Journal of Intensive Medicine 4 (2024) 347–354

Contents lists available at ScienceDirect

Journal of Intensive Medicine

journal homepage: www.elsevier.com/locate/jointm

Original Article

Risk factors and mortality rates of carbapenem-resistant Gram-negative bacterial infections in intensive care units ☆

Tulay Orhan Kuloglu [1,#], Gamze Kalin Unuvar [2,#,*], Fatma Cevahir [3], Aysegul Ulu Kilic [2], Emine Alp [4]

[1] *Infection Control Committee, Faculty of Medicine, Erciyes University, Kayseri, Turkey*
[2] *Department of Infectious Diseases, Faculty of Medicine, Erciyes University, Kayseri, Turkey*
[3] *Programme of First and Emergency Aid, Sakarya University, Sakarya, Turkey*
[4] *Department of Infectious Diseases, Faculty of Medicine, Yıldırım Beyazıt University, Ankara, Turkey*

ARTICLE INFO

Managing Editor: Jingling Bao

Keywords:
Multidrug resistance
Gram-negative bacteria
Infection
Intensive care units

ABSTRACT

Background: The prevalence of hospital-acquired infections caused by carbapenem-resistant gram-negative bacteria (CRGNB) is increasing worldwide. Several risk factors have been associated with such infections. The present study aimed to identify risk factors and determine the mortality rates associated with CRGNB infections in intensive care units.

Methods: This retrospective case-control study was conducted at Erciyes University Hospital (Kayseri, Turkey) between January 2017 and December 2021. Demographic and laboratory data were obtained from the Infection Control Committee data and record system. Patients who had CRGNB infection 48–72 h after hospitalization were assigned to the case group, while those who were not infected with CRGNB during hospitalization formed the control group. Risk factors, comorbidity, demographic data, and mortality rates were compared between the two groups.

Results: Approximately 1449 patients (8.97%) were monitored during the active follow-up period; of those, 1171 patients were included in this analysis. CRGNB infection developed in 14 patients (70.00%) who had CRGNB colonization at admission; in 162 (78.26%) were colonized during hospitalization, whereas 515 (54.56%) were not colonized. There was no significant difference in age, sex (male/female) or comorbidities. The total length of hospital stay was statistically significantly longer (P=0.001) in the case group (median: 24 [interquartile range: 3–378] days) than the control group (median: 16 [interquartile range: 3–135] days). The rates of colonization at admission (25.5%; *vs.* 10.6%, P=0.001) and mortality (64.4% *vs.* 45.8%, P=0.001) were also significantly higher in the cases than in the control group, respectively. In the univariate analysis, prolonged hospitalization, the time from intensive care unit admission to the development of infection, presence of CRGNB colonization at admission, transfer from other hospitals, previous antibiotic use, enteral nutrition, transfusion, hemodialysis, mechanical ventilation, tracheostomy, reintubation, central venous catheter, arterial catheterization, chest tube, total parenteral nutrition, nasogastric tube use, and bronchoscopy procedures were significantly associated with CRGNB infections (P <0.05). Multivariate analysis identified the total length of stay in the hospital (odds ratio [OR]=1.02; 95% confidence interval [CI]: 1.01 to 1.03; P=0.001), colonization (OR=2.19; 95% CI: 1.53 to 3.13; P=0.001), previous antibiotic use (OR=2.36; 95% CI: 1.53 to 3.62; P=0.001), intubation (OR=1.59; 95% CI: 1.14 to 2.20; P=0.006), tracheostomy (OR=1.42; 95% CI: 1.01 to 1.99; P=0.047), and central venous catheter use (OR=1.62; 95% CI: 1.20 to 2.19; P=0.002) as the most important risk factors for CRGNB infection.

Conclusions: Colonization, previous use of antibiotics, and invasive interventions were recognized as the most important risk factors for infections. Future research should focus on measures for the control of these parameters.

☆ This article won the first prize in the field of oral presentation at the 11th Turkey EKMUD (Infectious Diseases and Clinical Microbiology Specialization Association) International Scientific Congress.

* Corresponding author: Gamze Kalin Unuvar, Department of Infectious Diseases, Faculty of Medicine, Erciyes University, Kayseri 38280, Turkey.
E-mail address: drgamzekln@hotmail.com (G.K. Unuvar).

# Tulay Orhan Kuloglu and Gamze Kalin Unuvar contributed equally to this work.

https://doi.org/10.1016/j.jointm.2023.11.007
Received 28 July 2023; Received in revised form 23 October 2023; Accepted 8 November 2023
Available online 9 January 2024

Introduction

In recent years, the prevalence of hospital-acquired infections caused by carbapenem-resistant Gram-negative bacteria (CRGNB) has been increasing worldwide.[1,2] This type of infection poses a real threat to patient safety and life. Recent studies have shown that infections with multidrug-resistant Gram-negative (MDRGN) bacteria are linked to high mortality rates (*i.e.*, 26%–80%). A meta-analysis has reported a 1.78 times higher mortality rate in patients with MDRGN infections *vs.* other infections. In addition, CRGNB infections increase healthcare costs and prolong the length of hospital stay. In intensive care units (ICUs), patients are at high risk of both colonization and infection with multidrug-resistant organisms.[3] The most commonly detected CRGNB are *Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*.[4,5] Clinicians face numerous challenges in the treatment of CRGNB infections in critically ill patients. The use of agents, such as colistin or tigecycline, is frequently associated with nephrotoxicity and unclear efficacy.[1,3] Moreover, the development of new drugs in recent years has been limited. Thus, the identification of patients at high risk is necessary to ensure the early implementation of infection prevention and control measures.

