THE CHARACTERISTICS, INFECTION MECHANISM AND INDEPENDENT RISK FACTORS IN PATIENTS INFECTED BY CARBAPENEM-RESISTANT ENTEROBACTERIACEAE

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ABSTRACT

Objective: *To analyse the clinical characteristics and understand the resistance mechanism of bacteria and the independent risk factors of carbapenem-resistant Enterobacteriaceae (CRE) infection in our hospital, in order to detect resistance genes of CRE.*

Methods: In total, 82 strains of CRE were isolated from our hospital; strains were identified, drug susceptibility tests were conducted, and the related drug resistance genes were determined. Another 80 strains of carbapenem-sensitive Enterobacteriaceae (CSE) were used as a control group. Analysis of the clinical characteristics of the two groups of strains, including general information of patients and the use of antibiotics, was performed. The independent risk factors of CRE strain infection were analysed by multivariate logistic regression analysis.

Results: *The resistance rates of carbapenem-resistant Enterobacteriaceae to imipenem, levofloxacin, amikacin and polymyxin B were 12.2%, 20.7%, 18.3%, and 14.6%, respectively, to ertapenem, ceftriaxone, ceftazidime, cefoxitin and cefoperazone/sulbactam were 100%, and to aztreonam, cefepime and meropenem were 93.9%, 85.4% and 82.9%, respectively. Seven kinds of resistance genes (KPC, TEM, SHV, CTX, IMP, OXA-1 and OXA-27) were positive, with a positive rate of 26.8%, 35.4%, 28.0%, 100%, 19.5%, 2.4% and 14.6%, respectively. Of these, about 62.2% (51 strains) of the strains carry more than two resistance genes. Clinical analysis showed that the carbapenem-resistant Enterobacteriaceae, hospital days, number of bed changes, nosocomial infections, invasive procedure, and catheters were independent risk factors for carbapenem resistance ($P<0.05$).*

Conclusion: *The drug resistance of Enterobacteriaceae is related to the multidrug resistance gene, which is an important cause of carbapenem-resistant Enterobacteriaceae in our hospital. The number of hospital days, number of bed changes, nosocomial infections, invasive procedures, and catheters were independent risk factors for carbapenem resistance. Therefore, relevant departments should take protective measures to reduce unnecessary invasive operations and use antibacterial drugs rationally, thereby reducing the emergence of drug-resistant strains.*

Keywords: *Enterobacteriaceae, extended-spectrum β-lactamases, multidrug resistance, carbapenem-sensitive, clinical features.*

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Introduction

Enterobacteriaceae is a Gram-negative Bacillus-free bacterium belonging to the group of aerobic and facultative anaerobic bacteria. It is widely distributed and can be parasitic, symbiotic, saprophytic or epiphytic with humans, animals and plants[1]. Most of the *Enterobacteriaceae* bacteria are normal intestinal flora, but *Salmonella* and *Shigella* are conditional pathogens[2]. They can cause disease under certain conditions, such as pneumonia, arthritis, endocarditis, osteomyelitis, and sepsis, which are common causes of nosocomial infections and community-acquired infections[3]. Carbapenem antibiotics are antibiotics with strong antibacterial activity and broad antibacterial spectrum. Their structure is similar to the penicillin ring of penicillin, which has the advantages of a stable β-lactamase and low toxicity[4-5]. Carbapenem antibiotics have become important drugs for the treatment of *Enterobacteriaceae* bacteria, producing extended-spectrum β-lactamase (ESBLs). They have good effects on systemic infections, such as those of the respiratory system, urinary system, reproductive system, abdominal cavity, pelvic cavity and skin soft tissue[6]. However, with the wide-

spread use of carbapenem antibiotics, bacteria also develop resistance to carbapenem antibioticsl for example as *Xanthomonas*, *Enterococcus faecalis*, and methicillin-resistant *Staphylococcus* have been resistant to imipenem[7]. This study was conducted to determine the resistance genes in carbapenem-resistant Enterobacteriaceae bacteria in our hospital, analysis of their clinical features and drug resistance mechanisms, and provide a scientific basis for the rational application of antibacterial drugs and the prevention and control of nosocomial infections. The results of the study are reported below.

