Epidemiological features, antimicrobial resistance profile and clinical outcomes of healthcare-associated infections in Islamic Republic of Iran

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Abstract

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

Aims: To investigate the incidence, microbial aetiology, antimicrobial resistance profile, and mortality rate of healthcare-associated infections in intensive care units in the Islamic Republic of Iran.

Methods: This observational study retrospectively reviewed the medical records of 1722 intensive care units patients with confirmed healthcare-associated infections at hospitals affiliated with Mashhad University of Medical Sciences in 2017–2019. Data was analysed using SPSS for Windows version 11. Categorical variables were described using frequency and percentage, whereas continuous variables were defined using mean (standard deviation) with 95% confidence interval (CI) for precision. Logistic regression analysis was used 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.

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 intensive care unit 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 intensive care unit 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, drug resistance, microorganism, antimicrobial resistance, mortality, Iran

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Introduction

Healthcare-associated infections can occur 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 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 in acute-care hospitals (*5*). The intensive care units (ICUs), in particular, are hotbeds for contracting infections (*5*). Even though they account for < 10% of all hospital beds, 20–50% of all healthcare-associated infections are contracted in ICUs (*6*). Immune compromise, 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 healthcare 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 on 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 targets 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 an ideal setting for the emergence and transmission of antibiotic-resistant bacteria (*10*). In this situation, clinicians may lack 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 aetiology, 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 diagnoses 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 or more of the following symptoms: fever, urgency, frequency, dysuria, suprapubic tenderness, or costovertebral angle pain/tenderness.

Data collection

We obtained details of hospitalized 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 among 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 (interquartile range, 2–12 days). Unfortunately, 45.2% of patients eventually died from infections acquired in the ICU (Table 1).

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.

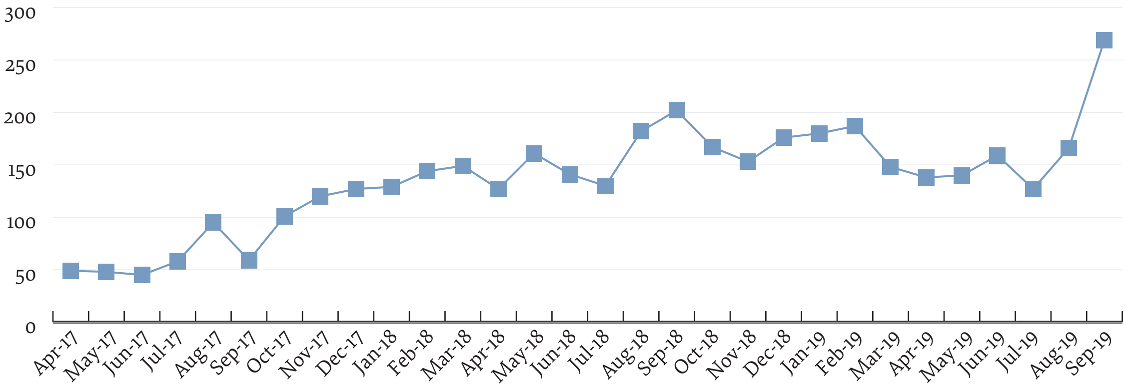
Device use, infection sites and nosocomial pathogens

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 among 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 among ICU patients (Table 2).

Independent predictors of 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 was associated with the following isolated pathogens: *Pseudomonas* spp. 59.9%, *Candida* spp. 59.5%,

Figure 1 Monthly distribution of healthcare-associated infections in intensive care units, Islamic Republic of Iran



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 highly resistant to ciprofloxacin (63.0%), vancomycin (63.0%), and ampicillin (47.2%). However, *Streptococcus* spp. was susceptible to most antibiotics, except for erythromycin and clindamycin, which recorded resistance of 36.9% and 30.7%, respectively.

