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Original Article

A retrospective study of risk factors for carbapenem-resistant *Klebsiella pneumoniae* acquisition among ICU patients

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Abstract

Introduction: Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) is rapidly emerging as a life-threatening nosocomial infection. In this study, we aim to identify risk factors, especially antibiotic use, for CRKP infection among intensive care unit (ICU) patients.

Methodology: This was a matched case-control study of a 67-bed ICU in a tertiary care teaching hospital from 1 January 2011 through 30 June 2013. The control cases were selected among the patients with carbapenem-susceptible *Klebsiella pneumoniae* (CSKP) and were matched with CRKP cases for year of ICU admission and site of infection. The clinical outcomes and antibiotic treatments were analyzed.

Results: One hundred and thirty patients were included in the study (65 cases and 65 controls). Bivariable analysis showed that age of patients ($p = 0.044$), number of antibiotic groups ($p = 0.001$), and exposure to carbapenems ($p < 0.001$) were associated with CRKP infection. Using multivariate analysis adjusted for age, prior hospitalization, number of antibiotic groups, and previous exposure to carbapenems, previous carbapenem exposure ($p < 0.001$) was identified as an independent risk factor for CRKP infection.

Conclusions: These data suggest that exposure to carbapenems is an independent risk factor for CRKP infection. Patients with this clinical factor should be targeted for interventions to reduce the subsequent risk of infection.

Key words: antibiotics; risk factors; multidrug resistance; carbapenem; *Klebsiella pneumoniae.*

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Introduction

Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) is increasingly being reported worldwide [1-5]. These strains are difficult to control because they spread easily within and between hospitals [6], and treatment options for CRKP infections are extremely limited [7]. These resistant strains are the source of hospital-acquired infections in severely ill patients, and CRKP was independently associated with death or a longer length of stay in the unit when patients with CRKP infection were compared to those infected with CSKP or those without these strains [8,9].

Identification of risk factors for CRKP infection would facilitate the choice and the efficacy of empirical therapy [10], especially in intensive care unit (ICU) settings. The ICU has been described as a factory for creating, disseminating, and amplifying antimicrobial resistance due to its extremely vulnerable population of critically ill patients, the heavy use of invasive procedures, and the frequent application of antimicrobials [11]. Many studies have shown that ICU stay itself is an independent risk factor for CRKP isolation [8,12]. However, information regarding risk factors for CRKP infection in ICU patients is scarce and inconsistent, especially on prior use of antibiotics [9,13,14]. We thus conducted a retrospective study to identify potential risk factors for the isolation of CRKP infection in the ICU, with an emphasis on elucidating the role of antibiotics.

Methodology

Study design

This study was conducted at the Second Affiliated Hospital, Zhejiang University School of Medicine, a 2,000-bed tertiary care teaching hospital in China. Patients admitted to the ICU with CRKP infection during the period of 1 January 2011 to 30 June 2013 were identified through the microbiology laboratory database of the hospital. For each patient with CRKP infection, a matched control patient was selected from the pool of patients with CSKP infection. The appropriate control patient was identified and matched to a case for the year of ICU admission and the site of infection.

Definition of pulmonary infection included the presence of new or progressive radiographic infiltrate associated with two of the three following criteria: (1) temperature > 38.0°C; (2) leukocyte count > 10,000/μL or < 1,500/μL; and (3) purulent tracheal aspirate. In addition, a positive tracheal aspirate in quantitative cultures (≥ 10^5 cfu/mL) or a positive bronchoalveolar lavage culture (≥ 10^4 cfu/mL) was required to confirm the diagnosis. Intracranial infection, bloodstream infection, and urinary tract infection were defined according to the Centers for Disease Control and Prevention (CDC) criteria [15]. Inclusion criteria were (a) admission in the ICU for medical or surgical treatments; and (b) intubation and mechanical ventilation for > 48 hours [14]. Exclusion criteria were (a) age < 18 years old; and (b) KP isolated but recovered < 48 hours after hospital admission, or patients in an outpatient setting.

