ABSTRACT

Carbapenemase-producing Enterobacteriaceae (CPE) is an important and increasing threat to global health. From July to September 2017, 20 inpatients at a tertiary care hospital in Korea were either colonized or infected with carbapenem-resistant Escherichia coli strains. All of the E. coli isolates co-produced blaNDM-5 and blaOXA-181 carbapenemase genes and shared ≥88% clonal relatedness on the basis of a cladistic calculation of the distribution of pulsed-field gel electrophoresis patterns. Rapid detection of CPE is one of the most important factors to prevent CPE dissemination because it takes long time for CPE to become negative.

Keywords: New Delhi metallo-enzyme carbapenemase; Oxacillin-hydrolyzing beta-lactamase; Escherichia coli; Carbapenemase-producing Enterobacteriaceae; Outbreak control

Carbapenemase-producing Enterobacteriaceae (CPE) is an important and increasing threat to global health. The most clinically significant carbapenemase genes include the following types: blaKPC, blakim, blavim, blanmd, and blaoxa, mostly identified from Klebsiella pneumoniae as the source of nosocomial outbreaks [1]. Specifically, blakim and blaoxa co-producing Enterobacteriaceae are emerging as a serious challenge for treatment, infection control, and public health [1-3]. Globally, the co-existence of blanmd and blaoxa genes was first detected in K. pneumoniae, followed by Escherichia coli [2]. Similarly, in Korea, a blanmd and blaoxa co-producing K. pneumoniae strain was first detected in 2014 [4], and by 2017, our hospital witnessed the first case caused by blanmd and blaoxa co-producing uropathogenic E. coli [5].

The period of surveillance continued from July to September of 2017. Twenty patients harbored CPE; we numbered the patients in order from P1 to P20. The E. coli strain carried by P5 and P6 was isolated from blood, while that carried by P1, P2, and P19 was isolated from urine. Other E. coli strains implicated in the outbreak were isolated as part of the stool surveillance procedure undertaken to detect the presence of CPE. During the surveillance period, CPE outbreak control action comprises of three steps which are coordinated by
infectious disease specialists. The steps as follows: First, immediately transfer the patient to a single-patient room when carbapenem-resistant Enterobacteriaceae (CRE) is detected at the site of infection. The ward 111 (111W), consisting of single-patient rooms, was used as the isolation ward. Second, collect stool specimens from patients who were hospitalized in the same room as the index patient. If CRE is detected in the stool surveillance study, the new patient harboring the CRE is also immediately transferred to the cohorting room or another single-patient room. This step is essential for screening CRE carrier. Third, decide about discontinuing patient isolation-and-contact-related precautions. Discontinuation of patient isolation depends on whether CRE is isolated in three consecutive rounds of testing, undertaken every 3–7 days with the same specimen type. If it is difficult to obtain the same type of specimen, for example, the cerebrospinal fluid, pleural fluid, or peritoneal fluid, only stool specimen is tested. If the cohort patient meets the criteria for isolation, the patient is moved to another ward for proper medical treatment. Else, if the condition of the patient is good, he/she is discharged, after detailed educating about self-hygiene. For the investigation of clinical and laboratory characteristics of CPE outbreak strains, data were extracted from the electronic medical records, followed by decoding. The study was exempted from the Institutional Review Board (IRB) of Yonsei Wonju Severance Christian Hospital according to the government regulation. Based on this exemption, the study also received a waiver of consent from the same IRB (approval no. CR318306).

Blood samples drawn for determining the bacteremia were handled in the same way, previously [5]. Urine specimen was inoculated onto 5% sheep blood agar plate (KOMED Life Science Co., Seongnam, Korea) and MacConkey agar plate (BD Diagnostic Systems, Sparks, MD, USA), and then incubated overnight at 35°C. All stool swab specimens for CPE screening were inoculated in the selective chromogenic medium (CHROMagar KPC, Hangang, Gunpo, Korea). The CRE isolates obtained from the clinical specimen were tested by the Modified Hodge test, carbapenemase inhibition test, and CarbaNP test (bioMérieux, Durham, NC, USA) [6], and then, the CPE suspects were tested by XpertCarba-R assay (Cepheid, Sunnyvale, CA, USA) [5]. Each time a CPE was isolated, the subcultured colony was delivered to the Korea Centers for Disease and Prevention (KCDC) for the confirmation of the carbapenemase genotype, and KCDC gave feedback about the type of carbapenemase genes present. The entire bacterial genome of 20 E. coli isolates was subjected to DNA fingerprinting by pulsed-field gel electrophoresis (PFGE) [7].

