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ORIGINAL ARTICLE

Clinical features of patients with carbapenem nonsusceptible *Klebsiella pneumoniae* and *Escherichia coli* in intensive care units: A nationwide multicenter study in Taiwan

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KEYWORDS
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Background: Patients in intensive care units (ICUs) are especially prone to colonization and infection by carbapenem-resistant *Enterobacteriaceae*. We conducted a multicenter investigation to study the clinical and microbiological characteristics of patients with

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Intensive care unit;
Klebsiella pneumoniae

carbapenem nonsusceptible *Klebsiella pneumoniae* and *Escherichia coli* in ICUs of Taiwanese hospitals.
Methods: Patients with carbapenem nonsusceptible *K. pneumoniae* and *E. coli* in ICUs from nine medical centers and eight regional hospitals in Taiwan were enrolled in 2012. Carbapenem nonsusceptibility was defined as a minimum inhibitory concentration of at least 2 mg/L for imipenem or meropenem. Clinical characteristics and risk factors for 30-day mortality were analyzed. Isolates were screened for antibiotic susceptibility and β-lactamase genes.
Results: A total of 66 cases infected ($n = 46$) or colonized ($n = 20$) with carbapenem nonsusceptible *K. pneumoniae* ($n = 60$) and *E. coli* ($n = 6$) were identified during the study period. Nineteen isolates had genes that encoded carbapenemases (28.8%), including *Klebsiella pneumoniae* carbapenemase-2 (KPC-2) ($n = 14$), imipenemase-8 (IMP-8) ($n = 1$), Verona integron-encoded metallo-β-lactamase (VIM) ($n = 3$), and New Delhi metallo-β-lactamase-1 (NDM-1) ($n = 1$). The in-hospital mortality associated with nonsusceptible *K. pneumoniae* and *E. coli* was 50%. The 30-day mortality of the 46 patients with infection was 50%. Septic shock was the only independent risk factor for 30-day mortality in patients with infection. The 30-day mortality rate was similar between patients with combination therapy and monotherapy.
Conclusion: Patients who acquired carbapenem nonsusceptible *K. pneumoniae* and *E. coli* in ICUs have a high mortality rate. Further clinical study is needed to deal with this emerging challenge.

Introduction

Carbapenems are potent and broad-spectrum β-lactam antibiotics traditionally reserved for the treatment of the most serious bacterial infections. The increasing prevalence of extended-spectrum β-lactamase (ESBL) producing *Enterobacteriaceae* is contributing to the increased consumption of carbapenems.[1] Because of the widespread use of carbapenems over the past decade, the emergence of carbapenem-resistant *Enterobacteriaceae* (CRE) has become an important challenge.[2,3] The most common CRE reported in the literature was *Klebsiella pneumoniae*, followed by *Escherichia coli* and/or *Enterobacter* species.[4,5] The estimated mortality rate ranged from 29% to 52% in patients with CRE infections, and from 40% to 50% in bloodstream infection.[3,6]

The two main mechanisms of carbapenem resistance are acquisition of carbapenemase genes, such as Ambler class A, B, and D β-lactamases; and a decrease in the uptake of antibiotics by a qualitative or/and quantitative deficiency of porin expression in association with overexpression of β-lactamases that possess very weak affinity for carbapenems.[7] The worldwide spread of *Enterobacteriaceae* expressing carbapenemase now represents a significant threat to public health and requires immediate efforts toward early detection and infection control.[8]

In Taiwan, the rate of nonsusceptibility to ertapenem among bloodstream isolates of *K. pneumoniae* increased from 0% in 2001 to 13.6% in 2008 [Clinical and Laboratory Standards Institute (CLSI) 2010 criteria].[9] Ertapenem-nonsusceptible *K. pneumoniae* bacteremia was associated with poor outcome.[10] The rate of nonsusceptibility to ertapenem in *E. coli* isolates increased from 0.1% in 1999 to 1.7% in 2007 (CLSI 2009 criteria).[11] The proportion of CRE isolates increased significantly from 1.4% in 2003 to 4.5% in 2009 in intensive care units (ICUs), according to the Taiwan Nosocomial Infection Surveillance system.[12] Patients in ICUs are especially prone to colonization and infection by CRE, and prolonged ICU stay is a risk factor for the acquisition of CRE.[13–15] In the first outbreak of intra- and interhospital dissemination of *Klebsiella pneumoniae* carbapenemase-2 (KPC-2) producing *K. pneumoniae* in Taiwan, 87.5% of the cases occurred in ICUs.[16]

Although CRE infections constitute a real clinical problem, few studies have focused on CRE infections in the ICU setting. Therefore, we conducted a multicenter investigation of the clinical and microbiological characteristics of patients who acquired carbapenem nonsusceptible *K. pneumoniae* and *E. coli* in ICUs of Taiwanese hospitals.

