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Original Article

Risk factors for carbapenem-resistant *Klebsiella pneumoniae* infection and associated clinical outcomes

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Abstract: Objective: To evaluate the risk factors and clinical outcomes of carbapenem-resistant *Klebsiella pneumoniae* (*K. pneumoniae*) (CRKP) infection. Materials and Methods: A case-control study was performed from January 2017 to September 2017. The risk factors and clinical outcomes of CRKP cases (n = 91) were compared with those of the controls infected with carbapenem-susceptible *K. pneumoniae* (CSKP) (n = 91). Antibiotic susceptibility was determined using Etest while the type of bacteria was identified by Vitek 2. Results: CRKP infection was associated with prior use of carbapenems, β-lactam antibiotics, tigecycline, and hormones; complications with cerebrovascular lesions; chronic obstructive pulmonary disease; as well as prolonged hospitalization. Multivariable analysis showed that the use of carbapenem independently correlates with carbapenem resistance in the multivariable analysis. Carbapenem resistance, mechanical ventilation, tracheotomy, deep vein cannulation, indwelling urinary tract catheter, ICU treatment, and high Acute Physiology, Age, Chronic Health Evaluation II (APACHE II) scores were related to in-hospital mortality. Conclusion: CRKP is a widely spread pathogen associated with high in-hospital mortality. Minimizing the use of antimicrobials, specifically the carbapenems, may be effective to reduce CRKP infection.

Keywords: Nosocomial infections, carbapenem-resistant *Klebsiella pneumoniae* (CRKP), risk factors, clinical outcomes

Introduction

Carbapenem-resistant enterobacteriaceae (CRE) cause numerous diseases which are spreadable and sometimes untreatable. CRE infection causes high morbidity and mortality [1-3]. *Klebsiella pneumoniae* (*K. pneumoniae*) is the most common CRE in human respiratory and intestinal tracts, and a conditional pathogen implicated in nosocomial infection [4]. Data in the China Antimicrobial Surveillance Network (CHINET) showed that the resistance rate of *K. pneumoniae* to meropenem and imipenem increased to 20.9% and 24.0% (2017) from 3.0% and 2.9% (2005), respectively [5]. As a consequence of extensive use of carbapenems, carbapenem-resistant *K. pneumoniae* (CRKP) has flourished, which affected the efficiency of antibiotic treatment and prolonged the disease course. In most cases, few therapeutic options exist for eliminating infections due to resistant KPC-producing *K. pneumoniae*, which led to high mortality [6-8]. The risk factors (RF) and outcomes of CRKP infection [9-12] have been extensively investigated. The RFs may be prolonged hospitalization, invasive procedures, as well as the administration of carbapenems, quinolones, and cephalosporins. In addition, aging, diabetes, and glycopeptide antibiotics have been determined as independent RFs for CRKP infection related death. In this study, we aimed to identify the RFs and the mortality of CRKP infection based on a cohort of patients.

Materials and methods

Patients sourcing

This case-control study was carried out at the First Affiliated Hospital of Nanjing Medical University and got approval from the responsible ethics committee. The informed consent was signed by all the patients. Included were the patients whose *K. pneumoniae* culture test-

Table 1. Basic characteristics of CRKP and control groups

Basic information	CRKP group (n = 91)	Control group (n = 91)	*P* value
Age ($\bar{x}$ ± s, years old)	64.0±14	64.0 ±14	1.00
Male/Female (n/n)	68/23	68/23	1.00
Type of specimens (n)			
Sputum	80	80	1.00
Mid-stream urine	4	4	1.00
Blood	3	3	1.00
Alveolar lavage fluid (ALF)	2	2	1.00
Discharge	2	2	1.00

ed positive between January 2017 and September 2017. Each patient whose *K. pneumoniae* isolate was identified during the study period was considered an eligible subject, regardless his/her repeated positive results. The patients with CRKP were assigned into the CRKP group.

Imipenem-resistant *K. pneumoniae* isolates and/or *K. pneumoniae* isolates with meropenem minimum inhibitory concentrations (MICs) ≥2 μg/ml as determined by Vitek 2 system were screened as possible carbapenemase producers. The antimicrobial susceptibility testing was interpreted with Clinical Laboratory Standards Institute (CLSI, 2017).

Totally, 115 CRKP strains were isolated and 91 patients were enrolled. For each case, one control was selected from the patients admitted within the study period with matchable gender, age, etc. All medical records of the patients were analyzed: demographics; medical history and co-morbid conditions; institutions treating the patient before being transferred to our hospital; locations of these institutions; wards; hospital course; treatments administrated before getting infected (such as dialysis, chemotherapy, steroid administration, radiotherapy, hematopoietic stem cell transplantation, surgery, etc.); source of infection; length of stay; ICU treatment; and outcomes. The severity of condition was determined with APACHE II scores.

