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Major article

Fecal carriage of carbapenem-resistant *Enterobacteriaceae* in a Chinese university hospital

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Fecal colonization
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Risk factors

Background: Carbapenem-resistant *Enterobacteriaceae* (CRE) is widespread in China. To date, no study available has specifically determined the prevalence and risk factors of inpatients with CRE intestinal colonization in this region.
Methods: Stool samples were screened for the presence of CRE in a Chinese university hospital. A case-control study was performed to identify risk factors associated with CRE fecal colonization. Case patients were those who had CRE colonization. Control subjects had no microbiologic evidence of CRE colonization. Clinical data were obtained from the medical record.
Results: The prevalence of CRE was 6.6% (20/303 patients), of which 8 had carbapenemase-producing isolates. KPC-2, IMP-4, and NDM-1 were detected from these isolates. Hospital readmissions (odds ratio [OR], 58.067; 95% confidence interval [95% CI]: 5.517-611.134; $P = .001$), sickbed changes (OR, 45.904; 95% CI: 8.484-248.376; $P < .001$), invasive procedures (OR, 8.322; 95% CI: 1.996-34.690; $P = .004$), and vancomycin (OR, 11.552; 95% CI: 1.155-115.574; $P = .037$) were independently associated with CRE colonization.
Conclusion: This study demonstrated that asymptomatic intestinal carriage of CRE was relatively common in one region of China. Our study suggested that the implementation of effective infection control measures is urgently required to control the transmission of CRE in health care facilities in this country.

INTRODUCTION

Carbapenem-resistant *Enterobacteriaceae* (CRE) have been widespread in many locations in recent years and predominantly attributed to the production of carbapenemases.[1] These enzymes can confer high-level resistance to most β-lactam antibiotics, including cephalosporins and carbapenems. Therefore, therapeutic options are very limited for patients infected with CRE, and a higher mortality rate has been observed among patients infected with CRE in comparison with those infected by antibiotic-susceptible pathogens.[2] The spread of carbapenem-resistant pathogens is of serious concern, and controlling of these types of infections poses a great clinical challenge in hospitals.[3]

Carriage of CRE may precede infection, and carriers, particularly asymptomatic ones, may serve as an important reservoir for dissemination of resistant bacteria within the hospital settings[4] and are at relatively high risk of subsequent CRE infection. Researches conducted to date have focused on identifying the prevalence of CRE among *Enterobacteriaceae* clinical isolates in China,[5-7] and no data are available on the intestinal carriage of CRE in patients.

The aims of this study were to evaluate the prevalence of CRE intestinal colonization among hospitalized patients in a Chinese university hospital and to identify risk factors associated with CRE fecal colonization. Knowledge of risk factors associated with development of CRE fecal colonization would help identify which high-risk patients to target for the prevention of CRE spread.

MATERIALS AND METHODS

Patients and setting

The study was conducted in Fujian Medical University Union Hospital in Fuzhou, Fujian province, from November 2011 to January 2012. The Fujian Medical University Union Hospital is a

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Table 1
Clinical, epidemiologic, and genotypic characteristics of the 21 CRE

Patient	Sex (age, y)	Isolation date (month/y)	Ward	Days of hospital stay before culture/total days	Carbapemase gene*
1	M (68)	12/2011	Neurology	12/14	IMP-4
2	M (1)	1/2012	Cardiac surgery	28/37	IMP-4
3†	F (62)	1/2012	Nephrology	11/24	
4†	F (62)	1/2012	Nephrology	11/24	
5	M (56)	1/2012	Hepatobiliary surgery	1/20	
6	F (27)	1/2012	Endocrine	1/6	
7	F (7)	1/2012	Pediatrics	12/19	IMP-4
8	M (54)	1/2012	Thoracic surgery	6/10	
9	F (39)	1/2012	Neurology	1/6	
10	F (29)	1/2012	Oncology	1/5	
11	F (13)	1/2012	Otolaryngologic	1/17	
12	F (5)	1/2012	Burns	2/34	
13	M (2)	1/2012	Pediatrics	3/9	IMP-4
14	F (1)	1/2012	Hematology	2/5	
15	F (61)	1/2012	Hepatobiliary	1/3	
16	M (3)	1/2012	Burns	4/9	KPC-2
17	M (21)	2/2012	Hematology	1/1	KPC-2, NDM-1
18	M (81)	2/2012	Oncology	5/8	
19	M (78)	2/2012	Urology	2/13	KPC-2
20	M (67)	2/2012	Neurology	1/9	
21	M (66)	2/2012	Hepatobiliary	2/14	KPC-2