Several risk factors have been associated with an increased risk of infection. These factors include exposure to antibiotics (particularly carbapenems), use of invasive procedures (catheterization, mechanical ventilation), and exposure to the hospital environment (particularly the ICU). Colonization in asymptomatic carriers also increases the risk of infection and is considered a potential origin of cross-transmission for patients.[6]

Carbapenem resistance is a serious problem in our hospital. During active surveillance, it was observed that the rates of carbapenem resistance in the ICUs of our hospital increased between 2017 and 2021. During this period, the rate of carbapenem resistance increased for *A. baumannii* (from 96.5% to 100%), *K. pneumoniae* (from 49.2% to 79.6%), and *P. aeruginosa* (from 45.8% to 93.1%). Therefore, recognizing the risk of carbapenem resistance, particularly in the most vulnerable patient populations, is critical to reduce the risk of mortality, length of hospital stay, and associated costs. In clinical practice, the screening of patients at risk is an essential preventive measure. This approach allows for the early identification of carriers and the implementation of infection prevention and control measures.[6]

The present study aimed to identify risk factors and determine the mortality rates associated with CRGNB infections in ICUs.

Methods

Setting and patients

This retrospective case-control study was conducted at Erciyes University Hospital (Kayseri, Turkey) between January 2017 and December 2021. Adult patients (age: >18 years) hospitalized in five ICUs (*i.e.*, internal, general surgery, anesthesia, neurosurgery, and thoracic) for >48 h were included. This tertiary university hospital has a total of 61 intensive care beds. In the general surgery ICU of our hospital, one nurse provides treatment and care to two patients. However, in the other ICUs, one nurse manages three patients due to staff shortage. Data were obtained from the active Infection Control Committee, patient-based surveillance, and hospital electronic record systems.

Patients who had CRGNB infection 48–72 h after ICU admission were assigned to the case group, while those who were not infected with CRGNB during hospitalization formed the control group. Only the first detection of CRGNB was considered for each patient. The collected data included demographics, diagnostic category, comorbidities (chronic heart failure, chronic obstructive pulmonary disease, liver disease, diabetes mellitus, chronic kidney disease, malignancy, and chronic hypertension), comorbid index, use of invasive procedures (*e.g.*, bladder/urinary catheter, peritoneal dialysis catheter, hemodialysis catheter, intubation/mechanical ventilator, tracheostomy, central venous catheter [CVC], arterial catheter, pulmonary tube, peripheral venous catheter, drainage catheter, percutaneous endoscopic gastrostomy, colostomy, ileostomy, etc.), colonization with CRGNB, history of operation, total days of hospitalization, community-acquired infections, use of antibiotics before colonization or infection, transfer from other units or other hospitals, and outcome (discharge from hospital or death). The types of ICU admission included medical admission (*e.g.*, respiratory disease, infection, sepsis, gastrointestinal disease, cardiovascular disease, neurological disease) or admission for postoperative follow-up.

Infection prevention and control measures for CRGNB

Since 2005, patients admitted to the ICUs in our hospital were regularly screened for CRGNB with rectal swabs at the time of admission and once per week. According to the protocol, patients who exhibited positivity for CRGNB in clinical specimens or rectal swabs were transferred to an isolation room within the ICU alone or together with another positive patient. Use of personal protective equipment, compliance with hand hygiene, and contact precautions were implemented. In the ICU, patient rooms were cleaned and disinfected twice daily, and terminal disinfection was performed at least thrice before the admission of a new patient. Isolation was terminated following three negative rectal swab tests obtained during weekly screening. All positive rectal culture results were evaluated in coordination with the microbiology laboratory, and the clinical team was informed regarding the patients for whom isolation was required. Daily visits to the ICU by infection control nurses and patient-based surveillance were carried out.

Definitions and bacterial isolation

Hospital-acquired infections were defined using the National Healthcare Safety Network hospital-acquired infection diagnostic criteria.[7]

Colonization was defined as the absence of infection requiring antimicrobial therapy despite positivity for CRGNB culture. The history of antibiotic use was defined as the use of antibiotics for >48 h within 2 weeks before the onset of infection.

Rectal swabs were obtained within 24 h of admission to the ICU for the assessment of bacterial colonization. The swabs were placed in tubes containing 1 mL of sterile Copan FecalSwab™

4C024S (Murrieta, California, USA) and immediately transferred to the Clinical Microbiology Laboratory for analysis.

The BD Phoenix (Becton Dickinson, Sparks, Maryland, USA) automated system was used for the identification of pathogens in the Microbiology Unit. The Kirby–Bauer disk diffusion method was used to confirm carbapenem resistance. The liquid microdilution method (Thermo Scientific™ Sensititre™ Complete Automated AST System, Billerica, Massachusetts, USA) was used to confirm colistin resistance. Minimum inhibitory concentrations were evaluated according to the European Committee for Antimicrobial Susceptibility Testing breakpoints.

Statistical analysis

The data were processed using version 25.0 of the Statistical Package for Social Sciences (SPSS; IBM Corp., Armonk, NY, USA). The chi-squared or Fisher's exact test was used for categorical variables. The Shapiro–Wilk test was performed to check the normality assumption of the data. The Mann–Whitney *U test* was used for the comparison of continuous variables. Variables with a *P*-value ≤0.05 in the univariate analysis were included in the multivariate logistic regression analysis.

