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Mortality rate and factors associated with mortality of carbapenem-resistant Enterobacteriaceae infection

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ABSTRACT

Background: Carbapenem-resistant Enterobacteriaceae (CRE) is a serious pathogen with high mortality. Recognition of factors associated with mortality and treating these modifiable factors are crucial to reducing mortality.
Objective: To determine the 30-day mortality and factors associated with a 30-day mortality of CRE infection.
Methods: A retrospective cohort study was conducted between January 1, 2015, and December 31, 2019. All patients diagnosed with CRE infection aged ≥18 years were included. Multivariate logistic regression was used for evaluating the factors associated with 30-day mortality and presented as adjusted odds ratio (aOR) with 95% confidence interval (CI).
Result: One hundred and ninety-four patients were enrolled. The 30-day mortality occurred in 75 patients (38.7%). The common antibiotic regimen was monotherapy and combination of carbapenem, colistin, amikacin, tigecycline, and fosfomycin. CRE isolates were susceptible to tigecycline (93.8%), colistin (91.8%), fosfomycin (89.2%), and amikacin (89.2%). The independent factors associated with 30-day mortality were an increasing simplified acute physiology (SAP) II score (aOR 1.11, 95% CI 1.05-1.16, p < 0.001), sepsis at time of CRE infection diagnosis (aOR 7.93, 95% CI 2.21-28.51, p = 0.002), pneumonia (aOR 4.48, 95% CI 1.61-12.44, p = 0.004), monotherapy (aOR 4.69, 95% CI 1.71-12.85, p = 0.003), and improper empiric antibiotic (aOR 5.13, 95% CI 1.83-14.40, p = 0.002).
Conclusion: The overall 30-day mortality of CRE infection was high. The factors associated with mortality were an increasing SAP II score, sepsis at time of CRE infection diagnosis, pneumonia, monotherapy, and improper empiric antibiotic. The study suggested that proper empiric antibiotic and combination antibiotics might reduce mortality from CRE infection.

Keywords: 30-Day mortality, Carbapenem-resistant Enterobacteriaceae, Factors

Introduction

Carbapenems are broad-spectrum antibiotics and have a good potency against gram-positive and gram-negative bacteria by penetrating the cell walls of bacteria, binding with penicillin-binding proteins (PBPs), and resulting in inhibiting cell wall synthesis, ultimately killing the bacteria. They are used as antibiotics of mostly last resort for fighting drug-resistant gram-negative pathogens (1,2). Carbapenem-resistant Enterobacteriaceae (CRE) have emerged and become a major problem of nosocomial infection after extensive use of carbapenems and its spread, with the consequent change in local epidemiology continuing to evolve rapidly worldwide (3-6). Among hospitalized patients, asymptomatic gastrointestinal colonization of CRE is challenging, which oversteps and significantly increases the risk of subsequent infections caused by these pathogens. The prevalence of CRE infection was shown to be 1.3 per 10,000 hospital admissions (1).

The mechanisms of resistance to carbapenems include β-lactamase production, efflux pumps, and mutations that alter the expression and/or function of porins and PBPs.

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Certain bacteria have combinations of these mechanisms that cause high levels of resistance to carbapenems (1,2). Cefiderocol and new beta-lactam-beta-lactamase inhibitors (BLBIs), that is, ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam, have been developed to fight with CRE infection (7). The Infectious Diseases Society of America (IDSA) and the European Society of Clinical Microbiology and Infectious Diseases (ESMID) have published updated guidance on the treatment of antimicrobial-resistant gram-negative infections (2,8). The new BLBIs and cefiderocol are preferred treatment options for CRE infection. New BLBIs and cefiderocol, however, are not widely available including in our center; therefore, monotherapy or combination of colistin, fosfomycin, tigecycline, amikacin, gentamicin, and carbapenem is usually used to combat CRE infection (9,10).

