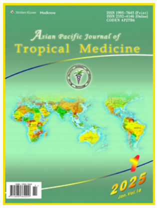

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Determinants of nosocomial infections and emerging antibiotic resistance in the Intensive Care Unit: A prospective evidence−based study

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ABSTRACT

Objective: To determine the incidence, risk factors, antibiotic resistance patterns, and outcomes of various nosocomial infections in Intensive Care Unit (ICU) patients.

Methods: The present prospective observational study was conducted in the multidisciplinary ICU of a tertiary care hospital for 6 months. Incidence, risk factors, and outcome parameters were calculated using Mann Whitney *U* test, *Chi*-square test, and stepwise univariate and multivariate logistic regression analysis.

Results: The overall incidence of nosocomial infections was 23.5% (74/314). Ventilator-associated pneumonia was the most common infection (54.1%, 52/96), followed by catheter-related bloodstream infections (22.9%, 22/96). Stress ulcer prophylaxis (a*OR* 7.691, 95% *CI* 2.202-26.860, *P*=0.001), endotracheal intubation (a*OR* 3.251, 95% *CI* 1.251-8.420, *P*=0.015), Foley's catheter (a*OR* 11.917, 95% *CI* 1.335-106.410, *P*=0.027), and ICU stay > 7 days (a*OR* 30.915, 95% *CI* 10.062-94.980, *P*=0.001) were statistically significant risk factors associated with nosocomial infection in ICU patients. Gram-negative bacteria showed a high degree of resistance to most of antibiotics except colistin and tigecycline. Infected group's mortality was significantly greater than the uninfected group (21.62% *vs.* 5.83% *P*<0.001) and had considerably longer ICU length of stay [21 (12) *vs.* 7 (4) days, *P*<0.001)] and duration of mechanical ventilation [20 (11) days *vs.* 0 (5) days, *P*<0.001].

Conclusions: This study highlights the high incidence rate of ventilator-associated pneumonia, with extensive drug resistance in ICU patients, highlighting the need for an optimized antimicrobial stewardship program to develop effective strategies for the management of nosocomial infections. Multifaceted interventions targeting modifiable risk factors are essential to reduce the occurences of these nosocomial infections in ICU patients.

KEYWORDS: Nosocomial infections; Extensively drug-resistant *Acinetobacter baumannii*; Mortality; Intensive Care Unit

Summary

Question: What are the incidence, risk factors, antibiotic resistance patterns, and outcomes of nosocomial infections in Intensive Care Unit patients?

Findings: The findings reveal a significant burden of nosocomial infections, with multidrug-resistant organisms being prevalent and invasive procedures emerging as major risk factors. Gram-negative bacteria exhibited high resistance to most antibiotics, except colistin and tigecycline. Patients with infections had worse outcomes, including higher mortality, longer ICU stays, and prolonged mechanical ventilation.

Meaning: By addressing a critical healthcare challenge, this study contributes to the understanding of nosocomial infections in resource-limited settings, providing valuable insights for policymakers and healthcare providers to improve patient outcomes and reduce hospital-acquired infections.

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1. Introduction

An infection that develops during a hospital stay without evidence indicating that it was present or incubating at the time of admission is known as a nosocomial or hospital-acquired infection (HAI)[1]. Intensive care units (ICUs) have become centers for nosocomial infections owing to their combination of severely ill patients, equipment, resistant bacteria, and overworked healthcare personnel[2]. Compared to patients in regular wards, critically ill individuals in intensive care units (ICUs) have a 5–10 times higher risk of developing nosocomial infections[3]. The terms catheter-related bloodstream infection (CRBSI), catheter-associated urinary tract infection (CAUTI), ventilator-associated pneumonia (VAP), and surgical site infection (SSI) are provided by the Centers for Disease Control and Prevention (CDC) to broadly classify the types of nosocomial infections[4].

Every year, HAIs affect approximately 100 million patients globally[5], and the annual burden of HAIs in developed countries suggests that 4 million patients are affected[6,7]. In India, a WHO study in 2021 estimated that the attributable mortality rate of HAIs in ICUs was 11%[8]. The overall incidence of ICU infections in India in 2021 was 27.9%, with VAP being the most common ICU-acquired infection, followed by CRBSI and CAUTI. The mortality rate of patients with nosocomial infections was 32.8%[9]. Recently, there has been an increase in the occurrence of antibiotic-resistant bacteria in ICUs linked to HAIs, resulting in a higher risk of infection in ICUs than in other wards and departments.

Antibiotics are the mainstay treatment for infections, and their improper use resulted in the emergence of highly resistant microorganisms and related infections, especially CRBSI and VAP, which are the main causes of significant morbidity and mortality in ICUs[9]. Thus, to limit infection, morbidity and mortality, and enhance quality of life, early detection of bacteria and proper antibiotic therapy is crucial[10].

It has been observed that there is scanty published data on nosocomial infections available from Indian ICUs. Understanding the regional burden of Nosocomial infection provides insights into local risk factors, pathogen profiles, and resistance patterns, which may differ from national or global trends. Studying patient-related factors (age, comorbidities) and healthcare-related factors (length of hospital stay, invasive procedures, ICU admission) is critical for targeted prevention. So, the study was conducted in the context of limited data regarding the epidemiology of nosocomial infections in Indian ICUs. Which can fill gaps and contribute to the evidence base for infection control programs in this region. The study aimed to determine the incidence, risk factors, antibiotic resistance patterns, and outcomes of nosocomial infections. The outcome was measured in terms of ICU length of stay (LOS), duration of mechanical ventilation, and associated mortality.

2. Subjects and methods

2.1. Study design

This study was prospective observational study conducted to assess incidence, risk factors, antibiotic resistance pattern and outcomes of nosocomial infections.

2.2. Study setting

The study was carried out in a 1 000 bedded tertiary care teaching hospital with 100 bedded capacities of interdisciplinary ICUs of the department of Critical Care Medicine for a period of 6 months from December 2023 to May 2024.

For data collection, sociodemographic and clinical profile sheets were prepared. Socio-demographic sheet include age, sex, length of ICU stay (days), source from where the patient was transferred to the ICU, reason for ICU admission, a detail history of each patient was taken regarding smoking, alcohol/drug abuse, pre antibiotic use, comorbidities like diabetes mellitus, hypertension, chronic kidney disease, ischemic heart disease, chronic liver disease, chronic obstructive pulmonary disease, malignancy, neurological dysfunction, and hypothyroidism. The following factors were recorded as present (during ICU stay) or absent in a particular patient before the development of ICU-acquired infection: stress ulcer prophylaxis, surgical procedure, endotracheal intubation, tracheostomy, mechanical ventilation, central venous catheter, arterial line, intracatheter, Foley's catheter, and nasogastric tube. The severity of the underlying disease was assessed using the Acute Physiology and Chronic Health Evaluation Score Ⅱ (APACHE Ⅱ) during the first 24 h of admission to the ICU. Organ/multiorgan dysfunction during the ICU stay was assessed using the sequential organ failure assessment (SOFA) score.

