strains of *Acinetobacter* spp., *Klebsiella* spp., and *Pseudomonas* spp. Were markedly resistant to most prescribed antibiotics, especially ciprofloxacin, ceftazidime, cefotaxime, cefepime, and piperacillin (*35*). With such high resistance to a variety of antibiotics, infections that were once curable with a short course of antibiotics could become incurable. In that case, it is reasonable to propose that the high mortality rate of 45.2% observed in our study could have been caused by antibiotic resistance. Hence, it becomes even more important for hospitals to prioritize the rational prescription of antibiotics in their infection control plans.

Our study had a few limitations. The Iranian Nosocomial Infections Surveillance System does not cover different scoring systems that can predict mortality in patients with critical conditions based on clinical and laboratory findings, such as acute physiology and chronic health evaluation (APACHE), sequential organ failure assessment (SOFA), and mortality in emergency department sepsis (MEDS) scores. Thus, we were unable to evaluate the impact of such variables on mortality at ICU admission. The system does not record the hospitalization data of patients who did not contract healthcare-associated infections in ICUs. Therefore, we could not perform further analysis to identify the risk factors for healthcare-associated infections. Taking these factors into account, we strongly recommend conducting a prospective study, possibly with a larger sample size, to capture as much information as possible at ICU admission. Regardless of its limitations, our study offers valuable insight into the epidemiology and etiology of healthcare-associated infections in ICUs in northeast Islamic Republic of Iran.

Conclusion

We documented a high incidence of healthcare-associated infection in ICUs in north-east Islamic Republic of Iran. Because of the emergence of resistant microorganisms in ICUs, healthcare-associated infections in nearly half of ICU patients eventually lead to death, especially when caused by *Acinetobacter* spp., *Klebsiella* spp., or *Pseudomonas* spp. The use of endotracheal tubes and urinary catheters may further expose patients to the risk of healthcare-associated infection. Therefore, to reduce these infections, effective strategies to combat antibiotic-resistant bacteria must be implemented, along with stricter adherence to infection control programmes and enhancement of infection control using feasible and affordable tools and resources. Our findings could be used by policy-makers to develop more practical protocols for hand hygiene, reducing contact with patients, and using invasive devices. Staff training programmes, along with continuous supervision and monitoring, are also essential to prevent the spread of infection.

Acknowledgements

We would like to thank the Vice Chancellors for Research Affairs of Mashhad University of Medical Sciences and Iran University of Medical Sciences (IUMS) for financial support.

Conflict of interest: None declared.

Funding: This work was supported by Mashhad University of Medical Sciences and Iran University of Medical Sciences (Grant numbers 981547 and 16229).

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Table 1. Characteristics of patients in ICUs with healthcare-associated infections

Characteristics	Infected patients (n = 1722)[a]
Sex, n (%)	
Male	901 (52.3)
Female	821 (47.7)
Age, mean (SD)	57.30 (24.24)
Children, n (%)	
< 2 years	84 (4.8)
2–11 years	38 (2.2)
12–18 years	26 (1.5)
Adults, n (%)	
19–39 years	242 (14.0)
40–59 years	382 (22.1)
Elderly, n (%)	
> 60 years	950 (55.2)
Admission wards, n (%)	
Medical ICU	262 (15.2)
Surgical ICU	818 (47.5)
General ICU	642 (37.2)
Comorbidity, n (%)	
Cardiac diseases	304 (17.7)
Digestive system diseases	114 (6.6)
Respiratory diseases	217 (12.6)
Renal complications	29 (1.7)
Neurological disorders	33 (1.9)
Malignancies	79 (4.6)
Others	415 (24.0)
None	531 (30.8)
Time from admission to first infection, median (IQR)	5 (2–12) days
Length of stay, median (IQR)	20 (11–33) days
Mortality, n (%)	779 (45.2)

[a]Data are described as mean (SD) for continuous data and frequency for categorical data. The number of cases is presented with percentages. ICU = intensive care unit; IQR = interquartile range; SD = standard deviation.