Data collection

Data collected for all study patients included demographic characteristics, prior hospitalization, severity of illness (calculated by the acute physiology and chronic health evaluation [APACHE] II score), underlying diseases and co-morbid conditions, recent (≤ 14 days) surgical procedures, length of hospital stay, admission and duration of ICU stay, previous exposure to various antibiotic agents, and duration of treatment with antibiotics. For infected patients, antibiotic use was collected up until the point of CRKP or CSKP detection. If KP was isolated from multiple cultures, only the first occurrence was included in order to preserve the independence of the risk factors.

Microbiological testing

Strain identification was performed with the VITEK system (bioMérieux, Marcy l'Etoile, France). Antimicrobial susceptibilities were determined by the VITEK system or the disk diffusion method using the Clinical Laboratory Standards Institute (CLSI) standards. CRKP was defined as such when the minimum inhibitory concentration (MIC) of meropenem or imipenem was ≥ 4 mg/L, and the MIC of ertapenem was ≥ 1 mg/L [16].

Statistical analysis

Univariate analysis was performed to search for potential risk factors. Continuous data were analyzed using the *t* test for parametric data or the Mann-Whitney *U* test for nonparametric data, and categorical variables were compared using the χ^2 test. Variables associated with CRKP infection in the univariate analysis ($p < 0.1$) were included in a stepwise multiple logistic regression model. All p values were two-tailed; a p value of less than 0.05 was considered to reveal a statistically

Table 1. Univariate analysis of risk factors associated with carbapenem-resistant *K. pneumoniae* infection during ICU hospitalization

Variable[a]	CRKP (n = 65)	CSKP (n = 65)	OR (95% CI)	P
Demographic and clinical characteristics				
Male	45 (69.2%)	50 (76.9%)	0.68 (0.31–1.47)	0.323
Age[b]	64.12 ± 13.69	59.06 ± 14.61		0.044
Prior hospitalization[b]	27 (41.5%)	18 (27.7%)	1.86 (0.89–3.87)	0.097
APACHE II score on ICU admission	17.98 ± 5.55	17.54 ± 5.42		0.644
Comorbidities				
Neurological disorders	33 (50.8%)	27 (41.5%)	1.45 (0.73–2.90)	0.291
Chronic lung disease	20 (30.8%)	23 (35.4%)	0.81 (0.39–1.69)	0.576
Heart disorders	32 (49.2%)	23 (35.4%)	1.77 (0.88–3.58)	0.110
Diabetes	12 (18.5%)	8 (12.3%)	1.61 (0.61–4.25)	0.331
Prior surgery	31 (47.7%)	39 (60.0%)	0.61 (0.30–1.22)	0.159
Chronic renal failure	8 (12.3%)	3 (4.6%)	2.90 (0.73–11.47)	0.115
Steroid therapy	3 (4.6%)	3 (4.6%)	1.00 (0.194–5.15)	1.000
Malignancy	3 (4.6%)	5 (7.7%)	0.58 (0.13–2.54)	0.465
Trauma	14 (21.5%)	22 (33.8%)	0.54 (0.25–1.17)	0.117
Outcomes				
Hospital length of stay, days	33.49 ± 26.46	30.98 ± 22.44		0.561
ICU length of stay, days	29.40 ± 25.63	22.12 ± 17.40		0.061
Mortality	31 (47.7%)	25 (38.5%)	1.46 (0.73–2.93)	0.288

CRKP: carbapenem-resistant *Klebsiella pneumonia*; CSKP: carbapenem-susceptible *Klebsiella pneumonia*; APACHE: acute physiology and chronic health evaluation; ICU: intensive care unit; [a] Data are number (%) or patients or mean ± SD; [b] Factors that were included in the multivariate analysis

significant difference. All statistical analysis was performed using SPSS version 16.0.