Clinical sheets included signs of local infection, vital parameters, laboratory investigations such as haematology, biochemistry, microbiology, hormonal assays (procalcitonin and serum C-reactive protein levels), Arterial Blood Gas analysis, and date of discharge/death. Additionally, daily monitoring and assessments were carried out. The CDC standard definition of nosocomial infections was used. VAP, CRBSI, CAUTI, and SSI patients were classified according to the diagnosis by an ID specialist. Mortality, length of stay in the ICU, and duration of mechanical ventilation were used to measure the patient's outcomes.

2.3. Participants

The study included patients who stayed more than 48 hours in the ICU. Patients with new infection occurring at different anatomical site during the ICU stay were included in the group of infections acquired in the ICU and the noninfected group consisted of patients who were infected at the time of admission. Patients with burns, pediatric patients, pregnant women, ICU stays shorter than 48 hours, age ≤18 or ≥90 years, and readmission patients were excluded. Patients with solid organ/bone marrow transplantation, known human immunodeficiency virus seropositivity were also excluded.

The participants were selected from the patients admitted to the adult ICU of a tertiary care hospital in Western India. Convenience sampling method was used for the selection of participants meeting the inclusion criteria. The participant selection flowchart is shown in Figure 1. The patients were followed up during their hospital stay. Daily bedside visits, regular review of medical records, nursing notes, and microbiology reports, tracking of vital signs, laboratory parameters, and clinical status were included in the follow up.

In this study, patients with nosocomial infections were matched to uninfected patients using the following criteria: 1) Age (±5 years); 2) Sex; 3) Presence of comorbidities (*e.g.*, diabetes, hypertension); 4) Length of hospital stay before infection (±2 days); Use of invasive devices (*e.g.*, central venous catheters, foleys catheters). A 1:3 matching ratio was applied, resulting in 74 exposed patients (with confirmed nosocomial infections) matched to 240 unexposed patients (hospitalized for the same duration without infections). These criteria ensure comparability and minimize confounding factors.

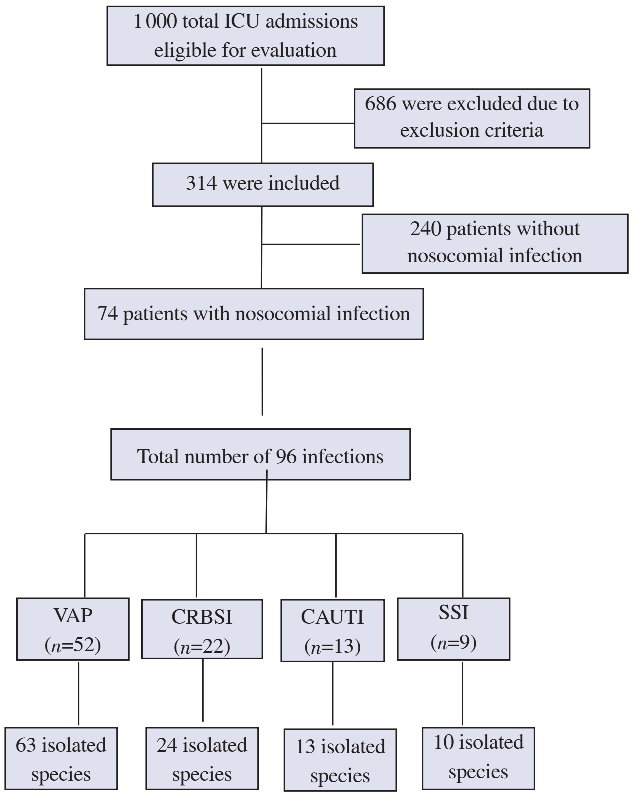

Figure 1. Patient identification and study flowchart. ICU: intensive care unit; VAP: ventilator-associated pneumonia; CRBSI: catheter-related bloodstream infection; CAUTI : catheter associated urinary tract infection; SSI: surgical site infection.

2.4. Variables and data sources

The outcomes assessed in this study include ICU length of stay, duration of mechanical ventilation, and mortality. ICU length of stay refers to the duration (in days) a patient spends in the ICU from admission to discharge, transfer, or death. The duration of mechanical ventilation is defined as the number of days a patient remains on mechanical ventilation, while mortality represents the death of a patient during hospitalization or within a specified period associated with a nosocomial infection.

Exposures contributing to the development of nosocomial infections were categorized into patient-related and hospital-related factors. Patient-related exposures include demographics (age and sex), comorbidities such as diabetes, hypertension, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), and malignancy, as well as severity of illness measured using APACHE Ⅱ and SOFA scores. Hospital-related exposures encompass the use of invasive devices (*e.g.*, central venous catheters, Foley catheters, and mechanical ventilation), surgical procedures, and hospitalization duration prior to infection.

Predictors of nosocomial infections include microbiological factors such as colonization with multidrug-resistant organisms, adherence to infection control protocols, and environmental factors like contaminated surfaces or improper sterilization. Potential confounders include baseline severity of illness, pre-existing colonization with resistant pathogens, prolonged hospitalization, and patterns of antibiotic use, all of which may bias the association between exposures and outcomes. Effect modifiers influencing the relationship between exposures and outcomes include patient age, as elderly individuals may have a higher risk and worse outcomes, and pathogen type, with infections caused by multidrug-resistant organisms being associated with poorer prognoses.

Data sources and measurement methods were carefully outlined. ICU length of stay is obtained from hospital admission and discharge records and calculated as the number of days from admission to discharge or transfer. Duration of mechanical ventilation was recorded from patient files as the total days of mechanical support. Mortality data was extracted from hospital discharge records, including the date and cause of death. Information on invasive devices, such as central venous catheters, Foley catheters, and mechanical ventilators, were derived from nursing documentation, with device usage measured in "device days."

Patient demographics, including age, sex, and comorbidities, were sourced from medical records, while severity of illness was assessed using APACHE Ⅱ scores calculated within the first 24 hours of ICU admission and SOFA scores recorded subsequently. Data on pre-antibiotic use was obtained from prescribing physicians' notes, documenting the patient’s antibiotic history. Consistent protocols for device management are implemented across wards to ensure comparability and reduce variability in practices.