Methods

Study population

From January 2012 to December 2012, 17 hospitals in Taiwan were involved in the study, including nine medical centers (the National Taiwan University Hospital, Taipei Veterans General Hospital, Tri-Service General Hospital, and Linkou Chang Gung Memorial Hospital in the north; the China Medical University Hospital in the center of the country; the Chi Mei Medical Center, Kaohsiung Chang Gung Memorial Hospital, and Kaohsiung Medical University Hospital in the south; and the Buddhist Tzu Chi General Hospital in the east), and eight regional hospitals included the Keelung Chang Gung Memorial Hospital, Taoyuan Armed Forces General Hospital, Hualien Armed Forces General Hospital, Chiayi Chang Gung Memorial Hospital, National Yang-Ming University Hospital, Taichung Armed Forces General Hospital, Kaohsiung Armed Forces General Hospital, and Kaohsiung Municipal Hsiaokang Hospital.

Bacterial isolates and antimicrobial susceptibility testing

During the study period, carbapenem nonsusceptible *K. pneumoniae* and *E. coli* isolates were collected from clinical specimens sent for culture to the microbiological laboratories of participating hospitals. A single strain was selected per patient. Carbapenem nonsusceptibility was defined as imipenem or meropenem minimum inhibitory concentration (MIC) of at least 2 mg/L. The isolates collected from each hospital were sent to the National Health Research Institutes, Miaoli, Taiwan and were stored at $-70^{\circ}C$ in 10% glycerol Luria-Bertani medium prior to analysis. A VITEK 2 automated system (bioMérieux, Marcy l'Etoile, France) was used for bacterial identification.

MICs were determined by broth microdilution (Sensititre, Trek Diagnostic Systems, Cleveland, OH, USA) for all antibiotics except tigecycline as described previously.[17] The CLSI M100-S22 interpretive breakpoints were used to interpret the MIC results for all antimicrobial agents studied, except tigecycline and colistin.[18] The susceptibility to colistin was defined based on the European Committee on Antimicrobial Susceptibility Testing (susceptible, MIC $\leq$ 2 mg/L; resistant, MIC $>$ 2 mg/L) as described previously.[19] The MICs for tigecycline were determined using the E-test (AB Biodisk, Solna, Sweden) on Mueller-Hinton media, and susceptibility to tigecycline was defined based on the Food and Drug Administration criteria (susceptible, MIC $\leq$ 2 mg/L; resistant, MIC $\geq$ 8 mg/L) as described previously.[20]

Data collection

The clinical data of patients with carbapenem nonsusceptible *K. pneumoniae* and/or *E. coli* isolated within 48 hours after admission to ICUs were retrospectively collected. Patients <20 years and those with incomplete medical records were excluded. Surveillance cultures were not performed during the study period, and all isolates were from clinical cultures. The study protocol received hospital institutional review board approval.

Infection or colonization, and the probable infectious source, were determined on the basis of microbiological results, medical record, and the judgments of two specialists in infection. Medical records were reviewed to extract pertinent information, including demographic characteristics, comorbid conditions, Charlson Comorbidity Index, duration of hospital stay, duration of therapy for infection with individual antimicrobial strains, ventilator status, and central venous catheter or Foley catheter status at the time of bacterial strains collection. The Acute Physiology and Chronic Health Evaluation (APACHE) II score was used to assess severity of illness at the time of bacterial strains collection.[21] Definitive antibiotic therapy was defined as antibiotics administered initially and continued after the results of susceptibility testing of cultures became known. Appropriate antimicrobial therapy was defined as administration of one or more antimicrobial agents to which the causative pathogen was susceptible *in vitro* after the onset of infection with an approved route and dose appropriate for end-organ function. Antimicrobial therapy that did not meet this definition was considered inappropriate. Appropriate empirical antimicrobial treatment referred to administration of *in vitro* active antimicrobials against the study isolates, within 24 hours from infection onset. Combination therapy was defined as administration of two antimicrobials with gram-negative activity for at least 48 hours after the susceptibility results became available, regardless of the *in vitro* susceptibility to each agent. The primary outcome measure was the all-cause 30-day mortality rate after the onset of infection.