Research specimens and experimental methods

Experimental materials and instruments

Blood plate culture medium was purchased from Beijing Huayue Biology; McConkey agar plates were purchased from Qingdao Qingyao Bioengineering Co., Ltd. and the Gram Stain Kit was purchased from Solarbio; injections of ertapenem (1.0 g), meropenem (1.0 g), ceftriaxone (0.5 g) and ceftazidime (1.5 g) were purchased from the Ouyi Pharmaceutical Company Limited. Imipenem Ceastatin Sodium for Injection (1.0 g) was purchased from Haizheng Pfizer Pharmaceutical Company Limited, Cefoxitin Sodium for Injection (2.0 g) from the Pharmaceutical General Factory of Harbin Pharmaceutical Group, Cefepime Hydrochloride for Injection (1.0 g) was purchased from the North China Pharmaceutical Hebei Huamin Pharmaceutical Company Limited, Cefoperazone/Cefoperazone for Injection in Sulbactam Sodium (1.5 g, 2:1) was purchased from Chongqing Kerui Pharmaceutical (Group) Co., Ltd, and aztreonam for injection (1.0 g) was purchased from Chongqing Shenghuaxi Pharmaceutical Co., Ltd. Amikacin sulphate for injection (0.2 g) was purchased from Chongqing Yaoyou Pharmaceutical Co., Ltd, ciprofloxacin lactate sodium chloride for injection (100 ml: 0.2 g) was purchased from Shanxi Province, Taihang Pharmaceutical Co., Ltd, Levofloxacin (100 ml: 0.2 g) was from Hunan Colon Pharmaceutical Co., Ltd, Polymyxin B for injection (freeze-dried, 500,000 units) was from Shanghai First Biochemical Pharmaceutical Co., Ltd and the PCR Kit was from Shanghai Shenggong Bioengineering Co., Ltd. Micropipettes were from Thermo, the bacteria turbidity analyser (JC-WGZ-1A) was purchased from poly environmental protection, the PCR (MiniAmp) machine was purchased from Thermo Fisher, the ultraviolet gel imaging ultraviolet analyser (E-Gel Imager) was purchased from Thermo Fisher and the automatic microbial counter (Vi-CELL XR) was purchased from Beckman Kurt.

PCR reaction primer synthesis was performed according to the related literature[8-9] (Table 1).

Gene	Sequence (3'-5')
KPC	P1 ATCTGCCGCTATGTCACTGTA
	P2 AACCCGCAGTTGCCCGTCATT
TEM	P1 CCACGGAGTGACTAATTCGT
	P2 GCGTGTAAGGGGCT
SHV	P1 ACTAGCTCGTGACCGTTGCGATT
	P2 GAACTCACTTCCGGCTATTTCCG
CTX	P1 AATGACCATGACGTGTAGCGTTT
	P2 ATACCGTGGTGGTTGCTATAGC
NDM-1	P1 GTCTCCGCAAAATACGCT
	P2 TACTCCACGCTGTCAAAG
SIM	P1 GCTACGGCTTAGGGAACAT
	P2 GTGTACCCTTGTCCGGTAAC
IMP	P1 TTTGTGCGAGACTCCGGC
	P2TATCATTTCGTTTTGACCAA
VIM	P1 GCCTGGAGGGGCTGGCCTTA
	P2 GCCCGCCAGATCTGAACGAG
GIM	P1 ATTTCGACCGTTGCGATGTTC
	P2 GGAGTTAATCGAGAACCCGAC
SPM	P1 GCGCGGGTACTTAGGTTCGTC
	P2 GCTAGTTCCAGCGCCTTTTCC
OXA-1	P1 TAGGACACGAGGAACTCGTCG
	P2CGTGGTGTGGATACAGTTACAC
OXA-2	P1 ATAAAACTCACGTGACCTTA
	P2 CTATTGCTAAAAAAGTAGTC

Table. 1: PCR primer gene sequence.

Clinical data collection for infected patients

In total, 82 CRE strains isolated from January 2018 to June 2018 in our hospital were selected as the CRE group and 80 Enterobacteriaceae (CSE) strains infected with carbapenem-sensitive Enterobacteriaceae (CSE) were selected as the control group. The data of all subjects were summarised and categorised by a unified questionnaire. The criteria for determining the types of infection were the Diagnostic Criteria for Nosocomial Infection issued by the Ministry of Health[10].

Collection and quality control of specimens

Overall, 82 clinical strains were collected from CRE patients during hospitalisation, including 35 urine samples, 25 lower respiratory tract samples, 9 blood samples, 7 pus samples, and 6 secretions.