2.5. Bias

The efforts were made to reduce potential bias by applying strict inclusion and exclusion criteria to ensure that patients with similar risk profiles were included in the analysis, using propensity score matching to control for potential confounders such as age, comorbidities, and the severity of illness, which could impact the likelihood of infection, conducting sensitivity analyses to compare results with those obtained from other hospital cohorts, which showed similar infection rates, suggesting that the findings may still have broader relevance.

2.6. Study size

A single population proportion formula was used to estimate sample size which was given below:

$$\text{Sample size } (n)= Z(1-\alpha/2)^2 p(1-p)/d^2=314 \text{ patients}$$

where Z is the standard normal value at 95% *CI*, p is the expected proportion, and d is desired degree of precision[11].

2.7. Statistical analysis

Means and standard deviations were used to denote continuous variables, whereas categorical variables were expressed as numbers and percentages. Missing data was analyzed using Complete Case Analysis which excludes cases with missing data from analysis. Patients' loss to follow up was addressed using survival analysis curve.

Comparison analysis of continuous variables in normal distribution was performed using independent Student's *t*-test,while the Mann-Whitney *U* test was employed to compare variables that were not normally distributed. The *Chi*-square test was used for comparisons of categorical variables. The risk factors for nosocomial infections were assessed using logistic regression models, and factors with significance in the univariate analysis were included in the multivariate regression model. The predictive performance of the final logistic regression model was assessed using the receiver operating characteristic (ROC) curve analyzing sensitivity and specificity. $P<0.05$ is considered as statistically significant. Statistical Package for the Social Sciences (SPSS) software version 27 was used for statistical analysis.

2.8. Ethical considerations

The study was approved by Bharati Vidyapeeth Medical College Institutional Ethics Committee (DHR Reg. No: EC/NEW/INST/2022/MH/0150), Pune (BVDUMC/IEC/176-29.03.2024). Patient informed consent was obtained and in case of unconscious or ventilated patients the intensivist signed the consent and the procedures adhered to the ethical guidelines of Declaration of Helsinki.

3. Results

During the study period 1 000 patients were admitted to the hospital and were screened for the potential eligibility based on study criteria. Following the screening, 314 patients met the inclusion criteria and were enrolled in the study. 686 Patients were excluded because of discharged within 24 hours and admitted for conditions outside the study scope.

Of the 314 enrolled patients, all completed the required follow up, and their data were analysed. Among the analysed cohort, 74 patients developed 96 nosocomial infections, representing the study's focus population.

3.1. Patients' demographic and clinical characteristics

Table 1 shows the patients' demographic and clinical characteristics. Out of 314 patients, the unadjusted estimate of developing 96 ICU-acquired nosocomial infections was 23.5% (74/314), with an infection rate of 30.5% (96/314). The remaining 240 patients (240/314, 76.4%) had not developed an infection. The age distribution was comparable between the groups, with a mean age of (53.8±16.2) years in the infected group and (54.7±16.5) years in the non-infected group; Infected group had slightly higher proportion of male (68.9% *vs.* 68.3%); Comorbid conditions such as neurological dysfunction (4.1% *vs.* 3.8%) and chronic liver disease (4.1% *vs.* 1.7%) were more prevalent in the infected group. Socially, a higher percentage of infected participants reported smoking (8.1% *vs.* 6.3%) and regular alcohol use (12.2% *vs.* 11.3%). But these differences were not significant.

Stress ulcer prophylaxis, endotracheal intubation, tracheostomy, mechanical ventilation, central venous catheter, intracatheter, Foley's catheter, nasogastric tube, and ICU stay>7 days were found to be statistically significantbetween the two groups.

Among the 314 participants, missing data were minimal across most variables. Demographic data were nearly complete and clinical characteristics had small gaps. Exposures and potential confounders, such as pre antibiotic use and invasive device usage, had similarly low levels of missing data, thus the overall proportion of missing data was low and unlikely to affect the robustness of the analysis.

3.2. Incidence of nosocomial infections

VAP was the most common accounting for 54.1% (52/96) of all infections. CRBSI was followed by VAP accounting for 22.9% (22/96). CAUTI accounted for 13.5% (13/96) and SSI constituted 8.3% (9/96) of all nosocomial infections. The incidence density of VAP was 32.25/1 000 ventilator days, CRBSI was 19.45/1 000 central venous catheter days, while that of CAUTI and SSI was 8.15/100 catheter days and 1.66/100 surgical days, respectively.

The most common isolate found to be associated with VAP was *Acinetobacter* (*A.*) *baumannii* (43.0%) followed by *Klebsiella (K.) pneumoniae* (17.0%), while for CRBSI the isolates were *Escherich* (*E.*) *coli* (21.0%) and *K. pneumoniae* (13.0%). Catheter-associated urinary tract infections were most commonly caused by *E. coli* (31.0%) *and K. pneumoniae* (31.0%), while for surgical site infections, the most common isolates were *E. coli* (40.0%) and *A. baumannii* (20.0%).

Table 1. Patient characteristics [*n* (%)].

Variables	Infected (*n*=74)	Uninfected (*n*=240)	*P*
Age*, years	53.8±16.2	54.7±16.5	0.678
Sex			
Male	51 (68.9)	164 (68.3)	0.924
Female	23 (31.1)	76 (31.7)	
Sources of admission			
Emergency room	28 (37.8)	102 (42.5)	0.547
Operation theatre	3 (4.1)	11 (4.6)	0.297
Ward	8 (10.8)	39 (16.3)	0.612
Outside hospital	14 (18.9)	34 (14.2)	0.169
Direct	21 (28.4)	54 (22.5)	0.889
Reasons for ICU admission			
Respiratory disease	10 (13.5)	56 (23.3)	0.124
Gastrointestinal disease	11 (14.9)	48 (20.0)	0.115
Neurological disease	20 (27.0)	41 (17.1)	0.258
Cardiovascular disease	1 (1.4)	8 (3.3)	0.769
Renal disease	4 (5.4)	24 (10.0)	0.287
Trauma	19 (25.7)	39 (16.3)	0.176
Surgery	1 (1.4)	5 (2.1)	0.773
Others	8 (10.8)	19 (7.9)	0.526
Comorbidities			
Diabetes mellitus	19 (25.7)	78 (32.5)	0.268
Hypertension	25 (33.8)	102 (42.5)	0.183
Chronic kidney disease	3 (4.1)	19 (7.9)	0.264
Ischaemic heart disease	2 (2.7)	21 (8.8)	0.100
Chronic liver disease	3 (4.1)	4 (1.7)	0.239
COPD	2 (2.7)	12 (5.0)	0.410
Malignancy	2 (2.7)	12 (5.0)	0.410
Neurological dysfunction	3 (4.1)	9 (3.8)	0.905
Hypothyroidism	1 (1.4)	8 (3.3)	0.338
Smoking$	6 (8.1)	15 (6.3)	0.577
Alcohol abuse	9 (12.2)	27 (11.3)	0.830
Stress ulcer prophylaxis	70 (94.6)	183 (76.3)	0.002
Prior antibiotic use	5 (6.8)	29 (12.1)	0.204
Surgical procedure	26 (35.1)	60 (25.0)	0.089
Endotracheal intubation	60 (81.1)	86 (35.8)	<0.001
Tracheostomy	11 (14.9)	5 (2.1)	0.001
Mechanical ventilation	58 (78.4)	91 (37.9)	<0.001
Central venous catheter	46 (62.2)	89 (37.1)	<0.001
Arterial line	13(17.6)	56 (23.3)	0.297
Intracatheter	38 (51.4)	163 (67.9)	0.010
Foley's catheter	73 (98.6)	191 (79.6)	0.004
Nasogastric tube	55 (74.3)	98 (40.8)	<0.001
APACHE Ⅱ score#	23 (7)	20 (7)	0.066
SOFA score#	6 (2)	5 (2)	0.237
ICU stay > 7 days	70 (94.6)	94 (39.2)	<0.001