The total number of patients in the outbreak group was 20 (10 males, 10 females; age, 52–93 years; mean age, 71 years). The hospital admission period of outbreak patients was from 8th May to 29th Nov., 2017. The inpatient days ranged from 8 to 128 days (mean, 43 days). None of the outbreak patients expired during the hospitalization period. During the one year of follow-up, 16 patients were able to follow-up. Of 16 follow-up patients, 10 patients were proven culture-negative for CRE. Of them, CPE conversion time from CPE positive to CPE negative was 12 to 205 days, with an average of 76 days (Table 1). Because stool CPE screening was performed for all patients who were admitted to same ward as CPE patients, the incidence of number of CPE patients per 1,000 admissions was increased to 9.96. At the same time, eight CPE patients were discharged in 2 weeks (Fig. 1). The most common underlying diseases were cancer (n = 7) and cardiac disease (n = 4). All outbreak E. coli isolates were resistant to all antimicrobial agents tested (ampicillin, ampicillin/sulbactam, timentin, piperacillin, piperacillin/tazobactam, cefepime, cefotaxime, ceftazidime, aztreonam, cefoxin, imipenem, meropenem, doripenem, gentamicin, tobramycin, ciprofloxacin, levofloxacin, and trimethoprim/sulfamethoxazole), except amikacin.
### Table 1. Clinico-epidemiological findings of the patients involved in the outbreak

| Patient No. | Specimen | Age (years) | Sex | Underlying diseases | Admission date | Ward movement | Reported date as CPE positive | Discharge date | Time to CPE conversion, days |
|-------------|----------|-------------|-----|---------------------|---------------|--------------|------------------------------|---------------|-------------------------------|
| P1          | Urine    | 76          | F   | Coronary artery disease | 8-May-2017    | 5W           | 14-Jul-2017                 | 14-Jul-2017   | 107                           |
| P2          | Urine    | 69          | F   | Pseudomembranous colitis | 13-Jul-2017   | 111W ← 92W   | 29-Jul-2017                 | 14-Aug-2017   | 12                            |
| P3          | Stool    | 78          | F   | Avascular necrosis of hip | 17-Jul-2017   | 92W          | 4-Aug-2017                 | 4-Aug-2017    | 51                            |
| P4          | Stool    | 79          | F   | Common bile duct stone  | 11-Jul-2017   | 92W          | 4-Aug-2017                 | 4-Aug-2017    | (287)                        |
| P5          | Blood    | 77          | M   | Esophageal cancer       | 7-Aug-2017    | EICU         | 4-Sept-2017                | 30-Sept-2017  | No follow-up                  |
| P6          | Blood    | 93          | F   | Septic shock           | 9-Aug-2017    | EICU         | 4-Sept-2017                | 1-Sept-2017   | No follow-up                  |
| P7          | Stool    | 68          | F   | Heart failure          | 18-Jun-2017   | EICU         | 8-Sept-2017                | 2-Oct-2017    | No follow-up                  |
| P8          | Stool    | 46          | M   | Cerebral infarction    | 7-Aug-2017    | EICU         | 8-Sept-2017                | 9-Nov-2017    | 17                            |
| P9          | Stool    | 77          | F   | Acute respiratory failure | 18-Aug-2017  | EICU         | 8-Sept-2017                | 8-Nov-2017    | 20                            |
| P10         | Stool    | 81          | M   | Septic arthritis       | 22-Aug-2017   | EICU         | 8-Sept-2017                | 29-Nov-2017   | (81)                         |
| P11         | Stool    | 77          | F   | Heart failure          | 23-Aug-2017   | EICU         | 8-Sept-2017                | 11-Sept-2017  | 211                           |
| P12         | Stool    | 60          | M   | Empyema, pressure sore | 23-Aug-2017   | 102W ← EICU | 8-Sept-2017                | 8-Sept-2017   | No follow-up                  |
| P13         | Stool    | 76          | M   | Heart failure          | 1-Sept-2017   | 73W ← EICU  | 8-Sept-2017                | 9-Sept-2017   | 85                            |
| P14         | Stool    | 70          | M   | Esophageal cancer       | 27-Aug-2017   | 111W ← 102W | 13-Sept-2017              | 17-Sept-2017  | (53)                        |
| P15         | Stool    | 63          | M   | Submandibular gland cancer | 16-Jul-2017 | 111W ← 102W | 13-Sept-2017              | 21-Nov-2017  | 130                         |
| P16         | Stool    | 75          | M   | Urinary tract infection | 18-Aug-2017   | 102W        | 13-Sept-2017              | 13-Sept-2017  | (131)  |
| P17         | Stool    | 80          | M   | Ascending colon cancer | 30-Aug-2017   | 102W        | 13-Sept-2017              | 13-Sept-2017  | (37)                      |
| P18         | Stool    | 63          | M   | Rectal cancer          | 8-Sept-2017   | 111W ← 102W | 13-Sept-2017              | 20-Sept-2017  | (48)                         |
| P19         | Urine    | 65          | F   | Cervix cancer          | 8-Sept-2017   | 22W         | 19-Sept-2017               | 19-Sept-2017  | 205                         |
| P20         | Stool    | 52          | F   | Cervix cancer          | 11-Sept-2017  | 111W ← 22W | 20-Sept-2017              | 29-Sept-2017  | 40                           |