Detection of genes encoding carbapenemase, AmpC β-lactamase, and ESBLs, and outer membrane protein analysis

Carbapenem nonsusceptible *K. pneumoniae* and *E. coli* isolates were screened for carbapenem-hydrolyzing ß-lactamase genes of Ambler class A (encoding *Klebsiella pneumoniae* carbapenemase-2 (KPC-2), nonmetallo-enzyme carbapenemase (NMC), imipenemhydrolyzing b-lactamase (IMI), Serratia marcescens enzyme (SME), and Guiana extended-spectrum b-lactamase (GES)), Ambler class B (encoding imipenemase (IMP), Verona integronencoded metallo-b-lactamase (VIM), New Delhi metallo-b-lactamase (NDM), German imipenemase (GIM), Sao Paulo metallo-b-lactamase (SPM), and Seoul imipenemase (SIM)), and Ambler class D encoding oxacillinase-48 (OXA-48)-type; plasmid-borne AmpC-like genes encoding CMY and DHA; and ESBL genes encoding CTX-M, TEM, and SHV using polymerase chain reaction (PCR) detection as described previously.[17] Outer membrane porins were isolated according to the rapid procedure and the profiles were identified using 12% sodium dodecyl sulfate-polyacrylamide gel electrophoresis followed by Coomassie blue staining (Gibco-BRL, Grand Island, NY, USA) as described previously.[17]

Statistical analyses

Continuous variables were compared with the Student *t* test (for normally distributed variables) or the Mann-Whitney *U* test (for non-normally distributed variables). Categorical variables were evaluated with the χ^2 or two-tailed Fisher exact test. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for all associations that emerged. Results are expressed as mean $\pm$ standard deviation or median (range; continuous variables), or as percentages of the group from which they were derived (categorical variables). Two-tailed tests were used to determine statistical significance; $p < 0.05$ was considered significant. To identify independent predictors of mortality, variables with $p < 0.1$ on univariate analysis were included in a multivariate logistic regression model. All statistical analyses were performed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

Characteristics of patients who acquired carbapenem nonsusceptible *K. pneumoniae* and *E. coli*

Carbapenem nonsusceptible *K. pneumoniae* and *E. coli* were identified in 66 patients [median age, 75 years (range,

Table 1 Clinical characteristics of 66 patients with carbapenem nonsusceptible *Klebsiella pneumoniae* and *Escherichia coli* in intensive care units

Characteristics	$n = 66$
Demographic data	
Age (y)	71.9 ± 13.7
Male sex	40 (60.6)
LOS prior to isolation, d, median, IQR	27, 15–61
Source of infection	
Colonization only	20 (30.3)
Lower respiratory tract infection	22 (33.3)
Catheter infection	7 (10.6)
Urinary tract infection	7 (10.6)
Intra-abdominal infection or biliary tract infection	6 (9.1)
Skin and soft tissue infection	2 (3.0)
Primary bacteremia	1 (1.5)
Brain abscess	1 (1.5)
Comorbidities	
Chronic kidney disease (stage ≥ 3)	36 (54.5)
Diabetes mellitus	35 (53.0)
Cerebrovascular disease	24 (36.4)
Renal dialysis	14 (21.2)
Malignancy	13 (19.7)
COPD	11 (16.7)
Immunocompromised state[a]	10 (15.2)
Liver cirrhosis	6 (9.1)
Charlson Comorbidity Index	4 ± 3
Prior healthcare exposure	
Hospitalization in the past 90 d	26 (39.4)
Surgery in the past 90 d	23 (34.8)
Prior use of antimicrobials in the past 14 d, ≥3 d	62 (93.9)
Invasive procedure in previous 2 wk	
Nasogastric tube	59 (89.4)
Indwelling urinary catheter	52 (78.8)
Indwelling central venous catheter	38 (57.6)
Renal dialysis at isolation	25 (37.9)
Mechanically ventilated at isolation	23 (34.8)
APACHE II score	27 ± 9
Outcome	
Presentation with septic shock	14 (21.2)
30-d mortality	25 (37.9)
In-hospital mortality	33 (50.0)
LOS after isolation, d	36.2 ± 36.6

[a] Immunocompromised patients included recipients of solid organ transplantation and patients with neutropenia (absolute neutrophil count < 500/mm^3), human immunodeficiency virus infection, immunosuppressant agents, and steroid therapy (prednisolone 20 mg/d, >7 days within 4 wk from isolation).
Data are presented as mean ± SD or *n* (%).
APACHE = Acute Physiology and Chronic Health Evaluation; COPD = chronic obstructive pulmonary disease; IQR = interquartile range; LOS = length of hospital stay.