*Data was expressed as Mean±SD, Student's *t* test was used; $Smoking is defined as having smoked more than 100 cigarettes in a lifetime; #Data was expressed as Median (IQR) and Mann Whitney *U* test was used. COPD: Chronic obstructive pulmonary disease; APACHE Ⅱ: Acute physiology and chronic health evaluation Ⅱ; SOFA: sequential organ failure assessment.

3.3. Risk factors associated with infection

Univariate and multivariate logistic regression analysis of the risk factors for nosocomial infections in ICU patients is shown in Table 2. Univariate analysis showed that the risk factors associated with nosocomial infections were stress ulcer prophylaxis, endotracheal intubation, tracheostomy, mechanical ventilation, central venous catheter, intracatheter, Foley's catheter, nasogastric tube, and ICU stay >7 days. Of these, stress ulcer prophylaxis (a*OR* 7.691, 95% *CI* 2.202-26.86, *P*=0.001), endotracheal intubation (a*OR* 3.251, 95% *CI* 1.25-08.420, *P*=0.015), Foley's catheter (a*OR* 11.91, 95% *CI* 1.335-106.4, *P*=0.027), and ICU stay>7 days (a*OR* 30.91, 95% *CI* 10.06-94.98, *P*=0.001) were found to be statistically significant risk factors for nosocomial infection, thus could be independent risk factors for the development of nosocomial infections according to the multivariate logistic regression analysis results.

Sensitivity analysis was performed to assess the robustness of the study results examining the effects of different assumptions. The independent discrimination of the risk factors for nosocomial infections is depicted in Figure 2. The area under the curve (AUC) for ICU stay >7 days was 0.777 (95% *CI* 0.724-0.830), higher than the AUC for all comparable risk factors like stress ulcer prophylaxis (AUC=0.592, 95% *CI* 0.523-0.690), Foley's catheter (AUC=0.595, 95% *CI* 0.528-0.663), and endotracheal intubation (AUC=0.726, 95% *CI* 0.663-0.790, *P*<0.01). This indicates that an ICU stay >7 days was the most predictable risk factor, with a higher AUC responsible for developing nosocomial infection, followed by endotracheal intubation, Foley's catheter, and stress ulcer prophylaxis.

3.4. Antibiotic resistance patterns

A total of 88 Gram-negative isolates were found to be associated with nosocomial infections, based on the results depicted in Supplementary Table 1. Among these, 54 isolates were responsible for VAP, 16 isolates were associated with CRBSI, 11 isolates were associated with CAUTI, and 7 isolates were associated with SSI. *A. baumannii* shows (100.0%) resistance towards 3rd and 4th generation cephalosporins, piperacillin/tazobactam, aminoglycosides, carbapenems like imipenem and meropenem, fluoroquinolones and (50.0%) towards cotrimoxazole. Colistin was the most effective against extensively drug-resistant (XDR) *A. baumannii*. *K. pneumoniae* was also found to be resistant to 3rd and 4th generation cephalosporins (60.0%-80.0%), fluoroquinolones (54.5%), aminoglycosides (45.0%-60.0%) and carbapenems like ertapenem, imipenem (100.0%) and meropenem (85.7%). However, it showed sensitivity to colistin and tigecycline. *E. coli* isolates were found to extensively resistant to beta lactam-beta lactamase inhibitor particularly ampicillin/sulbactam (100.0%), amoxicillin/clavulanic acid and piperacillin/tazobactam (33.3%), 3rd and 4th generation

Table 2. Results of univariate and multivariate logistic regression analysis of putative risk factors for nosocomial infections in the intensive care unit (ICU).

