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Research Article

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# Clinical Significance of Stool Screening for Carbapenem-resistant Enterobacteriaceae in Hospitalized Aged Patients Transferred from other Hospitals in Japan

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**Abstract**

*Elderly patients transferred from other hospitals or nursing homes may have multiple underlying diseases and were often treated with antimicrobial agents. We aimed to detect CRE carriers by screening stool specimens from elderly patients over 65 who were transferred from other hospitals. A stool sample was collected from all the 2,201 patients aged older than 65 years old who were transferred to the Takagi hospital from other hospitals or nursing homes between July 9, 2017, and May 31, 2021. The rate of the carbapenem-resistant Enterobacteriaceae (CRE) carriers in the stool samples were 1.2%, and CRE-positive patients (n=26) had higher pulse rates and poorer performance status than CRE-negative patients (n=78). They had more extended hospital stays and more antibiotic use prior to admission. Gastrointestinal diseases were the most common cause of hospitalization. In multivariate analysis, more CRE-positive patients were hospitalized for antibiotic use and digestive diseases. In conclusion, patients with a history of antibiotic use and those hospitalized for digestive diseases are at higher risk of testing positive for CRE. CRE-positive patients were also suggested to be in poorer condition and to have a more extended hospital stay.*

**Keywords:** Carbapenem-Resistant Enterobacteriaceae/Digestive Diseases /Duration of Hospitalization/History of Antibiotic Use//Mortality/Stool Screening

## 1. Introduction

Carbapenem-resistant *Enterobacteriaceae* (CRE) are resistant to carbapenems and broad-spectrum β-lactams including meropenem [1-4]. CRE are usually defined with the drug susceptibility test as > 2 μg/mL of minimum inhibitory concentration (MIC) for meropenem and> 2 μg/mL of MIC for imipenem in addition to ≥ 64 μg/mL of MIC for cefmetazole [1, 5]. Clinically, CRE infection occurs mainly in patients with impaired infection defense, post-surgical patients, and patients with long-time medication of antimicrobial agents [1-4, 6, 7], whereas CRE might be infected in healthy individuals [1-4]. While CRE is sometimes carried asymptomatically in the intestinal tract and the other organs [8-10], CRE can be one of the causative organisms for hospital-acquired infection with several organ infections, including respiratory tract infections such as pneumonia, urinary tract infections, infections at surgical and trauma sites, catheter-related bloodstream infections, sepsis, and meningitis [1-4,6,7].

As significant problems in recent years, CRE has acquired resistance to other strains of fluoroquinolones, aminoglycosides, and other antimicrobial agents in addition to many broad-spectrum β-lactams including carbapenems, and the resistance to antibiotics causes difficulty in the treatment of CRE infections [1-3,7]. *Enterobacteriaceae*, including CRE, are originally intestinal commensals, which means that CRE stays and persists in the human gastrointestinal tract for a long period [1-4]. Currently, in Japan, CRE is estimated to account for around 0.3% of all Enterobacteriaceae [1, 3], whereas a worldwide increase in the number of CRE-infected individuals might cause significant exacerbation in morbidity and mortality [2, 11-13].

Carbapenems are broad-spectrum antimicrobial agents with antibacterial activities for almost all gram-negative, gram-positive, and anaerobic bacteria [2,14]. The increase in CRE is estimated to be caused by the rapid increase in the clinical use of carbapenems

in addition to inadequate sanitation and infection control in medical institutions on a global scale, including Japan [1-3, 15].

The elderly patient, transferred to the Takagi hospital from the other hospital or the nursing home, has several underlying medical conditions and is sometimes treated with an antimicrobial agent. The present study aims to find the CRE carrier in all the transferred patients, aged over 65 years old, from the other institute with a stool sample screening. In addition, the patient characteristics of the CRE carrier were evaluated with a case-control study.