Results

Demographic data

A total of 16,147 patients were admitted to the ICU for treatment and follow-up between January 2017 and December 2021. Of the 1449 patients (8.97%) followed up during active surveillance, 1171 were included in the study. The number of patients with CRGNB colonization at the time of admission and during hospitalization was 20 (1.71%) and 207 (17.68%), respectively; the number of patients without CRGNB colonization was 944 (80.61%). Of those, 691 patients (59.01%) developed CRGNB infection, whereas 480 (40.99%) did not have CRGNB infection. CRGNB infection developed in 14 patients (70.00%) who had CRGNB colonization at admission, in 162 patients (78.26%) who had CRGNB colonization during the hospitalization, whereas in 515 patients (54.56%) who had no CRGNB colonization at all (Figure 1). The demographic characteristics of the patients are presented in Table 1. There was no significant difference in terms of age, sex, or comorbidities between the case and control groups. The total length of hospital stay was statistically significantly longer in the case group than the control group (*P*=0.001). The rate of colonization at admission was significantly higher in the case group than in the control group (25.5% *vs.* 10.6%, respectively; *P*=0.001). In the case group, patients were mostly followed in the medical ICU. In the case group, patients were mostly transferred from other units and hospitals (*P*=0.032).

Risk factors and mortality

The mortality rates were significantly higher in the case group than in the control group (64.4% *vs.* 45.8%, respectively; *P*=0.001). Although the rates of community-acquired infections were not significantly different, previous antibiotic use was higher in the case group than the control group (93.6% *vs.* 81.7%, respectively; *P*=0.001). The most common infection in the case group was ventilator-associated pneumonia (279/691, 40.4%) and the control group was central line-associated bloodstream infection (CLABSI; 143/480, 29.8%) While there was no colonization in 74.2% (207/279) of the patients who devel-

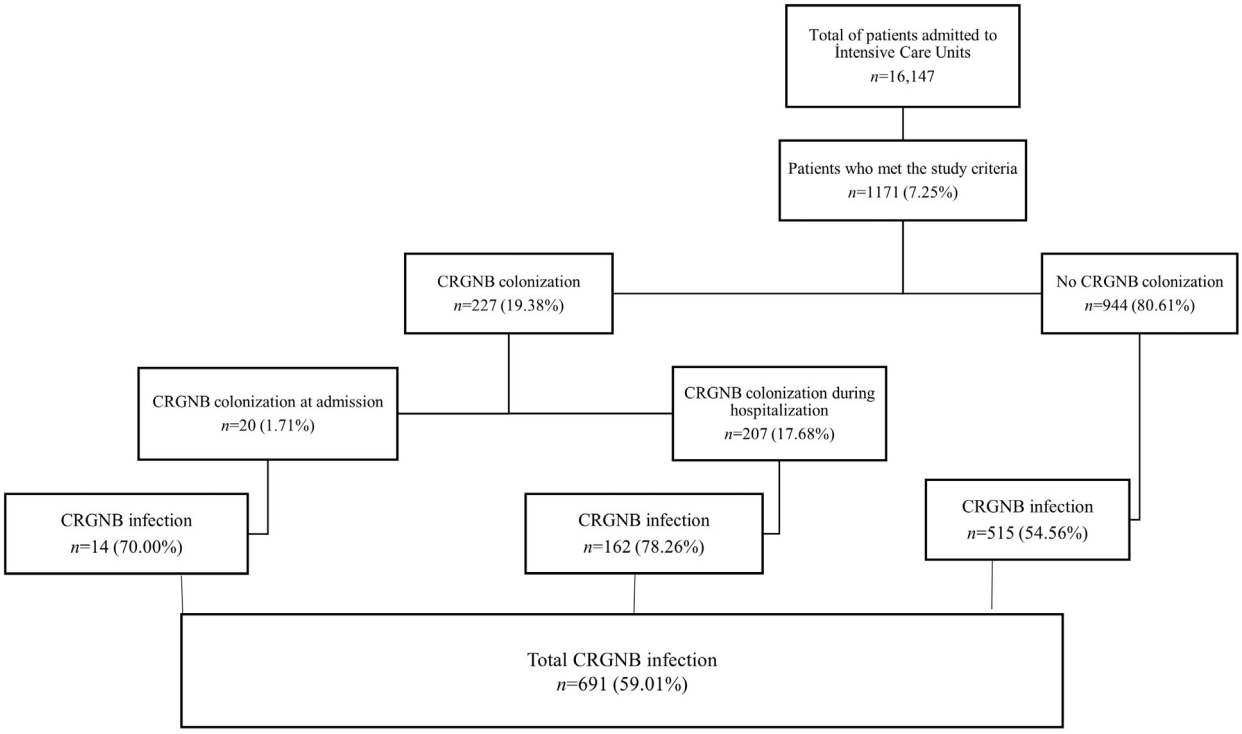

Figure 1. Distribution of patients colonized and infected with CRGNB.
CRGNB: Carbapenem-resistant Gram-negative bacteria.

Table 1
Demographic and characteristic data of patients infected and not infected with carbapenem-resistant Gram-negative bacteria.

