내과학 석사 학위논문

Investigation of Transmission Rate of Carbapenemase-Producing Carbapenem-Resistant Enterobacteriaceae (CP-CRE) among Close Contact Patients and Healthcare Workers Using Whole-Genome Sequencing

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ABSTRACT

Investigation of Transmission Rate of Carbapenemase-Producing Carbapenem-Resistant Enterobacteriaceae (CP-CRE) among Close Contact Patients and Healthcare Workers Using Whole-Genome Sequencing

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Introduction: To reduce transmission of carbapenemase-producing carbapenem-resistant Enterobacteriaceae (CP-CRE), screening is recommended for patients who shared a room with a newly detected CP-CRE-infected or -colonized patients and healthcare workers caring for CP-CRE-infected or –colonized patients. The aim of this study was to investigate the rate of positivity in screening tests among patients who shared a room with CP-CRE-infected or –colonized patients and healthcare workers, and to find risk factors for transmission.

Methods: This study was conducted in a 1,751-bed tertiary teaching hospital between January 2017 and December 2019. Index patients were defined as those with positive tests for CP-CRE from any infected or colonized site during hospitalization. When an index patient was detected in a shared room, we performed screening tests for patients whose stay overlapped with an index patient for at least one day and healthcare workers who were caring for an index patient. Rectal swabs for screening tests were cultured using MacConkey agar plates supplemented with meropenem. When CRE was isolated on screening test, we checked the presence and type of carbapenemase using PCR. If close contact patients or healthcare workers had CRE, whole-genome sequencing with remeasurement of MIC and multilocus sequence typing were performed to verify genetic relatedness with CRE from their index patients. When CP-CRE from close contact patients or healthcare workers had different types of carbapenemases with their index patients', the pairs were excluded from genetic analysis.

Results: During study period, a total of 47 index patients were identified. Among 47 index patients, 32 patients (68.1 %) tested positive for KPC-producing CRE, 15 patients (31.9 %) tested positive for NDM-1-producing CRE, and 2 patients (4.3 %) had OXA-48. Forty-seven index patients were found to have been in close contact with a total of 152 patients in a shared room and 54 healthcare workers. Out of 152 close contact patients, ten had carbapenemase-non-producing carbapenem-resistant Enterobacteriaceae (CNP-CRE) and seven had CP-CRE. None of healthcare works had CRE. Four close contact patients had the same type of carbapenemase with their CP-CRE index patients and all of them were KPC. Whole-genome sequencing with remeasurement of MIC revealed that 3 out of 4 pairs of CP-CRE index/secondary patients showed genotypic and phenotypic accordance between index patients and contacted patients. Consequently, the CP-CRE transmission rate in close contact patients in a shared room was calculated as 2.0% (=3/152). Risk factors for CPE transmission could not be analyzed due to small number of CP-CRE transmitted cases.

Conclusion: The CP-CRE transmission rate between CP-CRE index patients and close contact patients in shared rooms was about 2.0%. There was no CP-CRE transmission between CP-CRE index patients and healthcare workers.

Keywords : Carbapenemase-producing Enterobacteriaceae; Transmission; Infection control; Whole-genome sequencing

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INTRODUCTION

Carbapenems have been one of the most widely used antibiotics for several kinds of hospital- or community-acquired infections since they were developed in 1985.[1,2] As the amount of carbapenems used for treating infections has increased drastically, resistance against carbapenems has been reported more frequently than ever in Enterobacteriaceae.[3–5] Carbapenem-resistant Enterobacteriaceae (CRE) shows resistance against at least one of carbapenems, and causes more morbidity and mortality than carbapenem-susceptible Enterobacteriaceae.[6,7]

Especially, CRE producing carbapenemases, enzymes hydrolyzing carbapenems, is called carbapenemase-producing carbapenem-resistant Enterobacteriaceae (CP-CRE).[8] Carbapenem-resistance not related to carbapenemases but associated with porin deficiency or overexpression of efflux pumps is almost not transferable among bacteria.[9,10] On the other hand, CP-CRE can easily transmit their resistance genes to other bacteria by transferring plasmids.[9,10] As a result, CP-CRE is considered as a bigger hazard to public health than carbapenemase-non-producing carbapenem-resistant Enterobacteriaceae (CNP-CRE) and more strict infection control should be implemented when CP-CRE is detected in a patient.[11]

The Korea Disease Control and Prevention Agency established the guidelines for controlling transmission of CP-CRE. If CRE is cultured from a patient's specimen, polymerase chain reaction (PCR) test for detecting carbapenemase genes also should be implemented. When carbapenemase genes are detected from PCR, the patient should be isolated in a single room. Moreover, all the other patients who shared a room with this patient and all the healthcare workers who made contact with this patient should go through tests for CRE screening.[11]

However, it is not well known about the actual rate of positivity in CP-CRE screening for close contacts. A few studies reported the rate of positivity in CP-CRE screening as 2.8 - 3.2%.[12,13] One retrospective study reviewed 211 CP-CRE index patients and 1,369 contact patients between 2010 and 2017 in a tertiary teaching hospital, and carbapenemases of CPE index patients were transmitted to 44 close contact patients (3.2%).[13] Another study was conducted prospectively from 2015 to 2018 in households, and the rate of CP-CRE transmission from CP-CRE index patients to contact family members was calculated as 2.8% (5 cases among 177 contacts).[12]

The aims of this study were to calculate the actual rate of positivity in CP-CRE screening done for patients and healthcare workers exposed to CP-CRE-confirmed patients, and to analyze risk factors for CP-CRE transmission in a shared room.