## 2. Materials and Methods

### 2.1. Assessment of stool sample

A stool sample was collected from all the 2,201 patients aged older than 65 years old who were transferred to the Takagi hospital from other hospitals or nursing homes between July 9, 2017, and May 31, 2021. The stool was sampled within 48 hours from the stool or the rectum with the rectal swab for screening of CRE. The stool sample was cultured in the CHROMagar mSuper CARBA media (Kanto Chemical Co. Inc., Tokyo) [16, 17]. Antibiotic-resistant bacteria from the single colony on the agar culture media containing carbapenem were transferred to a tube containing water and were suspended. The precipitate was made by mixing ethanol with formic acid and acetonitrile. After centrifugation at 13,000 rpm, for 2 min, obtained supernatant was used for Mas spectrometry analysis using MALDI Biotyper (Bruker Daltonik GmbH). CRE was identified using software in MALDI Biotyper [18]. IMP-type metallo-β-lactamase was detected by immunochromatography [19], and the carbapenem resistance was evaluated using MicroScan (Beckman Coulter, Tokyo) according to the guideline by Clinical and Laboratory Standard Institute [18, 20].

### 2.2 Analysis of CRE-positive and -negative patients

CRE-positive patients were compared to those with CRE-negative in the stool samples who transferred to the Takagi hospital on the same day or the close day. The controls selected three patients for each positive case. The patient characteristics were reviewed in the medical records of the patient chart. The factors collected from the medical records were as follows; age, gender, weight, height, body mass index, blood pressure, pulse, smoking and drinking history, duration of hospitalization, mortality and cause of death, transfer source, use of antibiotics before the hospitalization to the Takagi hospital, major diseases leading to the hospitalization, comorbidities, and blood test at the hospitalization. The required nursing care level was elevated from level 0 to level 5 in concomitant with an increase in the care requirement [21]. The general condition of the patients was evaluated by Eastern Cooperative Oncology Group Performance Status at admission [22] as follows; status 0: fully active, able to carry on all pre-disease performance without restriction; status 1: restricted in physically strenuous activity but ambulatory and able to carry out work of a light sedentary nature like light housework and office work, status 2: ambulatory and capable of all self-care but unable to carry out any work activities up and about more than 50% of waking hours, status 3: capable of only limited self-care confined to bed or chair more than 50% of waking hours, status 4: wholly disabled and not able to carry on any self-care confined to bed and chair. The Declaration of Helsinki conducted the present study, and the protocol was approved by the Kouhou-kai ethical committee (# KR007) and the International University of Health and Welfare ethical committee (#21-Ifh-046). Informed consent must have been obtained. Please include a statement confirming that informed consent was obtained from all subjects.

## 3. Statistics

The data in case and control groups were compared using Chi-squared or Fisher's exact test for categorical variables and Student-t test for continuous variables. Multivariable logistic regression analysis was performed using the explanatory variables with significance levels ($P < 0.05$ on the two group comparison tests). The odds ratio (OR) and 95% confidence interval (CI) were estimated and shown in the tables. Statistical significance was defined as $P < 0.05$. JMP Pro 16.1.0 (SAS Institute Inc., Cary, NC, USA) was used for all analyses.

## 4. Results

The number of the CRE positive-patients detected in the stool sample was 26 out of 2,201 (1.2%). The characteristics of the CRE-positive patients (cases) compared to the controls are indicated in Table 1. The cases' pulse rate was faster than the controls ($P = 0.03$), and the performance status was significantly worse in the cases ($P = 0.02$). The duration of the hospitalization days was longer in the cases ($P = 0.01$), and the percentage of the patients who were treated with antibiotics agents before the hospitalization in the Takagi hospital was significantly higher in the cases compared to the controls (69.2% vs. 26.9%, $P < 0.01$). The other factors were not different between the cases and the controls.

| | Cases | Controls | *P* value |
|---|---|---|---|
| Number (males/females) | 26 (14/12) | 78 (32/46) | 0.26 |
| Age (year) | 80.5 ± 13.6 | 83.4 ± 11.1 | 0.28 |
| Body mass index (kg/m$^2$) | 18.5 ± 5.6 | 19.8 ± 4.3 | 0.21 |
| Smoking (+/-/unknown) | 3/20/3 | 7/61/10 | 0.92 |
| Alcohol (+/-/unknown) | 2/21/3 | 9/56/13 | 0.66 |
| Systolic blood pressure (mmHg) | 119 ± 20 | 126 ± 21 | 0.16 |
| Diastolic blood pressure (mmHg) | 66 ± 12 | 67 ± 14 | 0.56 |