The mortality rate of CRE infection is high as shown in many studies, varying from 31% to 53% (11-14). Recognition and identification of factors associated with mortality of CRE infection are important in clinical practice. Treatment of modifiable risk factors is useful for reducing the mortality of CRE infection. Previous reports demonstrated age, sepsis, shock, chronic renal failure, dialysis, neutropenia, high Acute Physiology And Chronic Health Evaluation (APACHE) scores, monotherapy, and inadequate empiric antibiotic were the factors associated with mortality (12,13,15-17). The study of the mortality rate and factors associated with mortality in CRE infection are still limited in Thailand. Hence, the study was conducted for evaluating the mortality rate and factors associated with CRE infection.

Methods

This was a retrospective cohort study that was conducted between January 1, 2015, and December 31, 2019, at Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, which is a 1,466-bed tertiary center in Northeast Thailand. The study was approved by the local Human Research Ethics Committee (approval number HE631252).

Patients and data collection

The study included patients aged ≥18 years who had been diagnosed with CRE infection by criteria from the Clinical and Laboratory Standards Institute (CLSI) 2015. In brief, CRE is defined as resistant to at least one carbapenem or producing a carbapenemase enzyme (18). The exclusion criteria were the patients who were colonized with CRE organisms without clinical signs and symptoms of infection.

The medical records of demographic data, laboratory results, microbiological and sensitivity profiles, treatment regimen, and 30-day mortality were reviewed. The simplified acute physiology (SAP) II score and sepsis at time of CRE infection diagnosis were obtained.

Definition and outcomes

The outcome was the 30-day mortality and factors associated with 30-day mortality. The 30-day mortality was death for any reason after CRE infection diagnosis within 30 calendar days. The empiric antibiotic regimen was selected depending on the gram stain of the specimen from source of infection, local data, and antibiogram of pathogens. The improper empiric antibiotic was defined as any antibiotic in the empiric treatment regimen for the pathogens that were not susceptible to antibiotic in the empiric regimen. The result of culture and drug susceptibility test was reported 72-96 hours after specimens were collected. The drug susceptibility test of microbiology was interpreted by CLSI 2015 (18). The treatment regimen was adjusted by the drug susceptibility test. The common antibiotic treatment is monotherapy or a combination of carbapenem, colistin, amikacin, tigecycline, and fosfomycin. The administration dose of these antibiotics was as follows: meropenem 1000 mg intravenous every 8 hours, imipenem-cilastatin 1000 mg intravenous every 8 hours, colistin 300 mg intravenous loading then 150 mg intravenous every 12 hours, fosfomycin 4 g intravenous every 8 hours, amikacin 750 mg intravenous every 24 hours, tigecycline 200 mg intravenous loading then 100 mg intravenous every 12 hours, sitafloxacin 100 mg oral every 12 hours, cotrimoxazole 15-20 mg of trimethoprim/kg/day intravenous divided every 8 hours. The renal dosage was adjusted where appropriate.

Statistical analyses

The categorical data were presented with numbers and percentages. The normal distributed continuous data are presented as mean and standard deviation (SD) while the non-normal distributed data were presented with median and interquartile range (IQR). A comparison of category data used the Chi-square test and Fisher's exact test depending on data. The nonparametric data used the Mann-Whitney U-test for comparison. The factors associated with 30-day mortality were evaluated by univariate logistic regression analysis. The stepwise backward multiple logistic regression analysis including factors with a p-value <0.2 on univariate analysis or factors with previous reports of clinical significance was performed. Crude odds ratio (cOR) and adjusted odds ratio (aOR) with their 95% confidence intervals (95% CI) were demonstrated. A p-value <0.05 was considered statistically significant. The statistical analysis was performed by Stata version 10.1 (StataCorp, Texas, USA).

Results

A total of 194 patients were included in the study. Of these, 110 patients (56.7%) were male. The mean age (SD) was 61.6 (16.7) years. The overall 30-day mortality occurred in 75 patients (38.7%). The most common source of infection was pneumonia (90 cases, 46.4%), intra-abdominal infection (43 cases, 22.2%), and urinary tract infection (41 cases, 21.1%). The nonsurviving patients had a significantly greater proportion of lung disease, sepsis at time of CRE infection diagnosis, and a higher SAP II score ($p < 0.05$). The nonsurviving patients had a significantly lower proportion of urinary tract infection and intra-abdominal infection ($p < 0.05$). The demographic data of patients are shown in Table I.