Variables	*OR*	95% *CI*	*P*	a*OR*	95% *CI*	*P*
Age, years	0.997	0.997-0.981	0.678	-	-	-
Sex						
Male	1					
Female	1.028	0.586-1.803	0.924	-	-	-
Sources of admission						
Emergency room	1					
Operation theatre	0.706	0.367-1.359	0.297	-	-	-
Ward	0.701	0.178-2.767	0.612	-	-	-
Outside hospital	0.527	0.212-1.314	0.169	-	-	-
Direct	1.059	0.475-2.359	0.889	-	-	-
Reasons for ICU admission						
Respiratory disease	1					
Gastrointestinal disease	0.424	0.146-1.231	0.115	-	-	-
Neurological disease	0.544	0.190-1.562	0.258	-	-	-
Cardiovascular disease	1.159	0.433-3.099	0.769	-	-	-
Renal disease	0.297	0.032-2.780	0.287	-	-	-
Trauma	0.396	0.103-1.516	0.176	-	-	-
Surgery	1.157	0.429-3.119	0.773	-	-	-
Others	0.475	0.048-4.740	0.526	-	-	-
Comorbidities						
Diabetes mellitus (Yes *vs.* No)	1.394	0.775-2.508	0.268	-	-	-
Hypertension (Yes *vs.* No)	1.449	0.840-2.500	0.183	-	-	-
Chronic kidney disease (Yes *vs.* No)	2.035	0.585-7.078	0.264	-	-	-
Ischaemic heart disease (Yes *vs.* No)	0.401	0.088-1.835	0.239	-	-	-
Chronic liver disease (Yes *vs.* No)	3.453	0.790-15.084	0.100	-	-	-
COPD (Yes *vs.* No)	1.895	0.414-8.665	0.410	-	-	-
Malignancy (Yes *vs.* No)	1.895	0.414-8.665	0.410	-	-	-
Neurological dysfunction (Yes *vs.* No)	0.922	0.243-3.498	0.905	-	-	-
Hypothyroidism (Yes *vs.* No)	2.517	0.310-20.462	0.388	-	-	-
Smoking (Yes *vs.* No)	0.756	0.282-2.023	0.577	-	-	-
Alcohol abuse (Yes *vs.* No)	0.915	0.410-2.045	0.830	-	-	-
Stress ulcer prophylaxis (Yes *vs.* No)	5.451	1.906-15.585	0.002	7.691	2.20-26.86	0.001
Prior antibiotic use (Yes *vs.* No)	1.897	0.707-5.090	0.204	-	-	-
Surgical procedure (Yes *vs.* No)	0.615	0.352-1.077	0.089	-	-	-
Endotracheal intubation (Yes *vs.* No)	7.674	4.051-14.536	<0.001	3.251	1.26-8.42	0.015
Tracheostomy (Yes *vs.* No)	8.206	2.751-24.480	0.001	3.242	0.85-12.35	0.085
Mechanical ventilation (Yes *vs.* No)	5.935	3.219-10.943	<0.001	1.772	0.68-4.61	0.240
Central venous catheter (Yes *vs.* No)	2.787	1.627-4.773	<0.001	0.808	0.32-2.06	0.656
Arterial line (Yes *vs.* No)	1.428	0.731-2.789	0.297	-	-	-
Intracatheter (Yes *vs.* No)	2.005	1.180-3.408	0.010	1.019	0.42-2.50	0.967
Foley's catheter (Yes *vs.* No)	18.727	2.5391-138.12	0.004	11.917	1.34-106.41	0.027
Nasogastric tube (Yes *vs.* No)	4.194	2.344-7.504	<0.001	1.661	0.74-3.73	0.219
APACHE Ⅱ score	1.047	0.997-1.099	0.066	-	-	-
SOFA score	1.071	0.956-1.201	0.237	-	-	-
ICU stay > 7 days (Yes *vs.* No)	27.181	9.603-76.932	<0.001	30.915	10.06-94.98	<0.001

COPD: chronic obstructive pulmonary disease; APACHE Ⅱ: Acute Physiology and Chronic Health Evaluation Score Ⅱ. -: data were not analyzed.

cephalosporins (100.0%), carbapenems (100.0%), aminoglycosides like gentamicin (33.3%), fluoroquinolones like ciprofloxacin (100.0%) and cotrimoxazole (100.0%) while it shows sensitivity against amikacin and tigecycline so it could be the drug of choice. 88.0% of *Pseudomonas (P.) aeruginosa* isolates were found to be least resistant to piperacillin/tazobactam (25.0%), cefoperazone/sulbactam (25.0%), and ceftazidime (25.0%); 33.0% of the isolates did not show resistance to any of the tested antibiotics, and 11.0% of the isolates were found to be carbapenem-resistant, with 100.0% resistance to imipenem and meropenem. Providencia rettegeri also showed 100.0% resistant to almost all the tested antibiotics except trimethoprim/sulfamethoxazole while *Serratia marcescens* shows 100.0% resistance to only benzylpenicillin and cefuroxime. Burkholderia cepacia and *Pseudomonas putida* showed no resistance to any of the tested antibiotics. However, 3.7% of *Stenotrophomonas maltophilia* showed the least resistance (50.0%) to ceftazidime and meropenem.

A total of 22 Gram-positive isolates were found to be associated with nosocomial infections based on the results shown in (Supplementary Table 2). Among these, 9 were associated with VAP, 8 with CRBSI, 2 with CAUTI and 3 were responsible for SSI. *S. aureus* and *Enterococcus* species were most frequently isolated pathogens among Gram positive isolates. Of the *S. aureus* isolates, 46.0% were methicillin-resistant and only showed sensitivity to vancomycin and teicoplanin. 16.0% Isolates of *Enterococcus* isolates were vancomycin-resistant enterococci, which showed sensitivity to linezolid. The *Micrococcus* species also showed 100.0% resistance to vancomycin and teicoplanin.

The association between microbiological isolates and outcomes is shown in Table 3. Among Gram positive and Gram-negative isolate, none of them was found to be associated with mortality in patients with nosocomial infections.

3.5. Patient outcomes

The outcomes of nosocomial infections in the infected and uninfected groups are shown in Table 4. The infected group had a significantly higher mortality (16/74) (21.62%) compared to the uninfected group (14/240) (5.83%; $P<0.01$) with significantly longer duration of mechanical ventilation [20 (11) *vs.* 0 (5)] days and ICU length of stay [21 (12) *vs.* 7 (4)] days ($P<0.01$). Figure 3 compares the survival curves of patients in the ICU with and without infection. It demonstrates that the cumulative percentage of patients who survive without an infection is greater than that of patients who have an infection.

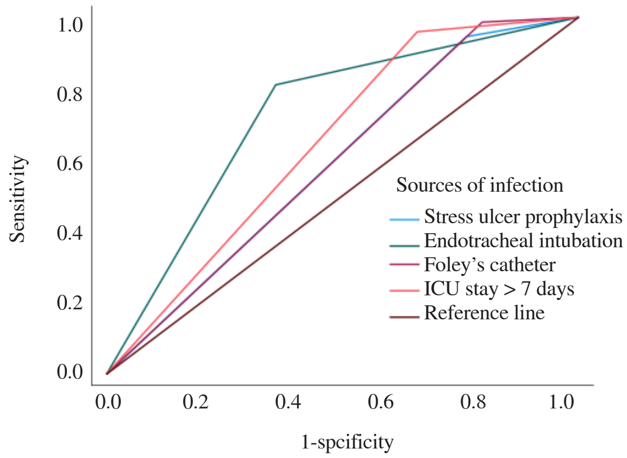

Figure 2. Independent receiver operating curve (ROC) corresponding to risk factors for the prediction of nosocomial infections in ICU patients.

Table 3. Association of microbiologic isolates and outcomes [*n* (%)].