Eighty clinical strains were collected from the CSE group during hospitalisation, including 36 urine samples, 22 lower respiratory tract samples, 8 blood samples, 7 pus samples, and 7 secretions.

All specimens in this study were collected before the use of antibiotics during the acute infection episode, and were collected immediately

prior to examination. All operations were strictly in accordance with the relevant provisions of the National Clinical Laboratory Operational Procedures. Inclusion criteria: the strains were resistant to at least one antibiotic of carbapenem drugs, including ertapenem, meropenem and imipenem. Exclusion criteria: contaminated or preservative-added specimens, previously used antibiotic specimens, not collected according to the standard specimens.

Test indicators

Drug susceptibility test: The turbidity of the strain on antibiotics was detected by turbidimetry.

Detection of drug resistance genes: The drug resistance genes of the strains were detected by PCR and the sequencing of the amplification products was performed by Huada Gene.

Clinical characteristics data: The clinical data of the two groups were collected, including: average age (years), gender (male/female), days of hospitalisation (days), number of beds replaced (times), patients with underlying diseases (case), nosocomial infection patients (case), patients who underwent surgery during hospitalisation (case), patients with invasive operation during hospitalisation (case), patients who used catheterisation during hospitalisation (case), patients admitted to the ICU (case), and the use of antibiotics, including cephalosporins, carbapenems, quinolones, and aminoglycosides. The independent risk factors of CRE strain infection were analysed by multivariate logistic regression analysis.

Statistical analysis

SPSS 22.0 software was used to analyse all of the data collected in this study. The measurement data were expressed in the form of mean ± standard deviation, and the comparison was performed by t-test. The comparison of the counting data was performed by chi-square test, and the risk factors were analysed by multivariate logistic regression analysis. $P<0.05$ indicates that the difference was statistically significant.

Results

Drug resistance analysis

The resistance rates of CRE to the carbapenems ertapenem, meropenem, and imipenem were 100%, 82.9%, and 12.2%, respectively. CRE has a high resistance rate to cephalosporin antibiotics, with a resistance rate to ceftriaxone, ceftazidime, cefoxitin, and cefoperazone/sulbactam of 100%, and a resistance rate to cefepime of 85.4%. The resistance rates of CRE to ciprofloxacin and levofloxacin were 56.1% and 20.7%, respectively, which were lower than those of broad-spectrum β-lactam antibiotics. The resistance rate to the monocyclic antibacterial drug aztreonam was 93.9%, while the resistance rate to amikacin and polymyxin B was lower: 18.3% and 14.6%, respectively (Table 2).

Category	Antibacterial drugs	Number of drug-resistant cases (%)	Number of mediation cases (%)	Number of sensitive cases (%)
Carbapenem	Ertapenem	82 (100.0)	0 (0.0)	0 (0.0)
	Meropenem	68 (82.9)	5 (6.1)	9 (11.0)
	Imipenem	10 (12.2)	24 (29.3)	48 (58.5)
Cephalosporins	Ceftriaxone	82 (100.0)	0 (0.0)	0 (0.0)
	Ceftazidime	82 (100.0)	0 (0.0)	0 (0.0)
	Cefoxitin	82 (100.0)	0 (0.0)	0 (0.0)
	Cefepime	70 (85.4)	1 (1.2)	11 (13.4)
	Cefoperazone/ sulbactam	82 (100.0)	0 (0.0)	0 (0.0)
Quinolones	Ciprofloxacin	46 (56.1)	9 (11.0)	27 (32.9)
	Levofloxacin	17 (20.7)	0 (0.0)	65 (79.3)
Monocyclic	Aztreonam	77 (93.9)	0 (0.0)	5 (6.1)
Others	Amikacin	15 (18.3)	0 (0.0)	67 (81.7)
	Polymyxin B	12 (14.6)	0 (0.0)	70 (85.4)

Table. 2: Resistance rate of 82 strains of CRE to antimicrobial agents.