| | | | |
|---|---|---|---|
| Pulse (/min) | 88 ± 22 | 79 ± 16 | 0.03* |
| Performance status (0~2/3~4) | 2/24 | 24/54 | 0.02* |
| Nursing care level (1/2/3/4/5/ unknown) | 3/1/3/8/4/7 | 11/15/11/12/13/16 | 0.31 |
| Duration of hospitalization (days) | 97.2 ± 181.7 | 39.4 ± 45.0 | 0.01* |
| Mortality during the hospitalization | 7/26 (26.9%) | 11/78(14.1%) | 0.15 |
| Transfer sources | | | 0.24 |
| From the other hospitals | 11/26 (42.3%) | 23/78 (29.5%) | |
| From the nursing homes | 15 /26(57.7%) | 55/78 (70.5%) | |
| Use of antibiotics agents before the hospitalization to the Takagi hospital | | | |
| | 18/26 (69.2%) | 21/78 (26.9%) | < 0.01* |

Data are mean ± SD.* = significant difference ($P < 0.05$).

**Table 1: The patients-characteristics of the cases (positive of carbapenem-resistant *Enterobacteriaceae*) and the controls (negative of carbapenem-resistant *Enterobacteriaceae*).**

As indicated in Table 2, there was no difference between the cases and the controls regarding the major diseases leading to hospitalization at the Takagi hospital, except for the digestive disease, which was higher in the cases compared to the controls (P < 0.02).

The comorbidities, including malignant and infectious diseases, indicated in Table 3 and the blood test results in Table 4 were not different between the two groups.

| | **Cases (n = 26)** | **Controls (n = 78)** | ***P* value** |
|---|---|---|---|
| Main diseases leading to the hospitalization | | | |
| | Total: 26 | Total: 78 | |
| Malignant diseases | 0 | 5 | 0.33 |
| Infectious diseases | 15 | 36 | 0.31 |
| Other diseases | 11 | 37 | 0.65 |
| Respiratory | 0 | 2 | N.A. |
| Cardiovascular | 0 | 4 | 0.57 |
| Digestive | 5 | 3 | 0.02* |
| Cerebral and neurological | 3 | 9 | N.A. |
| Endocrine and metabolic | 1 | 0 | 0.25 |
| Diabetes mellitus | 0 | 1 | N.A. |
| Kidney | 0 | 2 | N.A. |
| Blood | 0 | 1 | N.A. |
| Collagen | 0 | 1 | N.A. |
| Orthopedic | 2 | 13 | 0.35 |
| Mental | 0 | 1 | N.A. |

N.A.: not available. * = significant difference ($P < 0.05$).

**Table 2: The diseases leading to the Takagi hospital admission in the cases (positive of carbapenem-resistant *Enterobacteriaceae*) and the controls (negative of carbapenem-resistant *Enterobacteriaceae*).**

| | **Cases (n = 26)** | **Controls (n =78)** | ***P* value** |
|---|---|---|---|
| Comorbidities (cumulative total number) | | | |
| | Total: 65 | Total: 199 | |
| Malignant diseases | 3 | 7 | 0.71 |
| Infectious diseases | 1 | 2 | 0.57 |
| Other disease | 61 | 190 | 0.53 |
| Cardiovascular | 16 | 51 | 0.87 |

| | | | |
|---|---|---|---|
| Cerebral and neurological | 15 | 33 | 0.24 |
| Dementia | 9 | 36 | 0.43 |
| Orthopedic | 5 | 19 | 0.43 |
| Others | 16 | 51 | 0.87 |

N.A.: not available. * = significant difference ($P < 0.05$).

**Table 3: The comorbidity in the cases (positive of carbapenem-resistant *Enterobacteriaceae*) and the controls (negative of carbapenem-resistant *Enterobacteriaceae*).**

