Original Article

The epidemiology and risk factor of carbapenem-resistant enterobacteriaceae colonization and infections: Case control study in a single institute in Japan[☆]

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ABSTRACT

Introduction: While the emergence and spread of carbapenem-resistant enterobacteriaceae (CRE) carriage and infections are serious threats to public health worldwide, its prevalence and epidemiology are still unknown.

Methods and Patients: For the purpose of examining the prevalence, patients' background and risk factors for CRE carriage and infections, we conducted this case-control study. We retrospectively reviewed all patients isolating CRE at Aichi Medical University hospital from January 2010 until March 2017. The patients isolated with carbapenem-susceptible enterobacteriaceae (CSE) were randomly selected during the study period.

Results: A total of 26 patients, isolating 28 CRE infections were enrolled in this study. The detection rate of CRE carriage and infection was 0.22% (28/12,600). Compared to the CSE group, the CRE group had poorer PS and higher CCI scores. The CRE group tended to stay longer in hospital (121 v.s. 63 days, p = 0.052) and admission fee was much more expensive than CSE group (220,710 v.s. 69,904 JPY, p < 0.001).

PS 2—4 (ECOG) and CCI≧3 (p = 0.002), prior hospitalization within 90 days (p = 0.006) and prior antibiotics use within 90 days (p = 0.005) were risk factors for acquisition of CRE by univariate analysis. The combination of PS 2—4 and CCI≧3 was an independent risk factor for CRE carriage and infection by multivariate logistic regression analysis.

Conclusion: The combination of PS 2—4 (ECOG) and CCI score≧3 was an independent risk factor of CRE carriage and infections. The CRE group tended to stay longer in hospital, and the medical expense was much more expensive than those in the CSE group.

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1. Introduction

Enterobacteriaceae, including *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter* spp., *Citrobacter* spp., *Serratia* spp., *Proteus* spp., and *Morganella* spp., are all important human pathogens [1].

These pathogens can cause a variety of severe infections such as bloodstream infection, soft tissue infections, intra-abdominal infections, respiratory tract infections, and urinary tract infections [1—3]. Recently, while the emergence and spread of carbapenem-resistant enterobacteriaceae (CRE) are serious threats to public health worldwide [4,5], the epidemiology and risk factors of CRE carriage and infections are still unknown. In Japan, criteria for CRE are established based on minimum inhibitory concentration (MIC) values, and they are not the same as those of Europe or the United States. We conducted a case-control study for identifying the risk factors of CRE carriages and infections in Japan. This is the first

report documenting the risk factors of CRE carriages and infections in Japan, as far as we had searched.

2. Patients and methods

2.1. Patients and settings

For the purpose of examining the prevalence, patients' background and risk factors for CRE, we conducted a case-control study. We retrospectively analyzed all patients isolating CRE at Aichi Medical University hospital, a 900-bed, academic medical center in Nagakute city, Aichi, Japan from January 2010 until March 2017. The patients isolating carbapenem-susceptible *Enterobacteriaceae* (CSE) were randomly selected during the study period without clinical information based on medical records' list among patients isolating CSE. The age (±2 years) and sex were matched to the patients with CRE carriage and infections, and the ratio was CRE:CSE group = 1:2. We set a ratio of 1:2 in this study for two reasons as follows. 1) concern for sufficient numbers in stratified analysis; 2) the increase in power given the expected prevalence of exposure among the controls [6].

For identifying possible risk factors for CRE carriage and infections, the following factors were evaluated by comparing CRE and CSE groups. The factors are patients' characteristics, healthcare-associated factors (prior hospitalization within 90 days, prior history of antibiotics within 90 days, receiving homecare, a nursing home stay, regular visit to any medical institute, chemotherapy, hemodialysis, and use of immunomudulators), recent events [urinary catheter, mechanical ventilation, use of vasopressor or transferring to high care unit (HCU)/intensive care unit (ICU)], clinical outcomes (treatment, in-hospital mortality), length of hospital stay, medical cost needed if patients were admitted to hospital, specimens and microbial organisms isolated. Medical costs for admission were calculated by Diagnosis Procedure combination/Per-Diem Payment System (DPC/PDPS), which is the Japanese comprehensive reimbursement care system.