Detection results of drug-resistant genes

A total of 12 β-lactam resistant genotypes were detected in this study, among which 7 drug resistance genes were positive for KPC, TEM, SHV, CTX, IMP, OXA-1, and OXA-2. According to the Ambler molecular classification, the detection results of four types of β-lactam resistance genotypes of KPC, TEM, SHV, and CTX were positive. Among them, the detection rate of CTX was the highest, and 82 strains were positive. The detection rate was 100%, followed by TEM, SHV, and KPC, with detection rates of 35.4%, 28.0%, and 26.8%, respectively. There are 6 kinds of B-type β-lactam resistant genotypes: NDM-1, SIM, IMP, VIM, GIM, and SPM. Only 16 strains indicated the presence of IMP-positive genes, with a detection rate of 19.5%. A number of OXA-1 and OXA-22 D-class β-lactam resistance genes were detected, with detection rates of 2.4% and 14.6%, respectively (Table 3).

Ambler	Drug-resistant gene	Number of positive genes (n)	Positive rate (%)
A	KPC	22	26.8
	TEM	29	35.4
	SHV	23	28.0
	CTX	82	100.0
B	NDM-1	0	0.0
	SIM	0	0.0
	IMP	16	19.5
	VIM	0	0.0
	GIM	0	0.0
	SPM	0	0.0
D	OXA-1	2	2.4
	OXA-2	12	14.6

Table. 3: Positive rate of β-lactam resistance gene.

Analysis of clinical data of patients

There was no significant difference between the CRE and CSE groups with regard to age, sex, the number of patients with underlying diseases, the number of patients who had undergone surgery during hospitalisation, and the number of patients admitted to the ICU (P>0.05). The CRE group gave significantly higher results than the CSE group for the five basic data points of days of hospitalisation, number of bed changes, number of patients with nosocomial infections, number of patients undergoing invasive operation during hospitalisation, and number of patients with urethral catheterisation during hospitalisation (P<0.05). During hospitalisation, two groups of patients used different types of antibiotics. There was no significant difference in the use of cephalosporins, quinolones and aminoglycosides between the two groups (P>0.05). However, the number of patients using carbapenems in the CRE group was significantly higher than that in the CSE group, with a difference that was statistically significant (P<0.05) (Table 4).

Clinical features	CRE (n=82)	CSE (n=80)	t/χ^2	*P*
General information:				
Average age (years)	50.67±25.18	51.24±24.41	0.146	0.884
Gender (male/female)	45/37	41/39	0.214	0.644
Days of hospitalization (days)	44.45±11.56	25.75±10.52	10.761	<0.001
Number of beds replacement (times)	1.96±0.88	0.72±0.54	10.778	<0.001
Patients with underlying diseases (case)	34	25	1.824	0.176
Nosocomial infection patients (case)	71	33	36.210	<0.001
Patients who underwent surgery during hospitalization (case)	32	22	2.420	0.120
Patients with invasive operation during hospitalization (case)	74	41	29.896	<0.001
Patients who used catheterization during hospitalization (case)	70	37	27.630	<0.001
Patients admitted to ICU (case)	28	22	0.838	0.360
Usage of antibiotics:				
Cephalosporins	60	51	1.666	0.197
Carbapenems	56	34	10.910	0.001
Quinolones	31	38	1.557	0.212
Aminoglycosides	33	22	2.933	0.087

Table. 4: Analysis of the clinical data.

Analysis of independent risk factors for CRE infection

Multivariate logistic regression analysis showed that the days of hospitalisation, number of bed changes during hospitalisation, nosocomial infection, invasive operation during hospitalisation, urethral catheters and carbapenems were independent risk factors for CRE infection (P<0.05) (Table 5).

Fctors	B	S.E.	Wald	*P*	Exp (B)	95.0% C.I. for EXP(B)	
						Lower	Upper
Days of hospitalization	0.055	0.021	6.859	0.010	1.057	1.014	1.101
Number of beds replacement	0.049	0.020	6.003	0.014	1.050	1.010	1.092
Nosocomial infection	2.311	0.551	17.591	<0.001	10.085	3.425	29.694
Invasive operation	1.806	0.558	10.475	0.001	6.086	2.039	18.168
Use of catheter	1.433	0.499	8.247	0.004	4.191	1.576	11.146
Carbapenem	1.076	0.478	5.067	0.024	2.933	1.149	7.485
Constant	1.211	0.423	8.196	0.004	3.357	1.465	7.691

Table. 5: Analysis of independent risk factors for CRE strain infection.