Results

During the study period, there were 65 patients with CRKP infection in the ICU, and an equal number for controls was selected from the ICU. All patients received mechanical ventilation and were continuously monitored with a central venous catheter, an arterial catheter, and a urinary catheter at ICU admission. The common sites of infection were endotracheal aspirate (96 cases; 73.8%), bloodstream (14 cases; 10.8%), cerebrospinal fluid (6 cases; 4.6%), urinary tract (7 cases; 5.4%), surgical site (5 cases; 3.8%), and central venous catheter (2 cases; 1.5%).

Demographic and clinical characteristics of patients with *Klebsiella pneumoniae* are shown in Table 1. Statistically significant differences between CRKP and CSKP were only observed in patient age ($p = 0.044$). Antibiotic risk factor analysis of CRKP infection is presented in Table 2. Patients with CRKP infection had received a significantly higher number of antibiotic treatments ($p = 0.001$). Analysis showed that CRKP patients were more likely to have carbapenem exposure than were CSKP patients ($p < 0.001$). Variables included in the multivariate logistic regression were age, prior hospitalization, and number of antibiotic groups and carbapenems. Previous carbapenem exposure ($p < 0.001$) was an independent risk factor for CRKP infection (Table 2). No significant difference was found both in mortality and in hospital stay between CRKP and CSKP (Table 2).

Discussion

In this study, we assessed potential risk factors for the development of CRKP infection in ICU patients. Our analysis revealed that prior use carbapenems was independently associated with CRKP infection.

Several previous studies have assessed risk factors of CRKP infections among hospitalized patients, and ICU stay was found to be an independent risk factor [8,10,12,17,18]. ICUs are considered as the main source for multidrug-resistant bacteria spread. An earlier study based on data from a Greek ICU demonstrated that 72.6% of the patients were ultimately colonized by CRKP during their ICU stay [13]. Whether or not the prior use of antibiotics is associated with CRKP infection is still controversial. Some studies found that antibiotic exposure was a risk factor for CRKP acquisition [8,12,17,18]. In contrast, other studies found that CRKP acquisition was not associated with prior antibiotic therapy [9,10,19]. These differences may be related to the high rate of antibiotic exposure during ICU stay among the total study population, making it very difficult to assess the impact of antibiotic exposure [17].

Table 2. Effect of antibiotic treatment as a risk factor for carbapenem-resistant *K. pneumoniae* acquisition: prior antibiotic exposures and the days of treatment

Prior treatment with antibiotics[a]	CRKP	CSKP	OR (95% CI)	P
Number of antibiotic groups[b]	2.69 ± 1.42	1.88 ± 1.17		0.001
Carbapenems[b]	38 (58.5%)	17 (26.2%)	3.97 (1.89–8.34)	< 0.001
Days of treatment (mean ± SD)	10.95 ± 8.74	8.65 ± 7.44		0.351
β-lactam/β-lactamase inhibitor combinations	43 (66.2%)	46 (70.8%)	0.81 (0.39–1.69)	0.571
Days of treatment (mean ± SD)	10.09 ± 12.37	6.80 ± 7.70		0.133
Cephalosporins, third and fourth generations	13 (20.0%)	12 (18.5%)	1.10 (0.46–2.64)	0.824
Days of treatment (mean ± SD)	4.92 ± 3.71	6.08 ± 7.48		0.623
Cephalosporins, second generation	10 (15.4%)	7 (10.8%)	1.51 (0.54–4.24)	0.435
Days of treatment (mean ± SD)	3.20 ± 2.20	3.71 ± 1.50		0.600
Fluoroquinolones	9 (13.8%)	5 (7.7%)	1.93 (0.61–6.11)	0.258
Days of treatment (mean ± SD)	8.56 ± 9.49	5.60 ± 2.88		0.516
Aminoglycosides	2 (3.1%)	1 (1.5%)	2.03 (0.18–22.98)	0.559
Multivariate analysis				
Carbapenems			3.97 (1.89–8.34)	< 0.001