Variables	Total (*n*=1171)	Case group (*n*=691)	Control group (*n*=480)	*P*-value
Age (years)	59 (18–90)	63 (18–89)	62 (18–90)	0.514
Male gender	714 (60.97)	428 (61.9)	286 (59.6)	0.416
Comorbid index	4 (0–21)	4 (0–21)	4 (0–19)	0.983
Length of hospital stay (days)	20 (3–378)	24 (3–378)	16 (3–135)	0.001
Colonization day from admission	10 (2–51)	11 (2–51)	8 (2–23)	0.031
Colonization	227 (19.4)	176 (25.5)	51 (10.6)	0.001
The name of care units				
Internal medicine ICU	426 (36.4)	280 (40.5)	146 (30.4)	0.004
Neurosurgery ICU	191 (16.3)	108 (15.6)	83 (17.3)	
General surgery ICU	242 (20.7)	124 (17.9)	118 (24.6)	
Respiratory ICU	102 (8.7)	62 (9.0)	40 (8.3)	
Anesthesia ICU	210 (17.9)	117 (16.9)	93 (19.4)	
Year				
2017	271 (23.1)	144 (20.8)	127 (26.5)	0.142
2018	232 (19.8)	145 (21.0)	87 (18.1)	
2019	228 (19.5)	144 (20.8)	84 (17.5)	
2020	199 (17.0)	119 (17.2)	80 (16.7)	
2021	241 (20.6)	139 (20.1)	102 (21.3)	
Transfer from other units	660 (56.7)	392 (56.7)	268 (55.8)	0.761
Transfer from other hospitals	114 (9.7)	78 (11.3)	36 (7.5)	0.032
Mortality	665 (56.8)	445 (64.4)	220 (45.8)	0.001
Community-acquired infections	30 (2.6)	18 (2.6)	12 (2.5)	0.999
Use of antibiotic before colonization or infection	1039 (88.7)	647 (93.6)	392 (81.7)	0.001
Comorbidities				
Chronic heart failure	193 (16.5)	120 (17.4)	73 (15.2)	0.328
Chronic obstructive pulmonary disease	138 (11.8)	88 (12.7)	50 (10.4)	0.226
Liver disease	20 (1.7)	10 (1.4)	10 (2.1)	0.493
Diabetes mellitus	238 (20.3)	151 (21.9)	87 (18.1)	0.119
Kidney disease	171 (14.6)	111 (16.1)	60 (12.5)	0.089
Malignancy	251 (21.4)	144 (20.8)	107 (22.3)	0.551
Hypertension	233 (19.9)	145 (21.0)	88 (18.3)	0.264
Trauma	92 (7.9)	56 (8.1)	36 (7.5)	0.705
Invasive interventions				
Total parenteral nutrition	201 (17.2)	125 (18.1)	76 (15.8)	0.314
Enteral nutrition with NG or ND tube	499 (42.6)	342 (49.5)	157 (32.7)	0.001
Transfusion	307 (26.2)	198 (28.7)	109 (22.7)	0.023
Urinary catheter	1104 (94.3)	653 (94.5)	451 (94.0)	0.694
Peritoneal dialysis catheter	3 (0.3)	1 (0.1)	2 (0.4)	0.571
Hemodialysis	183 (15.6)	123 (17.8)	60 (12.5)	0.014
Intubation/mechanical ventilator	882 (75.3)	581 (84.1)	301 (62.7)	0.001
Tracheostomy	290 (24.8)	220 (31.8)	70 (14.6)	0.001
Reintubation	70 (6.0)	50 (7.2)	20 (4.2)	0.033
Central venous catheter	876 (74.8)	566 (81.9)	310 (64.6)	0.001
Arterial catheter	569 (48.6)	360 (52.1)	209 (43.5)	0.004
Chest tube	80 (6.8)	56 (8.1)	24 (5.0)	0.038
Peripheral catheter	628 (53.6)	349 (50.5)	279 (58.1)	0.010
Drainage catheter	260 (22.2)	150 (21.7)	110 (22.9)	0.624
NG tube	614 (52.4)	391 (56.6)	223 (46.5)	0.001
PEG	69 (5.9)	51 (7.4)	18 (3.8)	0.011
Bronchoscopy	46 (3.9)	35 (5.1)	11 (2.3)	0.021
Colostomy	50 (4.3)	28 (4.1)	22 (4.6)	0.658
Ileostomy	26 (2.2)	11 (1.6)	15 (3.1)	0.080
Operation	309 (26.4)	165 (23.9)	144 (30.0)	0.019

Data are expressed as median (interquartile range) or *n* (%).
ICU: Intensive care unit; ND: Nasoduodenal; NG: Nasogastric; PEG: Percutaneous endoscopic gastrostomy.

oped ventilator-associated pneumonia in the case group, 24.7% (69/279) were colonized during their hospitalization and 1.1% (3/279) were colonized before hospitalization. In the control group (patients who did not have CRGNB infection), colonization was not observed in 86.0% (123/143) of the patients who developed CLABSI, while colonization was detected in 13.3% (19/143) during hospitalization and 0.7% before hospitalization.

The rates of enteral nutrition, transfusion, hemodialysis, mechanical ventilation, tracheostomy, reintubation, CVC use, arterial catheterization, chest tube, nasogastric tube use, percutaneous endoscopic gastrostomy, and bronchoscopy history were significantly higher in the case group than the control group (P <0.05). In contrast, the rates of peripheral catheter use and history of operation were significantly higher in the control group than the case group (P <0.05).

The univariate analysis revealed that prolonged hospitalization, time from ICU admission to infection development, presence of CRGNB colonization at admission, transfer from other hospitals, previous antibiotic use, enteral nutrition, transfusion, hemodialysis, mechanical ventilation, tracheostomy, reintubation, CVC use, arterial catheterization, chest tube, nasogastric tube use, and bronchoscopy procedures were significantly associated with CRGNB infections (P <0.05).

The multivariate analysis identified the total length of stay in the hospital, colonization, previous antibiotic use, intubation/mechanical ventilator, tracheostomy, and CVC use as the most important risk factors for the occurrence of CRGNB infection (Table 2).

