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Brief Communication

Nosocomial Outbreak Caused by NDM-5 and OXA-181 Carbapenemase Co-producing *Escherichia coli*

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No conflicts of interest.

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 *E. coli* isolates co-produced $bla_{\text{NDM-5}}$ and $bla_{\text{OXA-181}}$ 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: bla_{KPC}, bla_{IMP}, bla_{VIM}, bla_{NDM}, and bla_{OXA}, mostly identified from *Klebsiella pneumoniae* as the source of nosocomial outbreaks [1]. Specifically, bla_{NDM} and bla_{OXA} co-producing *Enterobacteriaceae* are emerging as a serious challenge for treatment, infection control, and public health [1-3]. Globally, the co-existence of $bla_{\text{NDM-5}}$ and $bla_{\text{OXA-181}}$ genes was first detected in *K. pneumoniae,* followed by *Escherichia coli* [2]. Similarly, in Korea, a $bla_{\text{NDM-5}}$ and $bla_{\text{OXA-181}}$ coproducing *K. pneumoniae* strain was first detected in 2014 [4], and by 2017, our hospital witnessed the first case caused by $bla_{\text{NDM-5}}$ and $bla_{\text{OXA-48}}$ 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

Author Contributions

Conceptualization: HYK, YU. Data curation: HYK, YU. Formal analysis: YU. Investigation: JSH, KA. Methodology: YU. Project administration: YU. Resources: GYH, YKK, HRJ. Software: KA, YU. Supervision: YU. Validation: KA, YU. Visualization: KA, YU. Writing - original draft: KA. Writing - review & editing: KA, YU.

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.

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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	51W	14-Jul-2017	14-Jul-2017	107
P2	Urine	69	F	Pseudomembraous 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[a]	4-Aug-2017	4-Aug-2017	51
P4	Stool	79	F	Common bile duct stone	11-Jul-2017	92W[a]	4-Aug-2017	4-Aug-2017	(287)[b]
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[c]	8-Sept-2017	2-Oct-2017	No follow-up
P8	Stool	46	M	Cerebral infarction	7-Aug-2017	EICU[c]	8-Sept-2017	9-Nov-2017	17
P9	Stool	77	F	Acute respiratory failure	18-Aug-2017	EICU[c]	8-Sept-2017	8-Nov-2017	20
P10	Stool	81	M	Septic arthritis	22-Aug-2017	EICU[c]	8-Sept-2017	29-Nov-2017	(81)[b]
P11	Stool	77	F	Heart failure	23-Aug-2017	EICU[c]	8-Sept-2017	11-Sept-2017	211
P12	Stool	60	M	Empyema, pressure sore	23-Aug-2017	102W ← EICU[c]	8-Sept-2017	8-Sept-2017	No follow-up
P13	Stool	76	M	Heart failure	1-Sept-2017	73W ← EICU[c]	8-Sept-2017	9-Sept-2017	85
P14	Stool	70	M	Esophageal cancer	27-Aug-2017	111W ← 102W[d]	13-Sept-2017	17-Sept-2017	(53)[b]
P15	Stool	63	M	Submandibular gland cancer	16-Jul-2017	111W ← 102W[d]	13-Sept-2017	21-Nov-2017	130
P16	Stool	75	M	Urinary tract infection	18-Aug-2017	102W[d]	13-Sept-2017	13-Sept-2017	(131)[b]
P17	Stool	80	M	Ascending colon cancer	30-Aug-2017	102W[d]	13-Sept-2017	13-Sept-2017	(37)[b]
P18	Stool	63	M	Rectal cancer	8-Sept-2017	111W ← 102W[d]	13-Sept-2017	20-Sept-2017	(48)[b]
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[e]	20-Sept-2017	29-Sept-2017	40

[a]Patients who were hospitalized in the same room (92W) as the patient No. P2.
[b]Number in parentheses means stool sample continued to yield CPE during the follow-up.
[c]Patients who were hospitalized in the same room (EICU) as the patient No. P5 and P6.
[d]Patients who were hospitalized in the same room (102W) as the patient No. P12.
[e]Patient 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 bla_{NDM} and bla_{OXA} genes. KCDC confirmed that the exact CPE genes were bla_{NDM-5} and $bla_{OXA-181}$. The 20 *E. coli* isolates showed highly clonal similarity (>88%) on the basis of PFGE patterns. Therefore, the outbreak of bla_{NDM-5} and $bla_{OXA-181}$ coproducing *E. coli* is likely to be concluded as clonal spread in this study (**Fig.2**).