37–96)] during the study period. The demographic and clinical characteristics and comorbidities of the patients are shown in Table 1. Infection was diagnosed in 46 patients and colonization was detected in the remaining 20 patients. The most commonly occurring infectious syndromes were lower respiratory tract infection ($n = 21$, 31.8%), followed by central venous catheter infection ($n = 8$, 12.1%), urinary tract infection ($n = 7$, 10.6%), and intra-abdominal infection or biliary tract infection ($n = 6$, 9.1%). The in-hospital mortality associated with isolation of nonsusceptible *K. pneumoniae* and *E. coli* was 50%. The mean length of hospital stay after isolation of these pathogens was 36.2 days.

Microbiological characteristics of carbapenem nonsusceptible *K. pneumoniae* and *E. coli* isolates

During the study period, 60 patients had carbapenem nonsusceptible *K. pneumoniae* strains isolated from one or more samples including: sputum ($n = 23$), urine ($n = 16$), central venous catheter tip ($n = 7$), blood ($n = 5$), wound ($n = 3$), bronchoalveolar lavage ($n = 2$), pleural effusion ($n = 1$), bile ($n = 1$), ascites ($n = 1$), and brain abscess ($n = 1$). Carbapenem nonsusceptible *E. coli* strains were also identified from the bile ($n = 3$), sputum ($n = 1$), wound ($n = 1$), and urine ($n = 1$) of six patients.

The most common mechanisms of carbapenem resistance were the production of AmpC-mediated β-lactamases or ESBLs plus porin mutations, which were identified in 47 cases (43 *K. pneumoniae*, 4 *E. coli*). A total of 19 (28.8%) isolates had genes that encoded carbapenemases, including *KPC-2* ($n = 14$, 13 *K. pneumoniae*, 1 *E. coli*), *IMP-8* (1 *K. pneumoniae*), *VIM-1* (3 *K. pneumoniae*), and *NDM-1* (1 *E. coli*). Meropenem or imipenem MICs were ≥8 mg/L for 45 (68.2%) isolates, 4 mg/L for seven (10.6%) isolates, and 2 mg/L for 14 (21.2%) isolates. Most isolates were susceptible to colistin ($n = 61$, 92.4%) and tigecycline ($n = 5$ 4, 81.8%); about half were moderately susceptible to gentamicin ($n = 32$, 48.5%).

Risk factors for 30-day mortality in 46 patients with infection

The 30-day mortality of 46 patients infected with carbapenem nonsusceptible *K. pneumoniae* and *E. coli* infection was 50%. Diabetes mellitus (OR 3.56, 95% CI 1.05–12.05, $p = 0.04$), presentation of septic shock (OR 28.6, 95% CI 3.28–249.73, $p = 0.002$), appropriate therapy at any time and for at least 48 hours (OR 0.10, 95% CI 0.02–0.05, $p = 0.008$), and APACHE II score (OR 1.13, 95% CI 1.03–1.23, $p = 0.009$) were associated with mortality in univariate analysis (Table 2). In multivariate analysis (adjusted for diabetes mellitus, appropriate therapy at any time and for at least 48 hours, APACHE II score, and presentation of septic shock), the only independent risk factor for 30-day mortality was presentation of septic shock (OR 12.14, 95% CI 1.13–129.91, $p = 0.04$; Table 3).

We further determined the 30-day mortality rate in patients who received antimicrobial therapy for at least 48 hours for carbapenem nonsusceptible *K. pneumoniae* and *E. coli* infection. Four cases were excluded from this analysis because death occurred within 48 hours after receiving antimicrobial therapy. Table 4 showed the detailed information of amtimicrobial therapy among the remaining 42 patients. The 30-day mortality for the 42 patients was 45.2%. Of these 42 patients, the 30-day mortality rate was

Table 2 Univariate analysis of risk factors for 30-day mortality among 46 patients infected with carbapenem nonsusceptible *Klebsiella pneumoniae* and *Escherichia coli* in intensive care units