| | Cases | Controls | *P* value |
|---|---|---|---|
| Total protein (g/dL) | 6.5 ± 6.5 | 6.7 ± 6.8 | 0.37 |
| Albumin (g/dL) | 3.0 ± 0.60 | 3.2 ± 0.6 | 0.15 |
| White blood cells (μL) | 8848 ± 3793 | 9727 ± 5261 | 0.44 |
| Hemoglobin (g/dL) | 11.1 ± 2.2 | 12.6 ± 10.8 | 0.49 |
| Platelets (μL) | 22.5 ± 8.8 | 22.8 ± 10.6 | 0.89 |
| Aspartate aminotransferase (IU/L) | 41.0 ± 58.9 | 39.3 ± 52.7 | 0.90 |
| Alanine aminotransferase (IU/L) | 34.4 ± 59.7 | 32.3 ± 58.7 | 0.88 |
| Lactate dehydrogenase (IU/l) | 216 ± 85 | 241 ± 84 | 0.22 |
| Blood urea nitrogen (mg/dL) | 20.4 ± 11.5 | 24.0 ± 17.5 | 0.33 |
| Creatinine (mg/dL) | 0.71 ± 0.33 | 1.13 ± 1.50 | 0.18 |
| Estimated glomerular filtration rate (mL/min) | 96.0 ± 107.6 | 68.0 ± 39.4 | 0.06 |
| Total cholesterol (mg/dL) | 154.6 ± 48.4 | 151.0 ± 39.1 | 0.73 |
| Triglycerides (mg/dL) | 104.0 ± 88.7 | 97.1 ± 50.2 | 0.73 |
| Glucose (mg/dL) | 157.2 ± 86.2 | 144.0 ± 58.1 | 0.42 |
| Hemoglobin A1c | 5.8% ± 0.4% | 6.2% ± 0.9% | 0.28 |
| C-reactive protein (mg/dL) | 4.6 ± 4.3 | 6.1 ± 7.6 | 0.38 |

Data are mean ± SD.

**Table 4: The results of the blood test at the hospitalization in the cases (positive of carbapenem-resistant *Enterobacteriaceae*) and the controls (negative of carbapenem-resistant *Enterobacteriaceae*).**

Table 5 demonstrates the results of the multivariate analysis among the factors with a significant difference from the univariate analysis. The multivariate analysis indicated that two factors (the use of antibiotics before the hospitalization to the Takagi hospital and the central hospitalized disease of digestive disease) were the risks for CRE-positive in the stool. The CRE infection was not detected among the CRE carriers as ER was not detected from the carriers' blood, sputum, and urine.

| | OR (95% CI) | *P* value |
|---|---|---|
| cases vs controls | | |
| Pulse (/min) | 1.03 (0.99-1.06) | 0.11 |
| Performance status (0~2/~4) | 3.60 (0.70-18.61) | 0.13 |
| Duration of hospitalization (/10 days) | 1.05 (0.97-1.14) | 0.25 |
| Use of antibiotics agents before the hospitalization to the Takagi hospital | 6.56 (2.08-20.91) | < 0.01* |
| Commodities of digestive diseases | 10.39 (1.68-64.4) | 0.01* |

Analyzed factors: *P* values less than 0.05 in univariate analysis. * = statistical significance. OR: odds ratio. 95% CI: 95% confidence interval.

**Table 5: Multivariate analysis compared the cases (positive of carbapenem-resistant *Enterobacteriaceae*) and the controls (negative of carbapenem-resistant *Enterobacteriaceae*).**

The mortality rate and the diseases which induced the mortality are shown in Table 6. The mortality rate tended to increase in the CRE-positive cases (26.9%) compared to the controls (14.1%), but not significant ($P = 0.15$). The rate of patients who died caused of infectious diseases tended to be higher in the CRE-positive cases (85.7%) than in the controls (54.5%), but not significant. The central infectious disease which caused the mortality was pneumonia.

| | Cases | Controls | *P* value |
|---|---|---|---|
| Number of patients died during the hospitalization | | | |
| | 7/26 (26.9%) | 11/78 (14.1%) | 0.15 |
| Diseases that caused mortality during the hospitalization | | | |
| Malignant diseases | 0 | 2 (18.2%) | 0.50 |
| Lung cancer | 0 | 2 (18.2%) | 0.50 |
| Infection diseases | 6 (85.7%) | 6 (54.5%) | 0.32 |
| Pneumonia | 5 (71.4%) | 4 (36.3%) | 0.33 |
| Sepsis | 1 (14.3%) | 2 (18.2%) | N.A. |
| Benign diseases | 1 (14.3%) | 3 (27.3%) | N.A. |
| Heart failure | 0 (0%) | 1 (9.1%) | N.A. |
| Senility | 1 (14.3%) | 2 (18.2%) | N.A. |
| Culture positive of carbapenem-resistant *Enterobacteriaceae* | | | |
| Blood | 0/26 | | |
| Sputum | 0/26 | | |
| Urine | 0/26 | | |

N.A.: not available.