2.2. Definition of CRE

The microbial organism identification and antimicrobial susceptibility profiles were determined using a MALDI Biotyper (Bruker Daitonics). CRE was defined as organisms if they met the following criteria, 1) minimum inhibitory concentrations (MIC) for meropenem $\geqq 2$ µg/mL, 2) MIC for imipenem $\geqq 2$ µg/mL and cefmetazol $\geqq 64$ µg/mL. For CRE organisms, a carbapenemase confirmation test was performed by a combined disc test (Etest MP/MPI) [SYSMEX bioMérieux]. Screening of carbapenemase was performed by a previously published PCR analysis methodology [7–9].

2.3. Performance status

General conditions were evaluated by using the Eastern Cooperative Oncology Group (ECOG) performance status (PS) [10]. (PS 0: fully active. PS 1: restricted in physically strenuous activity, can work office work or light house work. PS 2: up and about more than 50% of waking hours. PS 3: bed or chair more than 50% of waking hours. PS 4: completely disabled, PS 5: dead.) In medical practice, especially in the field of oncology, determining PS is an attempt to quantify cancer patients' general well-being and activities of daily life. This measure is used to determine whether they can receive chemotherapy, whether dose adjustment is necessary, and as a measure for the required intensity of palliative care [10].

2.4. Evaluation of comorbidities

Comorbidities were evaluated by the Charlson comorbidity index (CCI). This predicts the ten-year mortality for a patient who may have a range of comorbid conditions such as heart disease, acquired immunodeficiency syndrome (AIDS), or cancer (a total of 22 conditions). Each condition is assigned with a score of 1, 2, 3 or 6 depending on the risk of dying associated with this condition. Then, the scores are summed up and given a total score which predicts mortality. There are many variations of the CCI including the Charlson/Deyo, Charlson/Romano, Charlson/Manitoba, and Charlson/DHoores adaptations of the CCI. The clinical conditions and scores are as follows: 1 for each: myocardial infarct, congestive heart failure, peripheral vascular diseases, dementia, cerebrovascular diseases, chronic lung diseases, connective tissue diseases, ulcer and chronic liver diseases. 2 for each: hemiplegia, moderate or severe kidney diseases, diabetes with or without complications, tumor, leukemia or lymphoma. 3 for each: moderate or severe liver disease. 6 for each: malignant tumor, metastasis and AIDS. For a physician, it is helpful to decide how aggressively to treat a condition. For example, a patient may have a cancer, but also have a heart disease and diabetes which are so severe that the costs and risks of the treatment outweigh the short-term benefit from the treatment of the cancer. Since patients often do not know how severe their conditions are, the indexing nurses were originally supposed to go through the patients chart and determine whether the patient had a particular condition in order to calculate the index [11,12].

This study was approved by the Institutional Review Board of Aichi Medical University Hospital (IRB number 16-H107).

2.5. Statistical analysis

To identify risk factors for isolating CRE, the Fisher's exact or χ2 statistic test were performed using the 38 parameters among the patients. Factors showing *p*-value < 0.1, were considered candidate predictors significantly related to CRE isolation and were extracted and multivariate analysis was performed for these factors using the Logistic Regression model.

Differences were assumed to be significant if *p* < 0.05. Continuous variables with a normal distribution were compared using Student's *t*-test and the Wilcoxon rank-sum test for non-normally distributed variables. The χ2 statistic or Fisher's exact test were used to compare categorical variables. All the analyses were performed using JMP for Windows software, version 13.

3. Result

3.1. Prevalence of CRE carriage

During 1,921,595 patient-days, 12,600 enterobacteriaceae isolates were obtained and 28 CRE organisms were isolated. A total of 26 patients were enrolled in this study. The detection rate of CRE carriage and infection was 0.22% (28/12,600). The prevalence of CRE was 0.031% (4/12,600). Patients' characteristics were showed in Table 1. They were 14 males and 12 females. The median age was 77 years (range 16–99 years). Twenty-five patients (89%) had PS 2–4 (ECOG).

3.2. Factors of home care associated state

Prior hospital stay and antibiotics use within 90 days were seen in 17/26 (65%) and 20/26 (77%) of patients with CRE carriage and infection, respectively. Twenty-two of the 26 (85%) had a regular visit to a medical institute.