Table II shows the CRE pathogens and in vitro susceptibility. The most common pathogens were *Klebsiella pneumoniae*

TABLE I - Demographic data of patients

Parameters	Surviving group n = 119	Nonsurviving group n = 75	p-Value
Mean age in years (SD)	61.6 (16.0)	61.6 (17.8)	0.98
Male, n (%)	62 (52.1)	48 (64.0)	0.10
BMI (kg/m^2), mean (SD)	21.1 (4.0)	20.8 (3.5)	0.57
Comorbidity, n (%)	111 (93.3)	72 (96.0)	0.43
Diabetes mellitus, n (%)	36 (30.3)	21 (28.0)	0.74
Hypertension, n (%)	47 (39.5)	30 (40.0)	0.94
Dyslipidemia, n (%)	15 (12.6)	6 (8.0)	0.32
Neurological disease, n (%)	24 (20.2)	11 (14.7)	0.33
Cardiovascular disease, n (%)	18 (15.1)	18 (24.0)	0.12
Lung disease, n (%)	3 (2.5)	8 (10.7)	0.02
Liver disease, n (%)	11 (9.2)	12 (16.0)	0.16
Renal disease, n (%)	15 (12.6)	16 (21.3)	0.11
Malignancy, n (%)	45 (37.8)	18 (24.0)	0.05
Sepsis*, n (%)	38 (31.9)	69 (92.0)	<0.001
SAP II score*, mean (SD)	29.5 (11.6)	47.9 (13.4)	<0.001
Source of infection			
Pneumonia, n (%)	32 (26.9)	58 (77.3)	<0.001
Urinary tract infection, n (%)	36 (30.3)	5 (6.7)	<0.001
Intra-abdominal infection, n (%)	35 (29.4)	8 (10.7)	0.002
SSI, n (%)	8 (6.7)	3 (4.0)	0.43

BMI = body mass index; SAP = simplified acute physiology; SD = standard deviation; SSI = skin and soft tissue infection.
*Status at time of CRE infection diagnosis.

TABLE II - Pathogens and in vitro sensitivity

Parameters	Surviving group (n = 119)	Nonsurviving group (n = 75)	p-Value
Pathogens			
Klebsiella pneumoniae	90 (75.6)	63 (84.0)	0.16
Escherichia coli	18 (15.1)	7 (9.3)	0.24
Enterobacter spp.	8 (6.7)	4 (5.3)	0.70
Others*	3 (2.5)	1 (1.3)	0.57
In vitro sensitivity, n (% sensitive)			
Meropenem	32 (26.9)	16 (21.3)	0.38
Imipenem	24 (20.2)	15 (20.0)	0.98
Amikacin	105 (88.2)	68 (90.7)	0.60
Fosfomycin	110 (92.4)	63 (84.0)	0.07
Colistin	111 (93.3)	67 (89.3)	0.33
Tigecycline	114 (95.8)	68 (90.7)	0.15

Data were presented as n (%).
*Others: *Proteus mirabilis* (n = 1), *Citrobacter* spp. (n = 2) in surviving group, *P. mirabilis* (n = 1) in the nonsurviving group.