Variable	Non-survivors $n = 23$	Survivors $n = 23$	OR (95% CI)	p
Demographic variables				
Age (y)	74.0 ± 11.8	68.3 ± 16.1		0.18
Male sex	15 (65.2)	15 (65.2)		>0.99
Indwelling central venous catheter	18 (78.3)	15 (65.2)		0.33
Indwelling urinary catheter	20 (87.0)	17 (73.9)		0.27
Nasogastric tube	22 (95.7)	21 (91.3)		0.56
Mechanically ventilated at isolation	11 (47.8)	7 (30.4)		0.23
Renal dialysis at isolation	11 (47.8)	7 (30.4)		0.23
Comorbidities				
Diabetes mellitus	16 (69.6)	9 (39.1)	3.56 (1.05—12.05)	0.04
Cerebrovascular disease	4 (17.4)	9 (39.1)		0.11
Heart failure	4 (17.4)	4 (17.4)		>0.99
Chronic kidney disease	15 (65.2)	11 (47.8)		0.24
Renal dialysis	5 (21.7)	4 (17.4)		0.71
Liver cirrhosis	3 (13.0)	2 (8.7)		0.64
Malignancy	7 (30.4)	4 (17.4)		0.31
Immunocompromised state[a]	5 (21.7)	4 (17.4)		0.71
Charlson Comorbidity Index	4.7 ± 2.9	4.6 ± 2.8		0.87
Source of infection				
Lower respiratory tract infection	12 (52.2)	10 (43.5)		0.56
Central venous catheter infection	4 (17.4)	3 (13.0)		0.68
Urinary tract infection	3 (13.0)	4 (17.4)		0.68
Intra-abdominal infection or biliary tract infection	3 (13.0)	3 (13.0)		>0.99
Skin and soft tissue infection	1 (4.3)	1 (4.3)		>0.99
Treatment				
Appropriate empirical therapy	9 (39.1)	6 (26.1)		0.35
Appropriate therapy at any time and for at least 48 h	12 (52.2)	21 (91.3)	0.10 (0.02—0.55)	0.008
APACHE II score	32.3 ± 9.4	24.5 ± 7.3	1.13 (1.03—1.23)	0.009
Presentation with septic shock	13 (56.5)	1 (4.3)	28.6 (3.28—249.73)	0.002
Isolation of *K. pneumoniae*	21 (91.3)	20 (87.0)		0.64
KPC producing isolates	6 (26.1)	2 (8.7)		0.14

[a] Immunocompromised patients included recipients of solid organ transplantation and patients with neutropenia (absolute neutrophil count < 500/mm^3), human immunodeficiency virus infection, immunosuppressant agents, and steroid therapy (prednisolone 20 mg/day, >7 days within 4 weeks from isolation).
Data are presented as mean ± SD or n (%).
APACHE = Acute Physiology and Chronic Health Evaluation; CI = confidence interval; KPC = *Klebsiella pneumoniae* carbapenemase; OR = odds ratio.

Table 3 Multivariate analysis of risk factors for 30-day mortality among 46 patients infected with nonsusceptible *Klebsiella pneumoniae* and *Escherichia coli* in intensive care units

Variable	OR (95% CI)	p
Presentation with septic shock	12.14 (1.13—129.91)	0.04
Appropriate therapy at any time and for at least 48 h	0.22 (0.03—1.65)	0.14
APACHE II score	1.06 (0.94—1.19)	0.35
Diabetes mellitus	1.09 (0.21—5.68)	0.92

APACHE = Acute Physiology and Chronic Health Evaluation; CI = confidence interval; OR = odds ratio.

similar between the combination therapy and monotherapy groups (50.0% vs. 30.4%, $p = 0.29$).

Discussion

To our knowledge, this is the first study in Taiwan to evaluate the clinical and microbiological characteristics of carbapenem nonsusceptible *K. pneumoniae* and *E. coli* in ICU settings. Infection and colonization were diagnosed in 46 cases and 20 cases, respectively. The major mechanisms of carbapenem nonsusceptibility were the production of AmpC-mediated β-lactamases or ESBLs plus outer membrane porin mutations. The 30-day mortality was 50% among patients infected with these pathogens. The presentation of septic shock was the only independent risk factor for 30-day mortality among infected patients. The

Table 4 Detailed antimicrobial therapy of 42 patients infected with carbapenem nonsusceptible *Klebsiella pneumoniae* and/or *Escherichia coli* in the intensive care units