Discussion

In this retrospective study, we identified that length of hospital stay, colonization, previous antibiotic use, intubation, tracheostomy, and CVC use were associated with CRGNB infections. CRGNB infections are a global threat and a significant concern for clinicians. It has been estimated that >10 million deaths will occur due to antimicrobial resistance in the next 30 years. Therefore, it is crucial to identify risk factors for CRGNB infections and develop effective infection prevention and control strategies.[8–10] Moreover, the identification of risk factors will facilitate appropriate empirical treatment in clinical practice.[11]

CRGNB colonization during admission to the ICU has been associated with an increased risk of CRGNB infection and increased mortality rates. Colonized ICU patients can act as a reservoir for dispersion within the unit. Studies have shown that there is a horizontal transfer of carbapenemase genes between CRGNB.[12]

Colonization with CRGNB in the ICU may be due to the patient-to-patient spread, which occurs through healthcare workers, environments, or medical devices (as CRGNB can survive on surfaces for a long period of time). Various studies have reported the isolation of strains from patients colonized or infected with CRGNB, and isolates obtained from media and surfaces were clonally similar.[12] Studies conducted in high-risk patients followed up in clinics, such as the ICU, also support these findings.[12–14] Fernández-Martínez et al. [15] reported that MDRGN bacteria were detected in approximately 7% of patients with rectal swab cultures performed before admission to the ICU. A prospective observational study investigated 226 ICU patients over a period of approximately 25 months. The results revealed that 72.6% of patients were colonized with *K. pneumoniae* during their stay in the ICU, while 12.8% of patients had colonization before hospitalization.[16]

Another study evaluating risk factors for CRGNB colonization in the ICU in Thailand reported that 18.7% (6/32) of the patients colonized with CRGNB developed an infection during their stay in the ICU.[17] In a retrospective, observational, case-control study conducted between 2013 and 2015 by Madueño et al., [18] the rate of carbapenem-resistant *Klebsiella pneumoniae* (CRKP) infection was 30.5% in initially colonized patients. Based on this evidence, it has been suggested that colonized patients should be identified by rectal scanning and, if possible, isolated in single rooms to prevent the spread of CRGNB within the units.

Studies have reported that active surveillance reduces the spread of CRGNB infections, and the European Society for Clinical Microbiology and Infectious Diseases guidelines also recommended active screening culture to reduce the spread of these pathogens.[19,20] In a study involving 88 patients, Abramowicz et al. [21] reported a colonization rate of 41% and an infection rate of 59%. Notably, 21% of the patients had colonization before hospitalization, and 13% of the patients who developed infection had colonization before. This showed that 25% of the colonized patients were infected. The annual proportion of patients hospitalized in the ICU for >24 h with CRGNB colonization and/or infection was calculated. The investigators found that rectal screening for CRGNB reduced the time to the initiation of appropriate empirical antibiotic therapy from 4 days (in patients without or negative rectal screening) to 1 day (in patients with positive previous rectal screening).

Therefore, it was stated that, although rectal screening plays an important role in the prevention of infection, infection control measures (*e.g.*, proper disinfection of medical equipment and hand hygiene) may be sufficient to prevent the spread of CRGNB and reduce infection rates. The implementation of these methods effectively reduced the number of patients colonized or infected with CRGNB. The spread of CRGNB can be reduced by routine infection control measures, such as rectal scans, contact precautions, isolation, appropriate disinfectant use, hand hygiene, and staff training. Weekly rectal screening and standard infection control measures (supervision and feedback) were performed in a study evaluating the effects of advanced infection control measures on CRGNB colonization and infection in a pediatric ICU. It has been shown that compliance with hand hygiene increases as a result of active surveillance, thereby significantly increasing the rates of CRGNB prevalence and colonization. It has been found that improved infection control measures reduce CRKP infections in endemic areas.[20] A quasi-experimental study demonstrated that the rates of CRKP and carbapenem-resistant *P. aeruginosa* infection were significantly reduced following the combination of active surveillance, contact precautions, hand hygiene, education, supervision, feedback, and infection control measures.[22]

Table 2
Multivariate analysis of data of patients infected and not infected with carbapenem-resistant Gram-negative bacteria.

Variable	Case group (n=691)	Control group (n=480)	Multivariate analysis		P-value
			OR	95% CI	
Length of hospital stay (days)	24 (3–378)	16 (3–135)	1.02	1.01–1.03	0.001
Colonization	176 (25.5)	51 (10.6)	2.19	1.53–3.13	0.001
Mortality	445 (64.4)	220 (45.8)	1.58	1.19–2.07	0.001
Use of antibiotic before colonization or infection	647 (93.6)	392 (81.7)	2.36	1.53–3.62	0.001
Invasive intervention					
Intubation/mechanical ventilator	581 (84.1)	301 (62.7)	1.59	1.14–2.20	0.006
Tracheostomy	220 (31.8)	70 (14.6)	1.42	1.01–1.99	0.047
Central venous catheter	566 (81.9)	310 (64.6)	1.62	1.20–2.19	0.002

Data are expressed as median (interquartile range) or n (%).
CI: Confidence interval; OR: Odds ratio.

In the present study, the colonization rates were significantly higher in the case group *vs.* the control group (P=0.001). Multivariate analysis showed that colonization resulted in an approximately two-fold increase in the rate of CRGNB infection. The rates of colonization and infection recorded in this study are similar to those reported in the literature.[17,21] It has been previously demonstrated that colonization is an important risk factor for CRGNB infection. CRGNB infections, which require infection control measures, increase the costs due to prolonged hospitalization, laboratory testing, health care practices, and treatments.[23]

Identification and recording of rectal colonization lead to a substantial reduction in cost reduction and prevention of infections. A comparative cost-effectiveness analysis of various surveillance strategies (*e.g.*, screening and hospital-level registration in ICUs, and hospital-level screening and a regional registry system) was performed to detect asymptomatic CRGNB colonization. While the incidence of colonization decreased by 1.2% with predictive algorithms, it decreased by 7% on average after regional registration, thus resulting in savings of 572,000 US dollars per year.[24] As stated earlier in this article, rectal swab cultures are regularly performed in our hospital. In addition, in 2019, our hospital received the European Hand Hygiene Excellence Award. The colonization rates noted in this study were consistent with those reported in the literature.[21] This may be due to active rectal screening, the presence of feedback systems, and the active implementation of infection control prevention measures (*e.g.*, hand hygiene policy, personnel training, and contact precautions) in critically ill patients.