TABLE III - Treatment regimen of CRE infection

Regimen	Surviving group (n = 119)	Nonsurviving group (n = 75)	p-Value
Monotherapy	61 (51.3)	57 (76.0)	0.001
Meropenem/ imipenem-cilastatin	22 (18.5)	13 (17.3)	0.84
Colistin	19 (16.0)	40 (53.3)	<0.001
Fosfomycin	3 (2.5)	3 (4.0)	0.68
Amikacin	15 (12.6)	1 (1.3)	0.005
Tigecycline	0 (0.0)	2 (2.7)	0.15
Combination therapy	58 (48.7)	18 (24.0)	0.001
Fosfomycin/colistin	29 (24.4)	7 (9.3)	0.009
Fosfomycin/amikacin	7 (5.9)	1 (1.3)	0.16
Meropenem/colistin	14 (11.8)	3 (4.0)	0.06
Fosfomycin/tigecycline	1 (0.8)	1 (1.3)	1.00
Fosfomycin/meropenem	4 (3.4)	0 (0.0)	0.16
Fosfomycin/others*	2 (1.7)	0 (0.0)	0.52
Tigecycline/colistin	0 (0.0)	2 (2.7)	0.15
Tigecycline/meropenem	0 (0.0)	2 (2.7)	0.15

Data were presented as n (%)
CRE = carbapenem-resistant Enterobacteriaceae; fosfomycin/others = fosfomycin/sitafloxacin (n = 1), fosfomycin/cotrimoxazole (n = 1) in the surviving group.

(153 patients, 78.9%), *Escherichia coli* (25 patients, 12.9%), and *Enterobacter* spp. (12 patients, 6.2%). The CRE isolates were susceptible to 24.7% of meropenem, 20.1% of imipenem, 89.2% of amikacin, 91.8% of colistin, 89.2% of fosfomycin, and 93.8% of tigecycline.

Table III shows treatment regimen of CRE infection. One hundred and eighteen patients (60.8%) were treated with monotherapy and 76 patients (39.2%) were treated with combination therapy. The surviving patients had a significantly greater proportion that was treated with combination antibiotics than nonsurviving patients (p = 0.001). An improper empiric antibiotic was used in 107 patients (55.2%), 60 patients (50.4%) in the surviving group and 47 patients (62.7%) in the nonsurviving group (p = 0.09).

Table IV shows the factors associated with 30-day mortality that were analyzed by univariate and multivariate analysis. With univariate analysis, sepsis at time of CRE infection diagnosis (cOR 24.51; 95% CI 9.78-61.44; p < 0.001), increasing SAP II score (cOR 1.13; 95% CI 1.09-1.17; p < 0.001), pneumonia (cOR 9.28; 95% CI 4.72-18.22; p < 0.001), and monotherapy (cOR 3.01; 95% CI 1.59-5.71; p = 0.001) were significantly associated with 30-day mortality. With backward stepwise logistic regression analysis, sepsis at time of CRE infection diagnosis (aOR 7.93; 95% CI 2.21-28.51; p = 0.002), increasing SAP II score (aOR 1.11; 95% CI 1.05-1.16; p < 0.001), pneumonia (aOR 4.48; 95% CI 1.61-12.44; p = 0.004), monotherapy (aOR 4.69; 95% CI 1.71-12.85; p = 0.003), and improper empiric antibiotic (aOR 5.13; 95% CI 1.83-14.40; p = 0.002) were independent factors associated with 30-day mortality.

TABLE IV - Factors associated with 30-day mortality of CRE infection

Parameters	cOR (95% CI)	p-Value	aOR (95% CI)	p-Value
Age >60 years	0.76 (0.42-1.36)	0.35		
Sepsis*	24.51 (9.78-61.44)	<0.001	7.93 (2.21-28.51)	0.002
Increasing SAP II score*	1.13 (1.09-1.17)	<0.001	1.11 (1.05-1.16)	<0.001
Pneumonia	9.28 (4.72-18.22)	<0.001	4.48 (1.61-12.44)	0.004
Urinary tract infection	0.16 (0.61-0.44)	<0.001		
Monotherapy	3.01 (1.59-5.71)	0.001	4.69 (1.71-12.85)	0.003
Improper empiric antibiotic	1.65 (0.91-2.98)	0.09	5.13 (1.83-14.40)	0.002

aOR = adjusted odds ratio; cOR = crude odds ratio; CI = confidence interval; CRE = carbapenem-resistant Enterobacteriaceae; SAP = simplified acute physiology.
*Status at time of CRE infection diagnosis.