Table 2. Types of infection and nosocomial pathogens responsible for healthcare-associated infections in ICUs

Microorganisms	VAE	UTI	BSI	SSI	SST	PNE	Other sites	Total
Gram-positive bacteria, n (%)								
Staphylococcus spp.								573 (58.4)
S. aureus	110 (44.7)	15 (6.1)	37 (15.0)	41(16.7)	13 (5.3)	8 (3.2)	22 (8.9)	246 (25.0)
Staphylococcus epidermidis	13 (13.0)	5 (5.0)	58 (58.0)	14(14.0)	1 (1.0)	0 (0)	9 (9.0)	100 (10.1)
Co-NS[a]	69 (30.4)	16 (7.0)	88 (38.8)	31(13.6)	2 (0.9)	6 (2.6)	15 (6.6)	227 (23.1)
Streptococcus spp.								65 (6.6)
Streptococcus pyogenes	7 (46.6)	1 (6.7)	2 (13.3)	0 (0.0)	1 (6.7)	3 (20.0)	1 (6.7)	15 (1.5)
Streptococcus agalactiae	2 (9.5)	1 (4.7)	8 (38.1)	0 (0)	0 (0)	10(47.6)	0 (0)	21 (2.1)
Group D *Streptococcus*	1 (1.0)	1(1.0)	2 (2.0)	2 (2.0)	0 (0)	4 (4.0)	0 (0)	10 (1.0)
Streptococcus pneumoniae	9 (75.0)	0 (0)	2 (16.7)	0 (0)	0 (0)	1 (8.3)	0 (0)	12 (1.2)
Streptococcus viridans	3 (42.8)	0 (0)	1 (14.3)	0 (0)	0 (0)	2 (28.6)	1 (14.3)	7 (0.7)
Enterococcus spp.	39 (12.1)	133(41.3)	76 (23.6)	24 (7.4)	14 (4.3)	13 (4.0)	23 (7.1)	322 (32.8)
Corynebacterium diphtheriae	11 (84.6)	0 (0)	1 (7.7)	0 (0)	0 (0)	0 (0)	1 (7.7)	13 (1.3)
Other species[b]	7 (87.5)	0 (0)	0 (0)	1 (12.5)	0 (0)	0 (0)	0 (0)	8 (0.8)
Gram-negative bacteria, n (%)								
Acinetobacter spp.	596 (58.4)	35 (3.4)	114(11.1)	59 (5.8)	102(10.0)	66 (6.5)	48 (4.7)	1020(39.3)
Klebsiella spp.	308 (49.7)	85 (13.7)	83 (13.4)	37 (6.0)	48 (7.7)	27 (4.4)	31 (5.0)	619 (23.9)
Escherichia coli	99 (27.0)	135(36.8)	40 (10.9)	48(13.0)	15 (4.1)	16 (4.3)	14 (3.8)	367 (14.1)
Pseudomonas spp.	189 (47.0)	88 (21.9)	33 (8.2)	27 (6.7)	35 (8.7)	14 (3.5)	16 (4.0)	402 (15.5)
Enterobacter spp.	27 (42.2)	9 (14.1)	13 (20.3)	7 (10.9)	4 (6.2)	2 (3.1)	2 (3.1)	64 (2.47)
Proteus spp.	13 (41.9)	3 (9.7)	1 (3.2)	5 (16.1)	9 (29.0)	0 (0)	0 (0)	31 (1.1)
Stenotrophomonas maltophilia	20 (48.8)	1 (2.4)	17 (41.5)	0 (0)	0 (0)	1 (2.4)	2 (4.9)	41 (1.5)
Chlamydia pneumoniae	10 (47.6)	3 (14.3)	1 (4.8)	2 (9.5)	0 (0)	2 (9.5)	3 (14.3)	21 (0.8)
Other species[c]	9 (34.6)	5 (19.2)	6 (23.1)	3 (11.5)	0 (0)	3 (11.5)	0 (0)	26 (0.9)
Fungi, n (%)								
Candida spp.	68 (13.5)	389 (77.2)	21 (4.2)	9 (1.8)	1 (0.1)	11 (2.2)	5 (1.0)	504 (98.8)
Aspergillus spp.	1 (100.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.2)
Total	1611 (39.5)	925 (22.7)	604 (14.8)	310 (7.6)	245 (6.0)	189 (4.6)	193 (4.8)	4077 (100)