Recorded comorbidities included renal failure, diabetes mellitus, hypertension, cardiovascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, active cancer, trauma, and history of transplantation. Continuous antibiotic use for ≥72 h during the stay was recorded.

Statistical analysis

With SPSS 20.0 (Chicago, IL, USA) as the analytical tool, dichotomized and categorical data were examined using Fisher's exact test or chi-squared test. ANOVA or *t*-test was used for continuous variables. Bivariate analyses were performed to test the corrections between dependent and independent variables. Those indicators with significant differences (P<0.1) were included in the multivariable analysis. The crude and adjusted odds ratios were estimated using Logistic regression analysis. The association of independent variables was expressed as OR with 95% CI. Alpha = 0.05. Graphpad Prism 8 was used to plot the figures.

Results

Basic characteristics of CRKP and control groups

Both groups included 68 males and 23 females, with the average age of (64.0±14) years. There were no differences among cases and controls regarding baseline data such as age, gender, and type of specimens, which were comparable (P>0.05) (**Table 1**).

Univariate analysis

Univariable analysis (**Table 2**) showed that carbapenem-resistant *K. pneumoniae* infection was related to exposure to some antimicrobials, previous use of hormones, complications with cerebrovascular lesions or COPD, and long length of stay prior to bacterial isolation (P<0.05).

Multivariate analysis

We also screened out the independent RFs for CRKP infection using logistic multiple regression analysis. The variables with P<0.1 in the univariate analysis were further processed with the multivariate analysis. The results showed that use of β-lactam antibiotics (OR: 2.09, 95% CI: 1.38-3.15) prior to bacterial isolation was an independent RF for CRKP infection (**Table 3**).

Table 2. Univariate analysis of risk factors for CRKP infection

Risk factors	CRKP group (n = 91)	Control group (n = 91)	OR (95% CI)	*P* value
Antibiotic (used prior to bacterial isolation)				
Carbapenems	42.00	11.00	6.23 (2.94-13.24)	<0.0001
Glycopeptide antibiotics	10.00	5.00	2.12 (0.70-6.48)	0.18
β-lactam antibiotics	21.00	10.00	2.43 (1.07-5.51)	0.03
Tigecycline	10.00	2.00	5.49 (1.17-25.83)	0.02
Cephalosporins	38.00	45.00	0.73 (0.41-1.32)	0.30
Quinolones	9.00	6.00	1.56 (0.53-4.56)	0.42
Special treatment				
Hormones	12.00	4.00	3.30 (1.02-10.67)	0.04
Radiotherapy	1.00	0.00	1.01 (0.99-1.03)	0.32
Chemotherapy	2.00	5.00	0.39 (0.07-2.05)	0.25
Invasive procedures				
Mechanical ventilation	52.00	43.00	1.49 (0.83-2.67)	0.18
Tracheotomy	31.00	22.00	1.62 (0.849-3.09)	0.14
CVC	70.00	58.00	1.90 (0.99-3.63)	0.05
Surgery	52.00	58.00	0.76 (0.42-1.38)	0.36
Nasogastric intubation	45.00	38.00	1.36 (0.76-2.45)	0.30
Urinary catheterization	69.00	66.00	1.19 (0.61-2.31)	0.61
Implants	13.00	10.00	1.35 (0.56-3.26)	0.50
Dialysis	13.00	5.00	2.87 (0.98-8.41)	0.05
General information				
Mean length of hospitalization prior to bacterial isolation	19.60	11.70		<0.0001
ICU treatment	61.00	56.00	1.27 (0.69-2.33)	0.44
Mean APACHE II scores	12.60	12.40		0.23
Basic disease conditions				
Cardiovascular diseases	52.00	52.00	1.0 (0.56-1.80)	1.00
Cerebrovascular diseases	37.00	23.00	2.03 (1.08-3.81)	0.03
COPD	10.00	2.00	5.50 (1.17-25.83)	0.02
Malignant tumors	12.00	21.00	0.51 (0.23-1.10)	0.08
Renal failure	13.00	7.00	2 (0.76-5.27)	0.16
Diabetes	11.00	16.00	0.645 (0.28-1.28)	0.30
History of transplantation	3.00	0.00	1.03 (1.0-1.07)	0.08
Trauma	12.00	10.00	1.23 (0.50-3.01)	0.65

Table 3. Independent risk factors for CRKP infection

Risk factors	OR value	95% CI	*P* value
β-lactam antibiotics	2.09	1.38-3.15	<0.0001

Mortality-associated RFs in patients in the two groups

The RFs showing close association with *K. pneumoniae*-induced mortality included carbapenem resistance (OR: 2.23, 95% CI: 1.03-4.81), mechanical ventilation (OR: 5.932, 95% CI: 2.33-15.14), tracheotomy (OR: 2.504, 95% CI: 1.17-5.37), deep vein cannulation (OR: 19.17, 95% CI: 2.55-144.06), and urinary catheterization (OR: 3.204, 95% CI: 1.07-9.63). ICU treatment (OR: 2.607, 95% CI: 1.07-6.36) and high APACHE II scores were also associated with in-hospital mortality (**Table 4**, P<0.05) (**Figure 1**).