**Table 6: The diseases which caused mortality of the cases (positive of carbapenem-resistant *Enterobacteriaceae*) and the controls (negative of carbapenem-resistant *Enterobacteriaceae*).**

## 5. Discussion

The present study indicated, i) the rate of CRE-positive in the stool samples in the patients aged more than 65 years old who transferred from the other hospitals or the nursing homes to the Takagi hospital was 1.2% (26 patients out of 2,201); ii) the CRE infection was not diagnosed among the CRE-positive patients, and iii) the risk factors for the CRE-positive were the use of antibiotics before hospitalization to the Takagi hospital and the digestive diseases.

In the present study, the rate of stool CRE-positive in the patients aged 65 years or older transferred to our hospital from other hospitals or nursing homes was 1.2% (26 of 2,201 cases), while the CRE-positive rate in the Japan Nosocomial Infection Surveillance, nationwide survey program of the Ministry of Health, Labor and Welfare, was as high as 0.3%, which was also observed in this study. However, Yamamoto et al. reported CRE positivity in 12.2% of patients with fecal/urinary incontinence or tube feeding/urethral catheterization in 22 acute-care hospitals and 21 convalescent hospitals in northern Osaka Prefecture [23]. In this study, CRE positivity was more frequently found in patients with poor performance status in univariate analysis, and many of these patients were also in poor condition at the time of transfer and had a more extended hospital stay. Therefore, it is possible that this study's positivity rate was higher because it was conducted in a regional core hospital with patients aged 65 years or older who were transferred to the hospital. On the other hand, none of the 26 CRE-positive patients in this study had CRE detected in specimens other than stool, and no CRE infection developed; a systematic review by Tischendorf et al. reported a 16.5% risk of developing infection among CRE-positive patients [24]. Differences may have influenced these discrepancies in results in follow-up time and the general condition of the patients studied.

Of note in this study is that antibiotic use and gastrointestinal disease prior to admission to our hospital were risk factors for CRE-positive patients. Yamamoto et al. reported that long-term hospitalization, tube feeding, and antimicrobial exposure were risk factors for CRE positivity [23]. Asai et al. reported that poor general condition (ECOG PS2-4) and frequent complications were risk factors for CRE positivity [25]. The present study found CRE-positive patients among those hospitalized for gastrointestinal diseases. It is possible that Enterobacter and Klebsiella, typical CRE-associated bacteria, are endemic in the intestinal tract and that the balance of intestinal microbiota is abnormal and resistance is easily acquired in gastrointestinal diseases [26, 27]. Further studies are still needed in this regard.

In the present study, deaths among CRE-positive patients were 7 of 26 (26.9%) and 11 of 78 (14.1%) among CRE-negative patients, and although there was no statistically significant difference, a relatively high rate of death was observed in CRE-positive patients. Deaths due to infection were 85.7% (6/7) in CRE-positive

patients (5 cases of pneumonia and 1 case of sepsis) and 54.5% (6/11) in CRE-negative patients, with a relatively higher rate in CRE-positive patients (p=0.32), although there was no statistically significant difference. None of the patients had CRE detected in blood, sputum, or urine cultures, but the lack of improvement with antibiotic treatment suggests that CRE may have been involved, although it was not detected.

The present study has several limitations. First, the present study is a single-center and retrospective study, and our results should be assessed by further clinical prospective trial. Second, because data were collected from medical records, and not all cases were collected entirely, we could not exclude bias. Third, since we did not have complete medical information prior to admission to our hospital, we were unable to fully analyze the impact of the patient's underlying medical condition and treatment status.

## 6. Conclusions

The CRE-positive rate is high among elderly patients transferred from hospitals, especially those with a history of antibiotic use and those hospitalized for gastrointestinal diseases, suggesting the importance of measures to prevent nosocomial infections.

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**Conflict of Interest:** All authors declare no conflicts of interests.

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