[a]Includes Staphylococcus saprophyticus, Staphylococcus haemolyticus, Staphylococcus lugdunensis, and Staphylococcus simulans. [b]Inlcudes Micrococcus spp. and Bacillus cereus. [c]Includes Burkholderia spp., Citrobacter spp., Serratia spp., Morganella spp., and Salmonella typhi. BSI = bloodstream infection; Co-

NS = coagulase-negative staphylococci; PNE = pneumonia; SSI = surgical site infection; SST = skin and soft tissue infection; UTI = urinary tract infection; VAE = ventilator-associated event.

Table 3. Multivariable logistic regression analysis with hospital mortality as the dependent variable

Variable	Crude OR (95%CI)	P	Adjusted OR (95% CI)	P	Effect size
Age >60 years	2 (1.78–2.24)	<0.001	0.50 (0.44–0.57)	<0.001	0.99
Female sex	1.10 (0.98–123)	0.98	0.87 (0.77–0.99)	0.34	0.97
Comorbidity	0.60 (0.53–0.68)	<0.001	1.46 (1.28–1.65)	<0.001	0.99
Type of infection					
VAE	0.37 (0.23–0.59)	<0.001	0.75 (0.38–1.48)	0.40	0.56
BSI	0.38 (0.30–0.49)	<0.001	0.86 (0.56–1.31)	0.48	0.43
UTI	0.79 (0.65–0.96)	0.02	0.48 (0.29–0.82)	0.007	0.99
SSI	1.26 (0.96–1.66)	0.84	0.48 (0.32–0.72)	<0.001	0.079
SST	1.16 (0.99–1.36)	0.55	1.79 (1.17–2.73)	0.006	0.13
PNE	0.74 (0.52–1.069)	0.11	0.70 (0.45–1.092)	0.11	0.92
Microorganisms					
Staphylococcus aureus	0.59 (0.40–0.87)	0.009	0.62 (0.41–0.93)	0.02	0.98
Staphylococcus epidermidis	0.74 (0.45–1.20)	0.22	0.80 (0.47–1.35)	0.40	0.56
Co-NS[a]	0.68 (0.46–1.003)	0.05	0.74 (0.49–1.12)	0.16	0.89
Streptococcus spp.	0.76 (0.43–1.35)	0.36	0.92 (0.50–1.70)	0.81	0.43
Enterococcus spp.	1.13 (0.79–1.61)	0.48	1.19 (0.81–1.74)	0.36	0.63
Acinetobacter spp.	1.51 (1.122–2.051)	0.007	1.40 (1.01–1.93)	0.039	0.97
Klebsiella spp.	1.73 (1.26–2.38)	0.001	1.53 (1.09–2.15)	0.013	0.15
Escherichia coli	1.13 (0.80–1.60)	0.46	1.12 (0.77–1.63)	0.53	0.36
Pseudomonas spp.	1.86 (1.32–2.61)	<0.0001	1.93 (1.34–2.78)	<0.0001	0.99
Candida spp.	1.80 (1.30–2.50)	<0.0001	1.99 (1.37–2.89)	<0.0001	0.99

[a]*Includes Staphylococcus saprophyticus, Staphylococcus haemolyticus, Staphylococcus lugdunensis, and Staphylococcus simulans. BSI = bloodstream infection; Co-NS = coagulase-negative staphylococci; PNE = pneumonia; SSI = surgical site infection; SST = skin and soft tissue infection; UTI = urinary tract infection; VAE = ventilator-associated event.*

Table 4. Antimicrobial resistance profile in Gram-positive and Gram-negative bacterial isolates