Discussion

Resistant gram-negative *K. pneumoniae* causes various disorders, such as meningitis, pneumonia, wound and blood infection [13]. *K. pneumoniae* is an opportunistic pathogen that can survive in the hospital over a long period of time, and pose on patients more pathological,

Table 4. Analysis of mortality risk factors in *K. pneumoniae* infected patients

Risk factors	Number of deaths	Number of survived patients	OR value (95% CI)	*P* value
Carbapenem resistance	23	68	2.23 (1.03-4.81)	0.039
Mechanical ventilation	29	66	5.932 (2.33-15.14)	0.0001
Tracheotomy	16	37	2.504 (1.17-5.37)	0.016
CVC	34	94	19.17 (2.55-144.06)	<0.0001
Urinary catheterization	31	104	3.204 (1.07-9.63)	0.03
ICU	28	89	2.607 (1.07-6.36)	0.031
APACHEII scores	16.65	11.48		<0.0001

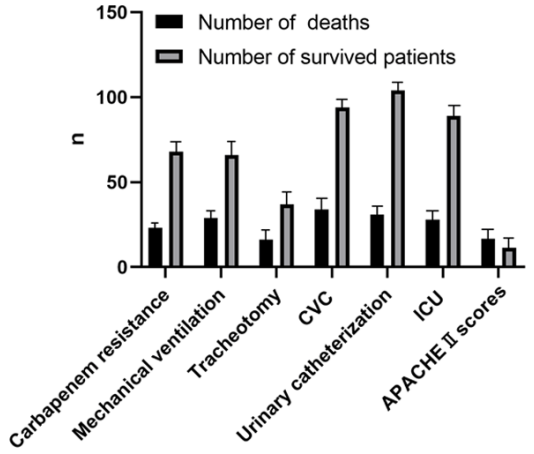

Figure 1. Analysis of mortality risk factors in *K. pneumoniae* infected patients.

psychological and economic burdens. Extended-spectrum β-lactamase (ESBL) enzymes produced by the bacteria can raise the host's resistance to antibiotic agents. ESBL-producing *K. pneumoniae* has been isolated in the hospitals around the world for years and rampant use of carbapenem increases its resistantance [14-18]. Since CRKP strain was first isolated in our hospital in 2005, many cases of CRKP infection have emerged in the ICU and other departments. Therefore, clarifying the RFs for CRKP infection has become an urgent need for such field.

In this study, we demonstrated that CRKP infection was associated with severity of illness, prolonged hospitalization, complications with cerebrovascular lesions and COPD, prior use of carbapenems, β-lactam antibiotics, tigecycline and hormones. Prior use of carbapenems is an independent RF. We also found that CRKP infection increased in-hospital mortality. The use of antibiotics showed causative association with CRKP infection. Antibiotics, such as carbapenem and β-lactamase inhibitors, were mainly administered for critically ill patients, thus increasing the patient's susceptibility to infection by multidrug-resistant organisms [19-21].

Our study showed that prior carbapenems use is an independent RF for CRKP infection, which is consistent with the results reported previously [22]. KPC-producing *K. pneumoniae* is an emerging pathogen associated with in-hospital mortality, which were usually treated with antimicrobial agents. Our research findings highlight the importance of minimizing unnecessary and inappropriate use of antimicrobial drugs, especially carbapenems. Restricting carbapenems can reduce drug selection pressure and antimicrobial resistance. Early identification of pathogens and less antibiotic therapy are crucial for preventing CRKP infection. Susceptible populations include the patients suffering from severe cerebrovascular diseases, COPD patients having a long history of hospitalizations and use of antibiotics, or those needing hormones to enhance their immune system. Antibiotic resistance, mechanical ventilation, tracheotomy, deep vein cannulation, urinary catheterization, ICU treatment, and high APACHE II scores are associated with high mortality in patients. Therefore, it is also necessary to reduce invasive procedures to avoid CRKP infection.

Our findings showed that KPC-producing *K. pneumoniae* strains were the main reason causing in-hospital infection and could raise in-hospital mortality. Early detection and effective measures should be taken to restrict the spread of carbapenemase-producing organisms.

Disclosure of conflict of interest

None.

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