Discussion

CRE infection has been an important health problem in recent decades (19). This study revealed that the most common CRE pathogens were *K. pneumoniae* (78.9%), *E. coli* (12.9%), and *Enterobacte*r spp. (6.2%), which are similar to previous reports (12,13,16,20-22). The mortality rate of CRE infection from several studies is high, from 31% to 53% (11-14). Similar to this current study, the overall 30-day mortality was 38.7%. The optimal antibiotic regimen that is the most effective with lowest side effects is still unknown, particularly for pneumonia treatment (2,8,19,23). The recent guidelines prefer new BLBIs and cefiderocol for the treatment of CRE infection (2,8). Furthermore, a growing body of evidence demonstrated new BLBIs and cefiderocol has a lower mortality in CRE infection than treatment regimen used in this study (23-27). These antibiotics were not available during the period of this current study. The best available regimen used in this study included monotherapy and a combination of carbapenem, colistin, amikacin, tigecycline, and fosfomycin. This is the one possible explanation that might contribute to the high mortality of this study.

The study revealed that the independent factors associated with 30-day mortality were sepsis at the time of CRE infection diagnosis, increasing SAP II score, pneumonia, monotherapy, and improper empiric antibiotic. Similar to this study, de Maio Carrilho et al reported pneumonia and urinary tract infection were the most frequent source of CRE infection. The mortality rate was 34.6% and higher in pneumonia patients. This study demonstrated shock was the independent factor associated with mortality (12). A study from China by Li et al evaluated the mortality rate in bloodstream infections of CRE. This study demonstrated mortality rate was 53.1% and sepsis was the independent factor for mortality (13). Lim et al reported a high disease severity index defined as an APACHE score ≥15 had a higher mortality risk (14). Seo et al also demonstrated higher APACHE II scores were independent risk factors of mortality of CRE bacteremia (15). Papadimitriou-Olivgeris et al reported that a SAP II score upon infection onset was associated with mortality of carbapenemase-producing *K. pneumoniae* bacteremia (28). These reports suggested that a high disease severity index is associated with mortality of CRE infection, like the current study.

Daikos et al revealed that monotherapy for CRE infection was associated with mortality (16). Likewise, Lim et al revealed that a combination antibiotic therapy had lower mortality risk (14). Furthermore, several studies demonstrated combination antibiotic therapy had a good outcome for CRE infection (17,28-31). Similar to this current study, a combination antibiotic therapy was associated with lower mortality. This finding was unable to be applied to new BLBIs and cefiderocol because the aforementioned studies did not include new BLBIs and cefiderocol in the studies. This current study endorsed the ESMID guidelines that are recommended for CRE infection treatment; in case new BLBIs are not available, the combination antibiotic therapy of drugs active in vitro should be considered (8).

Tumbarello et al revealed that inadequate empiric antibiotic therapy was associated with mortality of carbapenemase-producing *Klebsiella pneumoniae* bacteremia (17). Another study by Zilberberg et al revealed that CRE infection was threefold more likely of receiving inappropriate empiric antibiotic (46.5% vs. 11.8%, $p < 0.001$), and receiving inappropriate empiric antibiotic was also associated with rising mortality (32). This result is similar to this current study; improper empiric antibiotic therapy had a high occurrence (55.2%) and was associated with mortality. Active surveillance, local data, and an antibiogram may guide a physician to decide on the proper empiric antibiotic (33-35). This might reduce the mortality of CRE infection.

This study emphasized the mortality and factors associated with mortality of CRE infection. The study had some limitations. First, this was a retrospective study, some data were missing, and the selection bias was unable to be avoided. Second, some factors were found significantly associated with mortality of CRE infection in previous studies but could not be identified in this study, this might be because this study had a relatively small sample size. Third, the temporal relationship could not be determined according to the study design.

Conclusion

The overall 30-day mortality of CRE infection was high. The factors associated with mortality were an increasing SAP II score, sepsis at time of CRE infection diagnosis, pneumonia, monotherapy, and improper empiric antibiotic. The study suggested that proper empiric antibiotic and combination antibiotics might reduce mortality from CRE infection.

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