In our study, there was a 1.5-fold increase in mortality in patients infected with CRGNB *vs.* non-infected patients. These high rates may be related to the fact that our institution is a tertiary hospital and our patients experience complications. The comorbidity index was generally high. It is thought that the increase in mortality may be related to comorbidity. Since colonization is an important risk factor for the development of infection, its prevention is crucial. Active surveillance can provide useful background information on colonization. Especially in studies, early use of effective empirical antibiotics against infections developing after CRGNB colonization has been effective in reducing mortality.[25] In a study, mortality was lower in the empirical treatment group than in the standard treatment group (17% *vs.* 37.5%, respectively; P=0.004, odds ratio [OR]=0.32).[25]

Data have revealed that invasive procedures are linked to colonization and infection with resistant pathogens. It has been shown that invasive interventions play an essential role in increasing susceptibility to nosocomial infections than underlying diseases. Thus, they are responsible for the development of infections in colonized patients.[13] Yumamoto et al. [26] reported that the use of an enteral feeding tube may lead to the entry of CRGNB into the intestines; thus, this approach has been associated with a risk of rectal colonization.

In our study, the use of enteral nutrition and a nasogastric tube was identified as an important risk factor for CRGNB colonization and infection.[26] Madueño et al. [18] evaluated the risk factors for CRGNB infections and identified the number of CVC and in-hospital inter-unit transfers as independent risk factors. Falagas et al. [27] recognized invasive procedures, such as tracheostomy (P=0.02) and mechanical ventilator (P=0.02), as important risk factors for CRKP infections. In our study, the rate of CVC use (an invasive procedure frequently performed in the ICU) was significantly higher in patients infected with CRGNB (81.9%; P=0.001) than non-infected patients (64.6%; P=0.001). Compared with other invasive procedures, it also increases the rate of infection by approximately 1.6 times. Various protective measures have been proposed for the use of CVC, which is considered an important risk factor in studies. Long-term catheter use is associated with increased rates of CLABSI. Hence, it is recommended that the proper application of infection control bundles, continuous evaluation of compliance indicators, and definition of the need for continuous staff training.

Therefore, consistent with previous studies, avoidance of the femoral regions, strict adherence to hand hygiene, use of full barrier precautions, chlorhexidine skin preparation, and removal of unnecessary catheters may be recommended for the placement of CVC.[22] In a study investigating chlorhexidine-silver sulfadiazine-impregnated catheters, Maki et al. [28] showed that the catheters were well tolerated and reduced the incidence of catheter-related infections. It was demonstrated that the use of uncuffed CVC prolongs the time of secure attachment in the short term and contributes to cost reduction.

In a meta-analysis involving approximately 5075 patients, age, sex, and diabetes mellitus were not associated with carbapenem-resistant bacterial infections, whereas hospitalization in the ICU, antibiotic use, and invasive interventions were identified as risk factors.[11] Similarly, the present findings revealed that age, sex, and comorbidities were not risk factors, whereas previous use of antibiotics increased the risk of infection by 2–2.5 times. The most common comorbidity in the case and control groups was diabetes mellitus and malignancy, respectively. They are among the most common comorbid diseases in patients hospitalized in the ICU or clinic in our country. They are used to manage critically ill patients and, thus, are associated with high rates of invasive procedures and intensive use of antimicrobial agents. The latter practice results in increased antimicrobial resistance. Carbapenems play a major role in empirical treatment; thus, these agents have been linked to the emergence of infections with resistant Gram-negative bacteria.

It is well-established that the misuse and abuse of antibiotics contribute significantly to the increasing problem of antimicrobial resistance.[29] In several studies with multivariate analysis, antibiotic use has also been associated with infections caused by carbapenem-resistant bacteria. In a meta-analysis evaluating 92 studies published since 2007, the rate of CRGNB infection was 51.9%, indicating a significant relationship with antibiotic use.[14] In a meta-analysis of 17 studies involving 3079 cases in which antibiotic exposure was evaluated, exposure to antibiotics led to a 2.5-fold increase in the risk of CRKP infection (hazard ratio=2.53; 95% confidence interval [CI]: 1.56 to 4.11; P=0.001).[30] In a study of risk factors for CRKP infection in the ICU, antibiotic use was higher in the carbapenem-resistant group (73.2%) than the susceptible group (52.9%).[31] In our study, antibiotic use rates were significantly higher in the case group compared with the control group (93.6% *vs.* 81.7%, respectively; P=0.001). The multivariate analysis determined that antibiotic use resulted in an approximately 2.5-fold increase in the risk of infection (hazard ratio=2.37; 95% CI: 1.57 to 3.56; P=0.001). Therefore, rational use of antibiotics and antimicrobial management, as well as

a multidisciplinary approach in ICUs, are extremely important for the prevention of antimicrobial resistance.

The limitations of our study should be acknowledged. Firstly, this was a retrospective study. Secondly, the risk factors and demographic data of the patients (Acute Physiology and Chronic Health Evaluation, comorbidity index, etc.) could not be determined. Finally, some patients may have been missed due to insufficient data in the system.