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* 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 media for transmitting 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*). Another study found that only 56.6% of healthcare workers had good knowledge of hand hygiene (*24*). It is now evident that

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. bInlcudes Micrococcus spp. and Bacillus cereus. cIncludes 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.

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 causes of healthcare-associated infections as well as their microbial aetiology and patterns of antimicrobial resistance.

This 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 aetiology

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 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 was 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.

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.

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. was 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 among 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 aetiology 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 northeast 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 prevention and control programmes and enhancement of infection control using feasible and affordable tools and resources. Our findings could be used by policymakers 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.

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Caractéristiques épidémiologiques, profil de résistance aux antimicrobiens et résultats cliniques relatifs aux infections associées aux soins de santé en République islamique d'Iran

Résumé

Contexte : Les infections associées aux soins de santé représentent une cause majeure de mortalité dans le monde, en particulier dans les unités de soins intensifs où les patients gravement atteints disposent d'un espace physique limité.

Objectif : Étudier l'incidence, l'étiologie microbienne, le profil de résistance aux antimicrobiens et le taux de mortalité relatifs aux infections associées aux soins de santé dans les unités de soins intensifs en République islamique d'Iran.

Méthodes : La présente étude d'observation a rétrospectivement passé en revue les dossiers médicaux de 1722 patients hospitalisés en unités de soins intensifs présentant des infections associées aux soins de santé confirmées dans des hôpitaux affiliés à l'Université des sciences médicales de Mashhad entre 2017 et 2019. Les données ont été analysées à l'aide du logiciel SPSS pour Windows, version 11. Les variables catégorielles ont été décrites en recourant à la fréquence et au pourcentage, tandis que les variables continues ont été définies à l'aide de la moyenne (écart type) avec un intervalle de confiance (IC) à 95 % pour la précision. L'analyse de régression logistique a été utilisée pour estimer l'odds ratio brut (OR) et l'odds ratio ajusté (ORa) avec un IC à 95 %, et pour identifier les facteurs prédictifs univariés et multivariés de la mortalité liée aux infections associées aux soins de santé.

Résultats : Au total, 4077 agents pathogènes ont été isolés, ce qui correspond à un taux d'incidence des infections associées aux soins de santé de 22,1 %. Les organismes les plus fréquemment retrouvés étaient *Acinetobacter* spp. (25,0 %), *Klebsiella* spp. (15,1 %), *Staphylococcus* spp. (14,0 %) et *Candida* spp. (12,3 %). Les principaux types d'infections étaient des événements liés à la ventilation mécanique (39,5 %), des infections des voies urinaires (22,7 %) et des infections sanguines (14,8 %). Les comorbidités, les infections de la peau et des tissus mous et les infections dues à *Acinetobacter* spp., *Klebsiella* spp., *Pseudomonas* spp. et *Candida* spp. étaient significativement associées à une mortalité plus élevée chez les patients en unité de soins intensifs. Les bactéries à Gram positif étaient les plus résistantes à la ciprofloxacine (49,2 %), à la clindamycine (38,0 %) et à l'érythromycine (37,1 %). Les bactéries à Gram négatif étaient les plus résistantes à la ceftazidime (71,0 %), à la ciprofloxacine (65,2 %) et au céfotaxime (60,5 %). Le taux de mortalité global était de 45,2 %.

Conclusion : Les infections associées aux soins de santé chez près de la moitié des patients en unité de soins intensifs ont été mortelles, en particulier lorsqu'elles étaient causées par *Acinetobacter* spp., *Klebsiella* spp., *Pseudomonas* spp. ou *Candida* spp. Par conséquent, des stratégies efficaces pour lutter contre les bactéries résistantes aux antibiotiques doivent être mises en œuvre, ainsi qu'une observance plus stricte des programmes de lutte contre les infections.