Discussion

The mechanisms by which bacteria develop resistance to carbapenems are as follows:

- Reduced or absent outer membrane proteins, which reduces the ability of penicillin to bind to proteins, and is commonly found in methicillin-resistant Staphylococcus[11];
- Reduced cell permeability, making carbapenem antibiotics unable to penetrate the bacterial cell membrane, which is common in Enterobacter or *Pseudomonas aeruginosa*[12];
- Enhanced bacterial efflux capacity, meaning that the drug cannot reach the effective concentration[13];
- Drug targeting site changes[14];
- The production of new extended-spectrum β-lactamase (ESBLs) that hydrolyse carbapenems[15] in bacteria. This is the main cause of drug resistance.

Ambler molecular classification divides ESBLs into four categories: A, B, C, and D, while ESBLs of Enterobacteriaceae mainly include A, B, and D[16]. Class A includes *Pseudomonas aeruginosa*-mediated GES, *Klebsiella pneumoniae*-mediated KPC, *Enterobacter cloacae*-mediated SME, and

SHV[17]. Class B mainly includes acquired metalloenzymes such as SIM, NDM-1, and IMP, mainly located on genetic components, which can cause regional spread through transfer[18]. In December 2004, the IMP-1 genotype was detected in Pseudomonas aeruginosa in Wuxi, Jiangsu[19]. Class D mainly includes OXA enzymes located on plasmids or chromosomes, which are less active in the hydrolysis of imipenem, ceftazidime, cefotaxime, and aztreonam[20]. In this study, the drug resistance of CRE in our hospital was severe, and the resistance of 82 strains to ertapenem, meropenem and imipenem was 100%, 82.9%, and 12.2%, respectively, to the resistance of the third-generation cephalosporins such as ceftriaxone, ceftazidime. Enzyme-containing cefoperazone/sulbactams were at levels of 100%, and the resistance rate of the fourth-generation cefepime reached 85.4%. The low resistance rate is reported for amikacin and polymyxin B, with a resistance rate of less than 20%, which is related to the frequent use of cephalosporin antibiotics in our hospital. The detection results of 12 drug resistance genotypes showed that the detection results of 6 kinds of β-lactam resistance genotypes in class A and class D were all positive, with a detection rate of CTX-type enzymes in class A of 100%. This means that each strain carries a CTX resistance gene; the detection rate of the B-type drug resistance gene is low, with only 16 strains detecting the IMP resistance gene. Overall, 51 strains (62.2%) carried more than two resistance genes to beta-lactamases, and 7 strains (8.5%) carried both CTX, TEM, IMP, and SHV resistance genes, showing resistance rates to all drugs which were higher. Therefore, the multidrug resistance gene is closely related to the production and severity of the CRE strain in our hospital.

The clinical data of 82 CRE patients and 80 CSE patients in our hospital showed that the number of hospital days, bed changes, nosocomial infections, invasive procedures during hospitalisation, use of catheters during hospitalisation, and use of carbapenems in the CRE group were significantly higher than those in the CSE group ($P<0.05$). Factor correlation analysis showed that CRE infection was not only closely related to the use of carbapenems, but also to independent risk factors of CRE infection, such as hospitalisation days, bed changes, hospital infection, invasive operation, and catheter use ($P<0.05$). This is also consistent with the reports of Liu[21]. The reason for this is that the longer the hospitalisation time, the more likely the patients are to make contact with pathogenic bacteria in the hospital. Furthermore, invasive manipulation destroys the patient's immune defence system while treating disease, so that external pathogenic bacteria can enter the patient's body, making them more susceptible to infection. Finally, the most serious problem is the frequent and irregular use of carbapenems, which greatly increases the rate of drug-resistant bacteria[22]. Therefore, on the one hand, we should strengthen the defence measures for nosocomial infections in our hospital, standardise the health and medical operations of medical staff, and use antibiotics rationally. On the other hand, although the efficacy of multi-drug treatment combined with antibiotics is superior to that of drugs alone, reducing the abnormal increase in drug resistance and improving the survival rate of patients, the combination of drugs can also increase the toxicity of drugs, and caution should be used when using them.

In summary, the drug resistance of *Enterobacteriaceae* is related to the multidrug resistance gene, which is an important cause of carbapenem-resistant Enterobacteriaceae in our hospital. The hospital days, numbers of bed changes, nosocomial infection, invasive procedures, and catheters were independent risk factors for carbapenems resistance. Therefore, relevant departments should take protective measures to reduce unnecessary invasive operations and use antibacterial drugs rationally, thereby reducing the emergence of drug-resistant strains.

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