Conclusions

The results of this study showed that colonization, previous use of antibiotics, and invasive interventions were the most important risk factors for infections caused by resistant Gram-negative bacteria. It can be concluded that these factors prolong hospital stay and increase the mortality rate. Therefore, it is important to develop appropriate measures in this setting. Various infection prevention and control measures are necessary to reduce the spread of CRGNB. These measures include adherence to standard and contact precautions (*e.g.*, hand hygiene and the use of personal protective equipment, such as appropriate gloves and gowns), use of infection control bundles, active microbiological surveillance, feedback, assessment of non-compliance, reduction of the use of invasive devices as much as possible or shortening the duration of use, alternative procedures, cleaning and disinfection of environmental surfaces and reusable devices, multidisciplinary approach, collaboration, emphasis on antimicrobial prophylaxis, and development of antimicrobial management principles in the ICU. Additional prospective studies are warranted to resolve such uncertainties and better understand the carrier profile of these resistant microorganisms.

Author Contributions

Tulay Orhan Kuloglu: Methodology, Validation, Visualization, Writing – original draft, Resources. **Gamze Kalin Unuvar:** Conceptualization, Methodology, Validation, Software, Visualization, Writing – review & editing, Writing – original draft, Resources. **Fatma Cevahir:** Software, Formal analysis. **Aysegul Ulu Kilic:** Methodology, Investigation. **Emine Alp:** Conceptualization, Methodology, Supervision, Data curation.

Acknowledgments

We thank the infection control nurses for their assistance in obtaining the data.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethics Statement

The study was approved by the Erciyes University Non-Interventional Clinical Research Ethics Committee with the date of June 8, 2022 and decision number 2022/444.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

Data were obtained from Infection Control Committee records.

References

[1] Dinc G, Demiraslan H, Elmali F, Ahmed SS, Alp E, Doganay M. Antimicrobial efficacy of doripenem and its combinations with sulbactam, amikacin, colistin, tigecycline in experimental sepsis of carbapenem-resistant *Acinetobacter baumannii*. New Microbiol 2015;38(1):67–73.

[2] Ahmed SS, Alp E. Genotyping methods for monitoring the epidemic evolution of *A. baumannii* strains. J Infect Dev Ctries 2015;9(4):347–54. doi:10.3855/jidc.6201.

[3] Alhashem F, Tiren-Verbeet NL, Alp E, Doganay M. Treatment of sepsis: what is the antibiotic choice in bacteremia due to carbapenem resistant *Enterobacteriaceae*? World J Clin Cases 2017;5(8):324–32. doi:10.12998/wjcc.v5.i8.324.

[4] Metan G, Alp E, Yildiz O, Percin D, Aygen B, Sumerkan B. Clinical experience with tigecycline in the treatment of carbapenem-resistant *Acinetobacter* infections. J Chemother 2010;22(2):110–14. doi:10.1179/joc.2010.22.2.110.

[5] Ahmed SS, Alp E, Ulu-Kilic A, Dinc G, Aktas Z, Ada B, et al. Spread of carbapenem-resistant international clones of *Acinetobacter baumannii* in Turkey and Azerbaijan: a collaborative study. Eur J Clin Microbiol Infect Dis 2016;35(9):1463–8. doi:10.1007/s10096-016-2685-x.

[6] Palacios-Baena ZR, Giannella M, Manissero D, Rodríguez-Baño J, Viale P, Lopes S, et al. Risk factors for carbapenem-resistant Gram-negative bacterial infections: a systematic review. Clin Microbiol Infect 2021;27(2):228–35. doi:10.1016/j.cmi.2020.10.016.

[7] Identifying healthcare-associated infections (HAI) for NHSN surveillance. National Healthcare, Safety Network. https://www.cdc.gov/nhsn/pdfs/pscmanual/2psc_identifyinghais_nhsncurrent.pdf [accessed 8 December 2023].

[8] Meyer E, Schwab F, Schroeren-Boersch B, Gastmeier P. Dramatic increase of third-generation cephalosporin-resistant *E. coli* in German intensive care units: secular trends in antibiotic drug use and bacterial resistance, 2001 to 2008. Crit Care 2010;14(3):R113. doi:10.1186/cc9062.

[9] Falagas ME, Kopterides P. Risk factors for the isolation of multi-drug-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa*: a systematic review of the literature. J Hosp Infect 2006;64:7–15. doi:10.1016/j.jhin.2006.04.015.

[10] Aloush V, Navon-Venezia S, Seigman-Igra Y, Cabili S, Carmeli Y. Multidrug-resistant *Pseudomonas aeruginosa*: risk factors and clinical impact. Antimicrob Agents Chemother 2006;50 43e8. doi:10.1128/AAC.50.1.43-48.2006.

[11] Li J, Li Y, Song N, Chen Y. Risk factors for carbapenem-resistant *Klebsiella pneumoniae* infection: a meta-analysis. J Glob Antimicrob Resist 2020;21:306–13. doi:10.1016/j.jgar.2019.09.006.

[12] Paño Pardo JR, Serrano Villar S, Ramos Ramos JC, Pintado V. Infections caused by carbapenemase-producing *Enterobacteriaceae*: risk factors, clinical features and prognosis. Enferm Infecc Microbiol Clin 2014;32(Suppl 4):41–8. doi:10.1016/S0213-005X(14)70173-9.

[13] Giannella M, Trecarichi EM, De Rosa FG, Del Bono V, Bassetti M, Lewis RE, et al. Risk factors for carbapenem-resistant *Klebsiella pneumoniae* bloodstream infection among rectal carriers: a prospective observational multicentre study. Clin Microbiol Infect 2014;20(12):1357–62. doi:10.1111/1469-0691.12747.

[14] Cano A, Gutiérrez-Gutiérrez B, Machuca I, Gracia-Ahufinger I, Pérez-Nadales E, Causse M, et al. Risks of infection and mortality among patients colonized with *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae*: validation of scores and proposal for management. Clin Infect Dis 2018;66(8):1204–10. doi:10.1093/cid/cix991.