Organisms	Mortality (*n*=16)	Survived (*n*=58)	*P*	*OR*
Gram-negative isolates				
Acinetobacter baumannii	9 (28.1)	23 (71.8)	0.189	2.105 (0.638-6.943)
Klebsiella pneumonia	5 (26.3)	14 (73.6)	0.564	1.201 (0.334-4.315)
Pseudomonas aeruginosa	2 (25.0)	6 (75.0)	0.806	1.309 (0.223-7.677)
Burkholderia cepacia	0 (0.0)	2 (100.0)	0.451	-
Acinetobacter lwoffii	0 (0.0)	1 (100.0)	0.597	-
Pseudomonas aeruginosa (Carba-resistant)	0 (0.0)	1 (100.0)	0.594	-
Serratia marcescens	1 (20.0)	4 (80.0)	0.927	0.880 (0.079-9.783)
Escherich coli	3 (18.7)	13 (81.2)	0.753	0.998 (0.218-4.521)
Stenotrophomonas maltophilia	0 (0.0)	2 (100.0)	0.451	-
Pseudomonas putida	0 (0.0)	1 (100.0)	0.597	-
Providencia rettgeri	0 (0.0)	1 (100.0)	0.597	-
Gram-positive isolates				
Staphylococcus aureus	0 (0.0)	4 (100.0)	0.280	-
Staphylococcus aureus (MRSA)	0 (0.0)	5 (100.0)	0.224	-
Staphylococcus aureus (MSSA)	1 (50.0)	1 (50.0)	0.323	3.231 (0.189-55.339)
Staphylococcus epidermidis	0 (0.0)	2 (100.0)	0.451	-
Enterococcus faecalis	0 (0.0)	1 (100.0)	0.597	-
Enterococcus faecium	2 (50.0)	2 (50.0)	0.156	1.615 (0.135-19.285)
Micrococcus spp.	0 (0.0)	1 (100.0)	0.597	-
Enterococcus gallinarium	1 (100.0)	0 (0.0)	0.055	-

-: data not analyzed.

Table 4. Outcomes of nosocomial infections.

Outcome	Infected (*n*=74)	Uninfected (*n*=240)	*P*
Mortality*	16 (21.62)	14 (5.83)	<0.001[1]
Duration of mechanical ventilation (days)**	20 (11)	0 (5)	<0.001[2]
Length of ICU stay (days)**	21 (12)	7 (4)	<0.001[2]

*Data expressed as number (percentage), **Data expressed as Median (IQR), [1]*Chi*-square test, [2]Mann whitney *U* test, ICU: Intensive Care Unit.

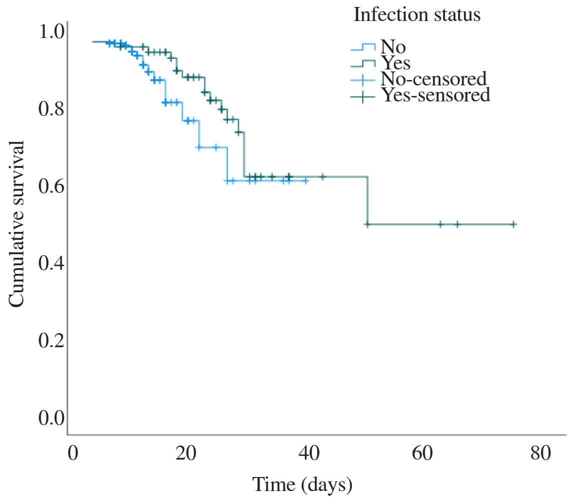

Figure 3. Survival curves for the intensive care unit (ICU) patients with infection status.

4. Discussion

The prospective design and systematic identification of various nosocomial infections in the ICU significantly increased the strength of this study. The incidence of infection in the present study (23.5%, 74/314) was higher than that reported by Kumar *et al.*, wherein (27.9%) of the patients developed infection[9]. This is because the incidence varies according to the setting, that is, the type of hospital or ICU, the patient population, and the precise definition and surveillance techniques used to identify an infection[12].

VAP was the most common nosocomial infection in our study, with a higher incidence compared to the study by Gunalan *et al.*[13]. Our VAP rate of 32.25/1 000 ventilator days was higher than those reported in previous studies[9,14]. The reason for the increased VAP incidence appears to be the larger patient loads, longer ventilation duration, underlying patient condition, and potential gaps in preventive practices[15]. *A. baumannii* and *K. pneumonia* were found to be the most common bacterial isolates associated with VAP which is similar to the observations reported by Chenchula *et al.* and Gunasekaran *et al.*[16,17]. The reason for the higher rate of *A. baumannii* is the strong propensity to form biofilms[18].

CRBSI was the second most common infection (22.9%) after VAP. This finding is in accordance with a study by Maqbool *et al.*, wherein the incidence of CRBSI was 19.8%[19]. The incidence rate of CRBSI reported in the present study (19.7/1 000 central venous catheter days) was higher than that reported by Singh *et al.* 7.2/1 000 central venous catheter days[20]. The significantly higher incidence of CRBSI in our study may be the result of improper use of invasive devices, differences in infection control preventive tactics, acquisition of multidrug-resistant isolates through invasive procedures, and excessive or inappropriate use of antibiotics. *E. coli* and *K. pneumonia* were the most common isolates accounting for 33.3% of CRBSI whereas some studies reported *A. baumannii* and *S. aureus* to be the most prevailing isolates[19,20]. The reason for the higher rate of *E. coli* might be that extraintestinal pathogenic *E. coli* colonizes the most common extra-intestinal site, that is, the urinary tract, which in turn is the common source of bloodstream infection[21].

CAUTI was the third most common nosocomial infection in our study (13.5%), in agreement with studies conducted by Kumar *et al.* and Parihar *et al.*[9,22]. The incidence rate of CAUTI reported in the present study (8.15/1 000 catheter days) was lower than that reported by Kripalani *et al.* and Parihar *et al.*[14,22]. The lower incidence of CAUTI may be the result of implementation of evidence-based practices, hand hygiene, continuous monitoring of adherence to CAUTI prevention bundles and staff education[23]. *E. coli* and *K. pneumonia* were found to be most commonly associated with the CAUTI accounting for 61.5% which is similar to the observations reported by Suryawanshi *et al.*[24].

SSI in the present study accounted for 8.3%, which is lower than that reported by Gupta *et al.*[25]. However, we found a much lower incidence in our ICU than in the study by Nair *et al.*, with an incidence of 23.9%[26]. The incidence rate of SSI reported in the present study was 1.66/100 surgical days, in contrast to the study by Gupta *et al.* wherein the incidence rate was found to be 10.3/100 surgery days[25]. The lower incidence in our setting may be due to the application of evidence-based preventive strategies, multidisciplinary quality improvement, surveillance, and risk factor mitigation. *E. coli* and *A. baumannii* were found to be most commonly associated with the SSI accounting for 60.0% which is in contrast to the study by Gupta *et al.* wherein the methicillin susceptible *S. aureus* (MSSA) and *K. pneumonia* were associated[25].