Antimicrobial regimens	*n* (%)	Mortality, *n* (%)
Appropriate antimicrobial therapy	33 (78.6)	12 (36.3)
Combination therapy	10 (23.8)	5 (50.0)
Tigecycline + colistin	5 (11.9)	2 (40.0)
Tigecycline + amikacin	2 (4.8)	1 (50.0)
Tigecycline + colistin + amikacin	2 (4.8)	1 (50.0)
Colistin + amikacin	1 (2.4)	1 (100.0)
Monotherapy	23 (54.8)	7 (30.4)
Tigecycline	10 (23.8)	2 (20.0)
Carbapenem[a]	6 (14.3)	2 (33.3)
Colistin	3 (7.1)	1 (33.3)
Fluoroquinolone[b]	2 (4.8)	1 (50.0)
Aminoglycoside[c]	2 (4.8)	1 (50.0)
Inappropriate antimicrobial therapy	9 (21.4)	7 (77.8)

[a] Two imipenem, three meropenem, one ertapenem.
[b] One levofloxacin, one ciprofloxacin.
[c] One gentamicin, one amikacin.

30-day mortality among patients receiving appropriate antibiotic treatment for at least 48 hours was not significantly different between those treated with a combination of antibiotics and those treated with one antibiotic.

In Taiwan, factors other than carbapenemases still account for the majority of *in vitro* resistance mechanisms responsible for carbapenem nonsusceptibility in *Enterobacteriaceae*.[22] One recent nationwide surveillance study using the same database as in the current study showed that the main mechanisms of carbapenem nonsusceptibility used by *K. pneumoniae* are AmpC β-lactamase or ESBLs and loss of outer membrane porins. Carbapenemase genes were detected in 22.3% of all isolates and the majority were *KPC-2*—producing isolates (16.6%).[17] Our emphasis was on ICU settings, where we found a high prevalence of isolates carrying carbapenemase genes (28.8%). Like a prior study in Taiwan showing that dissemination of KPC-2 producing *K. pneumoniae* originated in ICUs,[16] the current study showed that the spread of *KPC-2* producing *K. pneumoniae* and *E. coli* in ICU settings remains an important issue in Taiwan.

In one prospective surveillance study of ICU patients in Israel (from 2007 to 2008), recent surgery and severity of illness [Sequential Organ Failure Assessment (SOFA) score] were the independent risk factors for carbapenem-resistant *K. pneumoniae* acquisition.[15] In another retrospective study of carbapenem resistant *K. pneumoniae* infections in the ICUs of Greece (from 2009 to 2010), mortality at 14 days was significantly associated with patient age.[23] In our study, septic shock was the only independent risk factor for 30-day mortality, suggesting that critically ill patients infected with carbapenem nonsusceptible *E. coli* or *K. pneumoniae* have poor prognosis. Thus, there might be a need for new therapeutic management in patients with septic shock.

Nonrandomized studies suggest that combination antibiotic treatment, especially including carbapenems, increases the survival of critically ill patients with severe infections caused by carbapenemase-producing *Klebsiella* spp.[24] In a recent multicenter study in the ICUs of Greece during 2009 to 2010, mortality was lower in patients receiving combination therapy than in patients receiving other treatment regimens, but the difference was not statistically significant.[23] Likewise, in our study, the 30-day mortality rate was similar between combination and single therapy groups (50.0% vs. 30.4%, $p = 0.29$). Complicated underlying severity in these critically ill patients and small number of cases for evaluation may explain why no difference is found.

One recent study conducted in a medical center in central Taiwan during 2010—2011 found that 60% of patients with ertapenem-resistant *Enterobacteriaceae* required intensive care.[25] The overall 30-day mortality rate was 40.8%. In the current study, the mortality rate was higher in patients infected with carbapenem nonsusceptible *K. pneumoniae* and *E. coli* in an ICU setting. Our overview of clinical outcomes and analysis of the risk factors for mortality suggest that specific infection control strategies for CRE, periodic targeted surveillance, and development of new effective antimicrobial drugs may be the appropriate measures for dealing with infections caused by CRE in ICU settings in the future.

The main limitation of this study is that clinical data were obtained retrospectively from medical records. The practices of physicians or accuracy of information may vary. The retrospective design and small sample size because of the limited occurrence of these infections or colonization may have underpowered the study, reducing the power of the analysis to identify risk factors and detect significant differences.

In conclusion, patients with carbapenem nonsusceptible *K. pneumoniae* and *E. coli* are associated with high mortality rates (50%) in ICU settings. Carbapenemase genes were detected in 28.8% of all isolates. Septic shock was the only independent risk factor identified for 30-day mortality. Traditional forms of therapeutic management might not be adequate to deal with this critical problem. Further large-scale well-designed randomized controlled trials of therapeutic interventions for CRE infection are needed to tackle this challenge.

Conflicts of interest

All authors declare no conflicts of interest.

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