1Patients who were hospitalized in the same room (92W) as the patient No. P2.
2Number in parentheses means stool sample continued to yield CPE during the follow-up.
3Patients who were hospitalized in the same room (102W) as the patient No. P12.
4Patient who was hospitalized in the same room (22W) as the patient No. P19.

CPE, carbapenemase producing Enterobacteriaceae; F, female; W, ward; M, male; EICU, emergency intensive care unit.

XpertCarba-R assay (Cepheid) showed that all outbreak E. coli isolates carried blaNDM and blaOXA genes. KCDC confirmed that the exact CPE genes were blaNDM-5 and blaOXA-181. The 20 E. coli isolates showed highly clonal similarity (>88%) on the basis of PFGE patterns. Therefore, the outbreak of blaNDM-5 and blaOXA-181 coproducing E. coli is likely to be concluded as clonal spread in this study (Fig. 2).

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**Figure 1.** Epidemic curve caused by NDM-5 and OXA-181 coproducing Escherichia coli between July to November 2017.
The occurrence of carbapenem resistance has gained immense notoriety as an important public health threat because carbapenems have been used as the last option for the treatment of infections caused by multidrug-resistant gram-negative bacteria. Therefore, CDC has placed great emphasis on hand hygiene and rapid correspondence of CPE transmission [8, 9]. Interventions to control CPE are evolving as more data and experience become available [10]. CDC recommendations to prevent CRE transmission in healthcare settings are as follows: hand hygiene, contact-related precautions, healthcare personnel education, minimum and appropriate use of devices, timely laboratory notification, inter-facility communication/identification of CRE patients at admission, antimicrobial stewardship, environmental cleaning, patient and staff cohorting, contact screening of CRE patients, and active surveillance testing. When the source of CPE outbreak is clear, outbreak management is easier [11, 12]. However, it is rather difficult to determine the cause of a CPE outbreak; it could be a point or continuing source or nosocomial cross-transmission [4].

On discharge of CRE patients, terminal cleaning of the CRE patient rooms should be performed. In these situations, because of the time required to obtain the microbiological results for the initial CRE patient and to organize the survey, most or all patients who stayed in the ward at the same time as the index CRE patient have often been discharged. In such situations, it is necessary to screen contacts at maximum risk for transmission (e.g., roommates), even if they have been discharged or moved to another ward. Therefore, the basic concept for the prevention of CPE transmission is early detection of CPE, and CPE patients are recommended to return home when they are in a position to perform their daily tasks. To ensure rapid and sensitive detection of CPE, our laboratory moved from the modified Hodge test and carbapenemase inhibition test to Carba NP test. Stool CPE screening was performed for all patients who were admitted to same ward as CRE patients. All CRE

![Figure 2. Pulsed-field gel electrophoresis profiles of XbaI-digested total DNA of 20 NDM-5 and OXA-181 coproducing Escherichia coli isolates, compared to E. coli ATCC 25922.](https://icjournal.org)
with positive Carba NP test were confirmed by KCDC. The CRE or CPE colonized patients were then evaluated for early discharge by the infection control physician.

While some patients missed follow up in this study, conversion to CPE negativity also needed 12–205 days. Lai, et al. reported that persistent vancomycin-resistant Enterococcus carriers needed 39–421 days to become free of colonization [13]. Karki, et al. suggested that in the absence of recent risk factors such as hospitalization or antibiotic use, patients with a remote history of vancomycin-resistant Enterococcus colonization (>4 years) might no longer require isolation-and-contact-related precautions [14]. Although KCDC defined that three consecutive negative cultures for CRE is required to possibly confirm a patient as free of colonization, a criterion that accurately defines a status free of colonization has not yet been established by evidence-based studies.

Although our outbreak E. coli strain carried two different carbapenemase producing genes, namely, \(\text{bla}_{\text{NDM-5}}\) and \(\text{bla}_{\text{OXA-181}}\), all CPE patients who could be followed up, survived. There is no single best approach; instead, the decision should be guided by local epidemiology, resource availability, and the likely clinical impact of a CRE outbreak. In particular, in acute settings like ours, if the infection control team fails to ensure early control of CPE outbreak transmission, patients who can opt for homecare are advised an early discharge. For the proper functioning of these systems, it is imperative that the home-visit system infrastructure by the healthcare provider is built according to the national policy.

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