السمات الوبائية ومرتسمات مقاومة مضادات الميكروبات والحصائل السريرية للعدوى المرتبطة بالرعاية الصحية في جمهورية إيران الإسلامية

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الخلاصة

الخلفية: العدوى المرتبطة بالرعاية الصحية أحد الأسباب الرئيسية للوفاة في جميع أنحاء العالم، لا سيَّما تلك المرتبطة بوحدات الرعاية المركزة؛ حيث يكون الحيز البدني للمرضى المصابين بأمراض وخيمة فيها محدودًا.

الأهداف: استقصاء معدلات الإصابة، والسَّبَبيَّات الميكروبية، ومرتسم مقاومة مضادات الميكروبات، ومعدل الوفيات الناجمة عن العدوى المرتبطة بالرعاية الصحية في وحدات الرعاية المركزة في جمهورية إيران الإسلامية.

طرق البحث: استعرضت هذه الدراسة الرصدية، بأثر رجعي، السجلات الطبية لما مجموعه 1722 مريضًا من مرضى وحدات العناية المركزة الذين أصيبوا بعدوى مؤكدة مرتبطة بالرعاية الصحية في المستشفيات التابعة لجامعة مشهد للعلوم الطبية في الفترة من 2017 إلى 2019. وحُللت البيانات باستخدام برنامج SPSS في الإصدار 11 من نظام ويندوز. ووُصفت المتغيرات الفئوية باستخدام التواتر والنسبة المئوية، في حين عُرفت المتغيرات المستمرة باستخدام متوسط (الانحراف المعياري) مع فاصل ثقة قدره 95٪ توخيًا للدقة. واستُخدم تحليل الانحدار اللوجستي لتقدير نسبة الأرجحية الأولية ونسبة الأرجحية المُصحَّحة مع فاصل ثقة قدره 95٪، ولتحديد منبئات أحادية المتغيرات ومتعددة المتغيرات للوفيات الناجمة عن العدوى المرتبطة بالرعاية الصحية.

النتائج: تم في المجمل عزل 4077 من المُمرضات، فبلغ معدل الإصابة بالعدوى المرتبطة بالرعاية الصحية 22.1٪. وتبين أن المكْروبات الدقيقة الأكثر شيوعًا هي الجرثومة الراكدة (25.0٪)، والكلبسيلة بأنواعها (15.1٪)، والمكوّرات العنقودية الذهبية بأنواعها (14.0٪)، والمبيضات بأنواعها (12.3٪). وأما الأنواع الرئيسية للعدوى فشملت الأحداث المرتبطة بالتهوية (39.5٪)، وعدوى المسالك البولية (22.7٪)، وعدوى مجرى الدم (14.8٪). وارتبطت حالات المراضة المصاحبة، وعدوى الجلد والأنسجة الرخوة، وعدوى الجرثومة الراكدة بأنواعها والكلبسيلة بأنواعها والزائفة بأنواعها والمبيضات بأنواعها ارتباطًا كبيرًا بارتفاع معدل الوفيات بين مرضى وحدات العناية المركزة. وكانت الجراثيم الإيجابية الغرام أكثر مقاومة للسيبروفلوكساسين (49.2٪) والكليندامايسين (38.0٪) والإريثرومايسين (37.1٪). وأما الجراثيم السلبية الغرام فكانت أكثر مقاومة للسيفتازيديم (71.0٪)، وسيبروفلوكساسين (65.2٪)، وسيفوتاكسيم (60.5٪). وبلغ المعدل الإجمالي للوفيات 45.2٪.

الاستنتاجات: لقد وُجد أن العدوى المرتبطة بالرعاية الصحية في ما يقرب من نصف المرضى في وحدة الرعاية المركزة قاتلة، لا سيما عندما تسببها الجرثومة الراكدة بأنواعها، أو الكلبسيلة بأنواعها، أو الزائفة بأنواعها، أو المبيضات بأنواعها. لذلك يجب تنفيذ استراتيجيات فعالة لمكافحة البكتيريا المقاومة للمضادات الحيوية، إلى جانب الالتزام الصارم ببرامج مكافحة العدوى.

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