Stress ulcer prophylaxis, endotracheal intubation, Foley's catheter use, and ICU stay >7 days were significantly associated with nosocomial infections. As proton pump inhibitors and H2 blockers are used for stress ulcer prophylaxis, they inhibit gastric acid secretion, which subsequently increases gastric colonization and retrograde colonization, resulting in the development of VAP. This is supported by the observations of Kumar *et al.*[9]. The use of invasive devices, such as endotracheal intubation, almost always leads to an increased risk of infection, as demonstrated by Rosenthal *et al.*[27]. Inhibition of the natural cough reflex ET tube allows bacteria to enter the lower respiratory tract through micro aspiration along the endotracheal cuff, leading to the development of infection[28]. Foley's catheterization results in the biofilm formation between the catheter and the urethral mucus, uroepithelium disturbance and irritation contributing to the bacterial invasion and growth leading to infection development[29,30]. This has been supported by the observation of Nair *et al.* that the use of Foley's catheter increases the odds of CAUTI[26]. An ICU stay >7 days as an imperative risk factor for nosocomial infection has also been demonstrated by various authors[9,31]. This may be due to the length of ICU stay, which increases the time period for which devices are left in place, raising the risk of colonization by possible microbes and subsequent infection. However, as in previous research, it was unclear whether the condition developed as a result of the prolonged stay or whether the prolonged stay itself caused the infection[32,33].

A very high degree of antibiotic resistance was observed in the present study, particularly in Gram-negative isolates that demonstrated multidrug resistance (MDR) and extensive drug resistance (XDR). Extensively drug resistance isolates are *A. baumannii, K. pneumoniae, E. coli* and *P. aeruginosa* (Carba-resistant) which are resistant to more drugs than MDR isolates.

A similar resistance pattern of extensively drug-resistant *A. baumannii* has also been shown in various studies[34,35]. Colistin was found to be the most effective against XDR *A. baumannii* compared to other antimicrobials; hence, it may be a promising agent for treating XDR *A. baumannii* infections. The development of carbapenem enzymes, specifically OXA-48-like and NDM-1/5 enzymes, which are found in up to 73.2% and 24.4% of CRKP isolates, respectively, is the main factor driving resistance to carbapenem antibiotics[36]. The extensive use of carbapenems as the first empirical choice of drug in our ICU setting may be the reason for carbapenem resistance. All the *E. coli* isolates were found to be extensively resistant to beta-lactam-beta lactamase inhibitors, 3rd and 4th generation cephalosporins (100.0%), carbapenems (100.0%), aminoglycosides such as gentamicin (33.3%), fluoroquinolones, and cotrimoxazole (100.0%), while showing sensitivity against amikacin and tigecycline; therefore, it could be the drug of choice for treatment of XDR *E. coli* infection. In a similar study by Chakraborty *et al.*, a similar resistance pattern was observed in *E. coli*, except that it did not show resistance to 3rd and 4th generation cephalosporins[37]. This may be due to the unrestricted use of 3rd and 4th generation cephalosporins in our setting, which led to the development of resistance.

Among the Gram-positive isolates, *S. aureus* and *Enterococcus* species were the most frequently isolated pathogens. The rising prevalence of MDR is concerning because no beta-lactam antibiotics would be effective in this case, and increased vancomycin use increases the risk of developing vancomycin resistance. Approximately 16% of *Enterococcus* was vancomycin-resistant enterococci; however, they were sensitive to linezolid. Therefore, linezolid could be a last-resort antibiotic for the treatment of vancomycin-resistant enterococci infections. These findings are in accordance with those reported by Kumar *et al.*[34]. The increase in vancomycin resistance might be due to the overuse and misuse of vancomycin, which led to the emergence and spread of resistant strains in India.

After demonstrating association of microbiologic isolates with the mortality, the greater mortality was observed in patients with *A. baumannii, K. pneumonia and P. aeruginosa* among the Gram-negative isolates and *S. aureus* and *E. faecium* among Gram-positive isolates which was in accordance to the study reported by Ghanshani *et al.*[38]. The association of these isolates with mortality is due to the combination of antibiotic resistance (MDR and XDR), virulence patterns, and patient predisposing risk factors[39].

Nosocomial infections have been reported to be significantly associated with increased ICU length of stay, duration of mechanical ventilation, and mortality. Therefore, the observed nosocomial infections in the ICU were independent risk factors for mortality. Antibiotic resistance, pathogen virulence, delayed administration of appropriate therapy, invasive procedures, and underlying patient conditions collectively account for the longer length of stay in the ICU among patients with nosocomial infections compared to those without infections[40]. The study findings may be influenced by surveillance bias, underreporting, confounding, and incomplete records. Incidence and resistance patterns could be overestimated due to sampling and monitoring practices, while incomplete follow-up and attribution challenges may underestimate long-term outcomes. The study provides valuable insights into the incidence, risk factors, antibiotic resistance patterns, and outcomes of nosocomial infections in a tertiary care setting, addressing a critical public health issue. However, the findings must be interpreted with caution due to several limitations. Potential biases, including surveillance, selection, and attribution biases, may have influenced the reported incidence, associations, and outcomes.

While the observed trends align with those reported in similar studies, such as the increasing burden of multidrug-resistant organisms and the association of invasive procedures with higher infection risk, differences in study design, population, and healthcare practices may limit direct comparisons.

Overall, the results highlight the need for robust infection control practices and targeted interventions. While the study provides important insights into nosocomial infections in tertiary care settings, caution should be exercised when applying the findings to other settings, regions, or populations. Broader, multicenter studies with diverse patient populations and standardized methodologies are needed to enhance external validity and provide more representative data.

Conflict of interest statement

We declare that we have no conflict of interest

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Authors' contributions

ALR contributed to the concept and design of the study, drafting the manuscript, data curation, interpretation, critical revision of the article, final approval of the version to be published, writing-original draft, writing-review and editing, supervision and project administration. APM contributed in data analysis, interpretation of results, drafting sections of the manuscripts, writing-review and editing. JNS contributed to data identification, clinical diagnosis and assessment, data visualization and supervision. PDP involved in data collection, data curation, data analysis, interpretation, drafting the manuscript, critical revision of the article, writing-original draft and editing.

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Supplementary Table 1. Antibiotic resistance patterns of Gram-negative bacteria in intensive care unit (ICU) patients with nosocomial infections (%).