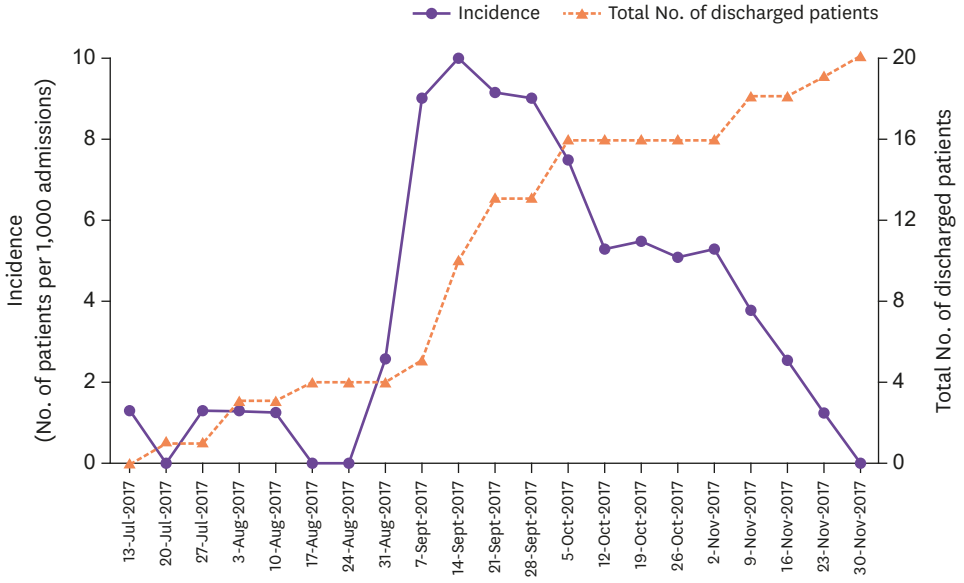

Figure 1. Epidemic curve caused by NDM-5 and OXA-181 coproducing *Escherichia coli* between July to November 2017.

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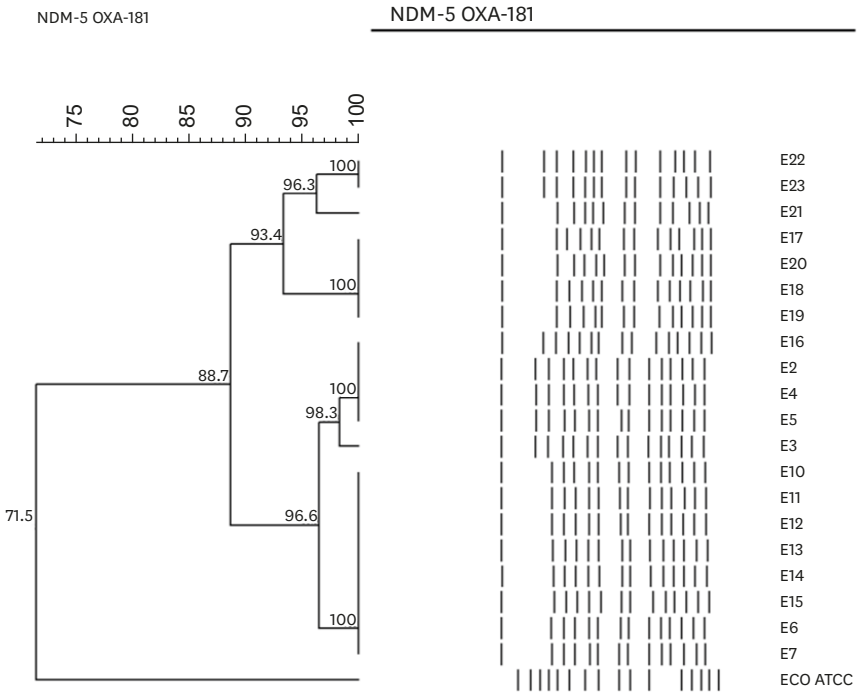

Figure 2. Pulsed-field gel electrophoresis profiles of *Xba*I-digested total DNA of 20 NDM-5 and OXA-181 coproducing *Escherichia coli* isolates, compared to *E. coli* ATCC 25922.

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 cabapenemase inhibition test to Carba NP test. Stool CPE screening was performed for all patients who were admitted to same ward as CPE patients. All CRE

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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, $bla_{\text{NDM-5}}$ and $bla_{\text{OXA-181}}$, 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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