*Carbapenemases detected in this study were as follows: Class A carbapenemases include KPC (*Klebsiella pneumoniae* carbapenemase), IMI-2 (imipenemase non-metallo carbapenemase), SME (*Serratia marcescens* enzyme), and GES (Guiana extended-spectrum β -lactamases). Class B carbapenemases include NDM-1 (New Delhi metallo-β-lactamases), IMP (imipenem-hydrolyzing metallo-β-lactamases), VIM (Verona integron-encoded metallo-β-lactamases), SPM (Sao Paulo metallo-β-lactamases), GIM (German imipenemase), and SIM (Seoul imipenemase). And Oxacillin-hydrolyzing metallo-β-lactamases (OXA).
†The 2 strains were isolated from the same patient.

2,200-bed tertiary care university hospital with an annual admission of more than 80,000 inpatients, serving a population of more than 7 million people in southern-eastern China. During the study period, a total of 303 inpatients was randomly recruited, and informed consent was obtained from all participants.

Microbiologic methods

Each subject self-collected and submitted fecal samples. Undiluted fecal samples were cultured on Mackonkay agar plates, onto which a 10-μg ertapenem disk was then placed, as described previously.[8] The plates were incubated at 35°C for 24 hours. Ertapenem-resistant *Enterobacteriaceae* isolates were selected and identified by Gram-Negative Identification Card (GNI) of the Vitek system (bioMèrieux, Marcy l'Etoile, France). Antimicrobial susceptibility testing was determined using the agar dilution method, according to the criteria established by the Clinical and Laboratory Standards Institute.[9]

The presence of potential antimicrobial resistance genes encoding β-lactamases, including the class A carbapenemases (KPC, GES-1, SME, and IMI), metallo-β-lactamases (NDM-1, IMP, VIM, SPM, GIM, and SIM), and OXA-type carbapenemase (OXA-48) were screened by polymerase chain reaction using primers as previously described.[10,11] The relationship of the strains was studied by Enterobacterial Repetitive Intergenic Consensus Sequences PCR (ERIC-PCR) with the primers ERIC-1 and ERIC-2.[12]

Case-control study

A case-control study was performed to identify risk factors associated with CRE intestinal colonization. Epidemiologic data were collected from all patients included in the study from the inpatient medical record. The following parameters were assessed: (1) general characteristics, such as age, sex, and other background information; (2) ward to which the patient had been assigned after admission; (3) previous use of antibiotics, particularly carbapenems, extended-spectrum cephalosporin, and quinolones; and (4) potential risk factors for the occurrence and spread of CRE, for example, the length of hospitalization before CRE culture, sickbed changes, invasive interventions, and hospital readmissions.

Statistical analysis

The distribution of continuous variables was tested, and normally and non-normally distributed variables were presented as mean ± standard deviation and median (interquartile range), respectively. Categorical variables were analyzed using the χ^2 or Fisher exact test, and continuous variables were analyzed using the Student *t* test. Multivariate analysis was performed using a logistic regression model with odds ratios (ORs) and 95% confidence intervals (CIs). Potential candidate variables were those with a P value $< .05$ in univariate analysis. All tests were 2-sided, and a P value $< .05$ was deemed to indicate statistical significance. Data were analyzed using SPSS 19.0 (SPSS Inc, Chicago, IL).

RESULTS

Overall, 20 (6.6%) patients were found to be colonized with CRE, and a total of 21 CRE was collected from fecal samples in this study. The characteristics, including isolation date, specimen, and ward distribution of 21 CRE, are shown in Table 1. These isolates showed a high-level resistance to various antibiotics (Table 2).

Of these CRE isolates, 8 (2.6%) produced carbapenemases. As shown in Table 1, 4 isolates produced KPC-2, and the other 4 isolates harbored IMP-4. Of note, 1 KPC-2-positive isolate coproduced NDM-1.

The results of ERIC profiles showed that the 10 carbapenem-resistant *Escherichia coli* isolates were categorized into 7 unrelated genotypes, and 7 carbapenem-resistant *Klebsiella pneumoniae* isolates were typed into 3 different genotypes, of which 1 genotype contained 4 strains. In addition, 2 carbapenem-resistant *Klebsiella oxytoca* were not closely related. These CRE were isolated from