Infections	Microorganisms	Benzylpenicillin	Ampicillin/Sulbactam	Amoxicillin/Clavulanic Acid	Piperacillin/Tazobactam	Cefuroxime	Ceftriaxone	Cefoperazone/Sulbactam	Cefepime	Ceftazidime	Ertapenem	Imipenem	Meropenem	Amikacin	Gentamicin	Ciprofloxacin	Tigecycline	Colistin	Trimethoprim/Sulfamethoxazole	Minocycline
SSI (*n*=7)	*E. coli (n=4)*	-	-	100	100	100	100	100	100	-	100	100	75	50	50	100	0	0	100	0
	A. baumannii (n=2)	-	-	-	100	-	100	100	100	-	-	100	100	100	100	100	-	0	50	-
	K. pneumoniae(n=1)	-	-	-	-	0	-	-	-	-	-	-	-	0	0	0	0	-	0	-
CAUTI (*n* =11)	*E. coli (n=4)*	100	100	100	100	100	100	66.6	75	-	100	100	75	0	50	100	0	0	75	-
	K. pneumoniae (n=4)	-	-	100	100	100	100	100	100	-	100	100	100	100	100	100	-	0	75	-
	P. aeruginosa (n=1)	-	-	-	0	-	-	0	0	0	-	-	-	0	0	0	-	-	-	-
	P. rettgeri (n=1)	-	-	-	100	100	100	100	100	-	100	100	100	100	100	100	-	-	0	-
	S. marcescens (n=1)	100	-	-	-	100	0	0	0	-	-	-	0	0	0	0	-	-	0	-
CRBSI (*n* =16)	*E. coli (n=5)*	-	100	75	75	80	80	75	75	-	100	100	75	20	0	100	-	0	60	-
	A. baumannii (n=2)	-	-	-	100	-	100	0	100	-	-	100	100	100	100	100	-	0	50	-
	K. pneumoniae (n=3)	-	100	100	100	66.6	66.6	66.6	100	-	100	100	100	33.3	66.6	100	0	0	66.6	-

	P. aeruginosa (n=2)	-	-	-	0	-	-	0	0	0	-	-	-	-	0	0	-	-	-	-
	B. cepacia (n=1)	-	-	-	-	-	-	100	-	100	-	-	0	-	-	0	-	-	-	0
	P. putida (n=1)	-	-	-	-	-	-	-	0	0	-	-	-	0	0	0	-	-	-	-
	S. marcesens (n=2)	100	-	100	-	100	0	0	0	-	-	-	0	0	0	0	-	-	0	-
VAP (*n* =54)	*E. coli (n=3)*	-	100	33.3	33.3	100	100	33.3	100	-	100	100	100	0	33.3	100	0	-	100	-
	A. baumannii (n=28)	-	-	-	100	100	100	59.2	96.0	-	-	100	100	100	96.2	96.2	-	0	55.5	-
	A. lwoffii (n=1)	-	-	-	100	-	100	-	-	-	-	100	100	100	100	100	-	0	100	-
	K. pneumoniae (n=11)	-	-	80	70	72.7	72.7	60	80	-	100	100	85.7	60	45.0	54.5	20	0	20	-
	P. aeruginosa (n=5)	-	-	-	25	-	-	25	0	25	-	-	-	0	0	0	-	-	0	-
	P. aeruginosa (Carba-resistant) *(n=1)*	100	100	100	-	-	-	100	0	0	-	100	100	0	0	-	-	-	-	-
	S. marcesens (n=2)	100	-	-	-	100	0	0	0	-	-	-	0	0	0	0	-	-	0	-
	B. cepacia (n=1)	-	-	-	-	-	-	-	-	0	-	-	-	-	-	-	-	-	-	0
	S. maltophilia (n=2)	-	-	-	-	-	-	-	-	50	-	-	50	-	-	-	0	-	0	0

VAP: ventilator-associated pneumonia; CRBSI: catheter-related bloodstream infection; CAUTI: catheter associated urinary tract infection; SSI: surgical site infection. *E. coli- Escherichia coli*, *A. baumannii- Acinetobacter baumannii, K. pneumoniae- Klebsiella pneumoniae, P. aeruginosa- Pseudomonas aeruginosa, P. rettgeri- Providencia rettgeri, S. marcescens- Serratia marcescens, B. cepacia- Burkholderia cepacia, P. putida- Pseudomonas putida, A. lwoffii- Acinetobacter lwoffii, S. maltophilia- Stenotrophomonas maltophilia.*

Supplementary Table 2. Antibiotic resistance patterns of Gram-positive bacteria in intensive care unit patients with nosocomial infections (%).

Infections	Microorganisms	Benzylpenicillin	Oxacillin	Gentamicin	Ciprofloxacin	Tetracycline	Trimethoprim/ Sulfamethoxazole	Teicoplanin	Tigecycline	Levofloxacin	Erythromycin	Clindamycin	Linezolid	Vancomycin
SSI (*n* =3)	*E. faecium (n=1)*	100		100	100	-	-	0	-	-	0	-	-	0
	S. aureus (MSSA) (n=1)	100	0	100	100	0	0	-	0	-	0	0	-	-
	E. gallinarium (n=1)	100	-	100	100	-	-	0	0	100	100	-	0	0
CAUTI (*n* =2)	*E. faecalis (n=1)*	100	-	-	100	100	-	-	-	100	100	-	0	0
	E. faecium (n=1)	100	-	100	100	100	-	100	-	-	100	-	0	100
CRBSI (*n* =8)	*Micrococcus spp. (n=1)*	0	-	-	-	-	-	100	-	-	0	0	0	100
	S. aureus (MSSA) (n=1)	0	0	0	-	0	100	-	-	-	-	-	-	-
	S. epidermidis (n=2)	100	100	100	100	-	-	-	-	-	-	-	-	-
	E. faecium (n=2)	100	-	100	100	0	-	0	-	50	50	-	-	0
	S. aureus (n=2)	100	0	0	100	0	0	-	-	-	100	100	-	-
VAP (*n* =9)	*S. aureus (MSSA) (n=1)*	0	-	0	100	0	0	-	-	100	0	0	-	-
	S. aureus (MRSA) (n=6)	100	100	66.6	100	0	33.3	0	0	100	60	-	-	0

S. aureus (n=2)	100	0	0	100	0	0	-	-	-	100	100	-	-

VAP: ventilator-associated pneumonia; CRBSI: catheter-related bloodstream infection; CAUTI: catheter associated urinary tract infection; SSI: surgical site infection. *E. faecium- Enterococcus faecium, S. aureus- Staphylococcus aureus, E. gallinarium- Enterococcus gallinarium, E. faecalis- Enterococcus faecalis, S. epidermidis- Staphylococcus epidermidis.*