Gram-positive bacteria	ERY	OXA	AMP	IPM	TET	GEN	DOX	CEF	CTX	FOX	CIP	CLI	SXT	MEM	VAN
Staphylococcus aureus															
Resistant, n (%)	126 (51.2)	16 (6.5)	17 (6.9)	18 (7.3)	11 (4.4)	19 (7.7)	15 (6.0)	11 (4.4)	17 (6.9)	102 (41.4)	109 (44.3)	130 (52.8)	36 (14.6)	13 (5.2)	6 (2.4)
Susceptible, n (%)	120 (48.2)	230 (93.5)	229 (93.1)	228 (92.7)	235 (95.6)	227 (92.3)	231 (94.0)	235 (95.6)	229 (93.1)	144 (58.6)	137 (55.7)	116 (47.2)	210 (85.4)	233 (94.8)	240 (97.6)
Staphylococcus epidermidis															
Resistant, n (%)	62 (62.0)	5 (5.0)	2 (2.0)	3 (3.0)	1 (1.0)	4 (4.0)	8 (8.0)	2 (2.0)	4 (4.0)	52 (52.0)	37 (37.0)	62 (62.0)	35 (35.0)	2 (2.0)	1 (1.0)
Susceptible, n (%)	38 (38.0)	95 (95.0)	98 (98.0)	97 (97.0)	99 (99.0)	96 (96.0)	92 (92.0)	98 (98.0)	96 (96.0)	48 (48.0)	63 (43.0)	38 (38.0)	65 (65.0)	98 (98.0)	99 (99.0)
Co-NS[a]															
Resistant, n (%)	121 (53.3)	18 (7.9)	22 (9.7)	26 (11.4)	18 (7.9)	30 (13.2)	17 (7.4)	15 (6.6)	23 (10.1)	96 (42.2)	114 (50.2)	129 (56.8)	64 (28.1)	21 (9.2)	4 (1.7)
Susceptible, n (%)	106 (46.7)	209 (92.1)	205 (90.3)	201 (88.6)	209 (92.1)	197 (86.8)	210 (92.6)	212 (93.4)	204 (89.9)	131 (57.8)	113 (49.8)	98 (43.2)	163 (71.9)	206 (90.8)	223 (98.3)
Streptococcus spp.															
Resistant, n (%)	24 (36.9)	2 (3.0)	4 (6.1)	1 (1.5)	13 (20.0)	13 (20.0)	2 (3.0)	3 (4.6)	3 (4.6)	6 (9.2)	10 (15.3)	20 (30.7)	10 (15.3)	3 (4.6)	5 (7.7)
Susceptible, n (%)	41 (43.1)	63 (97.0)	61 (93.9)	64 (98.5)	52 (80.0)	52 (80.0)	63 (97.0)	62 (95.4)	62 (95.4)	59 (90.8)	55 (84.7)	45 (69.3)	55 (84.7)	62 (95.4)	60 (92.3)
Enterococcus spp.															
Resistant, n (%)	24 (7.4)	1 (0.3)	152 (47.2)	2 (0.6)	90 (27.9)	48 (14.9)	7 (2.1)	4 (1.2)	9 (2.8)	5 (1.5)	203 (63.0)	24 (7.4)	13 (4.0)	3 (0.9)	203 (63.0)
Susceptible, n (%)	298 (92.6)	321 (99.7)	170 (52.8)	320 (99.4)	232 (72.1)	274 (85.1)	315 (97.9)	318 (98.8)	313 (97.2)	317 (98.5)	119 (37.0)	298 (92.6)	309 (96.0)	321 (99.1)	119 (37.0)
Overall resistance, %	37.1	4.3	20.5	7.2	13.8	11.8	5.1	4.1	5.8	27.1	49.2	38.0	16.4	4.3	22.8