CRKP: carbapenem-resistant *Klebsiella pneumonia*; CSKP: carbapenem-susceptible *Klebsiella pneumonia*; [a] Data are number (%) or patients or mean ± SD; [b] Factors that were included in the multivariate analysis

In accordance with previous prospective or retrospective studies, our results confirmed that prior exposure to carbapenems was an independent risk factor for CRKP infection [12,20,21]. However, in contrast with some other studies [18,20-22], we did not find that the use of cephalosporins, antipseudomonal penicillins, and fluoroquinolones was associated with increased CRKP infection; thus, the association of CRKP infection with fluoroquinolones remains controversial [8,12,17,21,22]. Our finding may be related to the high rate of exposure to β-lactam/β-lactamase inhibitor combinations during the patient's ICU stay and the scarce use of fluoroquinolones, aminoglycosides, or other antibiotics due to their side effects, pharmacological properties, administration issues, and efficacy limitations [7].

The risk associated with antibiotic exposure is probably cumulative, and there may be considerable variability in antibiotic consumption before hospitalization [23]. The relationship between prior antimicrobial use and antibiotic-resistant infection may not be linear (*i.e.*, the risk may not increase at a constant rate with increasing antimicrobial exposure) [24]. The finding of Kritsotakis *et al*. [18] that prior antibiotic exposures as continuous variables revealed dose-dependent effects of antibiotics on the risk of extended-spectrum β-lactamase (ESBL) CRKP infection, which was seen to increase with increasing duration of prior treatment with β-lactam/β-lactamase inhibitor combinations, fluoroquinolones, and carbapenems. A recent prospective study found that the duration of colistin, which is currently used as empirical treatment prior to CRKP isolation, was independently associated with increased frequency of CRKP infection ($p = 0.025$) [14]. However, we did not find this correlation, which might be related to our small sample size.

Some reports suggested that CRKP infection might be associated with adverse outcomes [6-9,13,14,20]. Especially for bloodstream infection (BSI) with CRKP, it is clear that the mortality from BSI caused by CRKP is increased compared to BSI caused by susceptible organisms [19,25,26]. In addition, finding CRKP in the bloodstream is associated with worse outcomes compared to isolation from other sites. In a case-control study, mortality was 71.9% for CRKP BSI, compared to 21.9% in patients with other sites of CRKP infection [27]. This is likely due in part to limited treatment options [7]. The mortality rate in our study was not statistically different between CRKP and CSKP patients. A plausible explanation for this might be that the number of CRKP-infected patients included in this study was relatively small. In addition, ICU mortality rate is influenced by many factors influenced, and several other factors (*i.e.*, total duration of mechanical ventilation or sedation) [14] not assessed in the present study also affect mortality. Therefore, future studies are needed to investigate the potential association between CRKP and mortality rate.

There are several potential limitations in this study. Firstly, this study was retrospective, conducted in a small center, and relied on clinical culture results, which may introduce bias in the data interpretation. Secondly, we should acknowledge that the number of patients included in this study is relatively small, although this is a common problem in most studies because the isolation of CRKP is a relatively rare phenomenon. Thirdly, co-infection with other pathogens is quite common [7]. As risk factors for multidrug-resistant organisms overlap, these pathogens are often multidrug resistant themselves [28], especially in the ICU. We did not exclude cases of polymicrobial infection, which improves the internal validity. Finally, in our analysis on antimicrobial use for a single CRKP infection episode, multiple antibiotics are often used, sequentially and/or in combination, and thus the interaction effect between antibiotics is likely cumulative and complex [18].

Conclusions

In the present study, the prior use of carbapenems was identified as an independent risk factor for the acquisition of CRKP. In this respect, antimicrobial stewardship and infection control measures are urgently needed for controlling the spread of CRKP infection in ICUs.

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Authors' contributions

YH, YP, LL and HD carried out the medical records database search, statistical analysis, and drafted the manuscript. HX, XY, and HD participated in the design and coordination of the study and helped to draft the manuscript. All authors read and approved the final manuscript

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