[15] Fernández-Martínez NF, Cárcel-Fernández S, De la Fuente-Martos C, Ruiz-Montero R, Guzmán-Herrador BR, León-López R, et al. Risk factors for multidrug-resistant gram-negative bacteria carriage upon admission to the intensive care unit. Int J Environ Res Public Health 2022;19(3):1039. doi:10.3390/ijerph19031039.

[16] Papadimitriou-Olivgeris M, Marangos M, Fligou F, Christofidou M, Sklavou C, Vamvakopoulou S, et al. KPC-producing *Klebsiella pneumoniae* enteric colonization acquired during intensive care unit stay: the significance of risk factors for its development and its impact on mortality. Diagn Microbiol Infect Dis 2013;77(2):169–73. doi:10.1016/j.diagmicrobio.2013.06.007.

[17] Kiddee A, Assawatheptawee K, Na-Udom A, Treebupachatsakul P, Wangteeraprasert A, Walsh TR, et al. Risk factors for gastrointestinal colonization and acquisition of carbapenem-resistant gram-negative bacteria among patients in intensive care units in Thailand. Antimicrob Agents Chemother 2018;62(8):e341 –318. doi:10.1128/AAC.00341-18.

[18] Madueño A, Gonzalez Garcia J, Aguirre-Jaime A, Lecuona M. A hospital-based matched case-control study to identify risk factors for clinical infection with OXA-48-producing *Klebsiella pneumoniae* in rectal carriers. Epidemiol Infect 2017;145(12):2626–30. doi:10.1017/S095026881700142X.

[19] Demiraslan H, Cevahir F, Berk E, Metan G, Cetin M, Alp E. Is surveillance for colonization of carbapenem-resistant gram-negative bacteria important in adult bone marrow transplantation units? Am J Infect Control 2017;45(7):735–9. doi:10.1016/j.ajic.2017.01.006.

[20] Karampatakis T, Tsergouli K, Iosifidis E, Antachopoulos C, Volakli E, Karyoti A, et al. Effects of an active surveillance program and enhanced infection control measures on carbapenem-resistant gram-negative bacterial carriage and infections in pediatric intensive care. Microb Drug Resist 2019;25(9):1347–56. doi:10.1089/mdr.2019.0061.

[21] Abramowicz L, Gerard M, Martiny D, Delforge M, De Wit S, Konopnicki D. Infections due to carbapenemase-producing bacteria, clinical burden, and impact of screening strategies on outcome. Med Mal Infect 2020;50(8):658–64. doi:10.1016/j.medmal.2019.12.011.

[22] Karampatakis T, Tsergouli K, Iosifidis E, Antachopoulos C, Karapanagiotou A, Karyoti A, et al. Impact of active surveillance and infection control measures on carbapenem-resistant Gram-negative bacterial colonization and infections in intensive care. J Hosp Infect 2018;99(4):396–404. doi:10.1016/j.jhin.2018.05.010.

[23] Birgand G, Leroy C, Nerome S, Luong Nguyen LB, Lolom I, Armand-Lefevre L, et al. Costs associated with implementation of a strict policy for controlling spread of highly resistant microorganisms in France. BMJ Open 2016;6(1):e009029. doi:10.1136/bmjopen-2015-009029.

[24] Lin G, Tseng KK, Gatalo O, Martinez DA, Hinson JS, Milstone AM, et al. Cost-effectiveness of carbapenem-resistant *Enterobacteriaceae* (CRE) surveillance in Maryland. Infect Control Hosp Epidemiol 2022;43(9):1162–70. doi:10.1017/ice.2021.361.

[25] Liang Q, Chen J, Xu Y, Chen Y, Huang M. Active surveillance of carbapenem-resistant gram-negative bacteria to guide antibiotic therapy: a single-center prospective observational study. Antimicrob Resist Infect Control 2022;11(1):89. doi:10.1186/s13756-022-01103-0.

[26] Yamamoto N, Asada R, Kawahara R, Hagiya H, Akeda Y, Shanmugakani RK, et al. Prevalence of, and risk factors for, carriage of carbapenem-resistant *Enterobacteriaceae* among hospitalized patients in Japan. J Hosp Infect 2017;97(3):212–17. doi:10.1016/j.jhin.2017.07.015.

[27] Falagas ME, Rafailidis PI, Kofteridis D, Virtzili S, Chelvatzoglou FC, Papaioannou V, et al. Risk factors of carbapenem-resistant *Klebsiella pneumoniae* infections: a matched case control study. J Antimicrob Chemother 2007;60(5):1124–30. doi:10.1093/jac/dkm356.

[28] Maki DG, Stolz SM, Wheeler S, Mermel LA. Prevention of central venous catheter-related bloodstream infection by use of an antiseptic-impregnated catheter. a randomized, controlled trial. Ann Intern Med 1997;127(4):257–66. doi:10.7326/0003-4819-127-4-199708150-00001.

[29] English BK, Gaur AH. The use and abuse of antibiotics and the development of antibiotic resistance. Adv Exp Med Biol 2010;659:73–82. doi:10.1007/978-1-4419-0981-7_6.

[30] Liu P, Li X, Luo M, Xu X, Su K, Chen S, et al. Risk factors for carbapenem-resistant *Klebsiella pneumoniae* infection: a meta-analysis. Microb Drug Resist 2018;24(2):190–8. doi:10.1089/mdr.2017.0061.

[31] Candevir Ulu A, Kurtaran B, Inal AS, Kömür S, Kibar F, Yapıcı Çiçekdemir H, et al. Risk factors of carbapenem-resistant *Klebsiella pneumoniae* infection: a serious threat in ICUs. Med Sci Monit 2015;21:219–24. doi:10.12659/MSM.892516.