Gram-negative bacteria	AMP	AMC	AMK	IPM	TZP	GEN	CAZ	CEF	CTX	CIP	SXT	LVX	MEM

Acinetobacter spp.													
Resistant, n (%)	20 (1.9)	7 (0.6)	662 (64.9)	462 (45.2)	76 (7.4)	686 (67.2)	814 (79.8)	164 (18.0)	692 (67.8)	764 (74.9)	555 (54.4)	30 (2.9)	352 (34.5)
Intermediate, n (%)	1 (0.1)	0 (0.0)	5 (0.5)	1 (0.1)	1 (0.1)	4 (0.4)	5 (0.5)	3 (0.3)	5 (0.5)	2 (0.2)	4 (0.3)	4 (0.3)	1 (0.1)
Susceptible, n (%)	999 (98.0)	1013 (99.4)	353 (34.6)	557 (54.3)	943 (92.5)	330 (32.8)	201 (19.7)	853 (81.7)	323 (31.7)	254 (24.9)	461 (45.3)	986 (96.8)	667 (65.4)
Klebsiella spp.													
Resistant, n (%)	22 (3.5)	4 (0.6)	240 (38.7)	219 (35.3)	24 (3.8)	312 (50.4)	434 (70.1)	113 (18.2)	348 (56.2)	384 (62.0)	305 (49.2)	11 (1.7)	131 (21.1)
Intermediate, n (%)	1 (0.1)	0 (0.0)	7 (1.1)	6 (0.9)	1 (0.1)	2 (0.3)	4 (0.6)	1 (0.1)	1 (0.1)	7 (1.1)	0 (0.0)	0 (0.0)	5 (0.8)
Susceptible, n (%)	596 (96.4)	615 (99.4)	372 (60.2)	394 (63.8)	594 (96.1)	305 (49.3)	181 (29.3)	505 (81.7)	270 (43.7)	228 (36.9)	314 (50.8)	608 (98.3)	483 (78.1)
Escherichia coli													
Resistant, n (%)	32 (8.7)	13 (3.5)	19 (5.1)	18 (4.9)	7 (1.9)	95 (25.8)	184 (50.1)	72 (19.6)	161 (43.8)	176 (47.9)	135 (36.7)	18 (4.9)	19 (5.1)
Intermediate, n (%)	1 (0.2)	2 (0.5)	17 (4.6)	4 (1.0)	7 (1.9)	6 (1.6)	4 (1.0)	4 (1.0)	3 (0.8)	3 (0.8)	0 (0.0)	0 (0.0)	1 (0.2)
Susceptible, n (%)	334 (91.1)	352 (96.0)	331 (90.3)	345 (94.1)	353 (96.2)	266 (72.6)	179 (48.9)	291 (79.4)	203 (55.4)	188 (51.3)	232 (63.3)	349 (95.1)	347 (94.7)
Pseudomonas spp.													
Resistant, n (%)	12 (2.9)	2 (0.4)	202 (50.2)	150 (37.3)	144 (35.8)	237 (58.9)	280 (69.6)	77 (19.1)	257 (63.9)	247 (61.4)	239 (59.4)	6 (1.4)	106 (26.3)
Intermediate, n (%)	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	2 (0.4)	4 (0.9)	0 (0.0)	0 (0.0)	4 (0.9)
Susceptible, n (%)	390 (97.1)	400 (99.6)	198 (49.4)	251 (62.5)	258 (64.2)	164 (40.9)	122 (30.4)	324 (80.7)	143 (35.7)	151 (37.7)	163 (40.6)	396 (98.6)	292 (72.8)
Overall resistance, %	3.5	1.0	46.6	35.2	10.4	55.2	71.0	17.6	60.5	65.2	51.2	2.6	25.2

[a]*Includes Staphylococcus saprophyticus, Staphylococcus haemolyticus, Staphylococcus lugdunensis, and Staphylococcus simulans. AMC = amoxicillin/clavulanic acid; AMK = amikacin; AMP = ampicillin; CAZ = ceftazidime; CEF = cefepime; CIP = ciprofloxacin; CLI = clindamycin; Co-NS = coagulase-negative staphylococci; CTX = cefotaxime; DOX = doxycycline; ERY = erythromycin; FOX = cefoxitin; GEN = gentamicin; IPM, imipenem; LVX = levofloxacin; MEM = meropenem; OXA = oxacillin; SXT, trimethoprim–sulfamethoxazole; TET, tetracycline; TZP, piperacillin/tazobactam; VAN, vancomycin.*

Figure 1. Monthly distribution of healthcare-associated infections in intensive care units (ICUs).