METHODS

Study design

This retrospective study was carried out from 1 January 2017 to 31 December 2019 and included patients from Seoul National University Hospital (SNUH) in Korea, a tertiary teaching hospital with 1,751 beds. Minimal inhibitory concentration (MIC) of each antibiotic was determined by MicroScan WalkAway (Omron Microscan systems Inc., Renton, WA, USA). Carbapenem-resistance was defined as reduced susceptibility to any carbapenem by Clinical and Laboratory Standards Institute criteria (imipenem, meropenem ≥ 2 μg/mL of MIC; ertapenem ≥ 1 μg/mL of MIC).[14] When CRE was detected from cultures of any clinical specimens, Carba NP test and PCR test for carbapenemase genes were conducted. The PCR tests targeted for carbapenemase genes such as *Klebsiella pneumoniae* carbapenemase (KPC), imipenemase (IMP), Verona integron-encoded metallo-β-lactamase (VIM), New Delhi metallo-β-lactamase (NDM), and oxacillinase (OXA).

CP-CRE index patients were defined as patients with positive tests for CP-CRE from any infected or colonized site during hospitalization and who had contacted with other patients in a shared room and healthcare workers before CP-CRE was identified. CP-CRE contact patients and healthcare workers were specified as people who had stayed in the same room for at least one day or contacted at least one time for caring with CP-CRE index patients before CP-CRE index patients were identified. If CP-CRE was detected from a patient, this CP-CRE index patient was isolated in a single room with contact precaution, and close contact patients and healthcare workers were gone through tests for CRE surveillance. Specimens from the CP-

CRE close contact patients and healthcare workers were taken as rectal swabs. CP-CRE screening tests utilized disc diffusion method by using meropenem (10 μg) disc and cut off value of meropenem-resistance was less than 25 mm by the European Committee on Antimicrobial Susceptibility Testing criteria.[15] If a CP-CRE contact patient showed positivity in CRE surveillance test, PCR test for carbapenemase genes was performed to check presence and a type of carbapenemases.

This study was approved by the institutional review board of the hospital (IRB No. H-2004-135-1117). The informed consent requirement was waived, since this study was retrospective, involved no interaction with patients, and was considered to be of minimal risk.

Whole Genome Sequencing & Multilocus Sequence Typing

To determine whether there was transmission of carbapenemases between the CP-CRE contact patients and their CP-CRE index patients, whole genome sequencing (WGS) was conducted in each CP-CRE index patient-secondary patient (a CP-CRE contact patient who had the same type of carbapenemases with the index patient) pair. Additionally, WGS was performed also in each pair of a CP-CRE index patient-a CNP-CRE detected patient to investigate possibility of transmission of CRE between a CP-CRE index patient and a close contact patient.

Isolates from each CP-CRE index patient-secondary patient pair or CP-CRE index patient-CNP-CRE detected patient pair were cultured in MacConkey agar plates. Bacterial deoxyribonucleic acid (DNA) was extracted using InstaGene Matrix (Bio-Rad Laboratories, Hercules, CA, USA) and the concentration was measured by the QuantFluor ONE dsDNA

System (Promega, Madison, WI, USA). The library was prepared using Nextera DNA Flex kit (Illumina Inc., San Diego, CA, USA) and run on iSeq ™ 100 System (Illumina Inc.) following the manufacturer's instruction. The fastq data obtained was assembled by the Microbial Genomics Module of the CLC Genomics Workbench (Qiagen, Aarhus, Denmark). Then, the same program was used to align and compare assembled reads of each pair. Bacterial strain-typing was also conducted by comparing each sequence with all reference sequences of four bacterial species (*K. pneumoniae, K. aerogenes, E. cloacae,* and *E. coli*), and phylogenies of the samples were drawn by the *k*-mer based tree construction according to neighbor-joining algorithm. To show consistency between genotyping results and phenotypic characteristics, MIC for imipenem and meropenem of each bacterium was remeasured by Sensititre (Thermo Fichser Scientific, Massachusetts, US).

Additionally, multilocus sequence typing (MLST) analysis was also conducted in each CP-CRE index patient-secondary patient pair or CP-CRE index patient-CNP-CRE detected patient pair to investigate the possibility of transmission of carbapenemases through plasmid-transfer. MLST was performed by NGS-MLST tool using CLC Genomics Workbench. Each PubMLST scheme was applied to each species for strain typing. Several housekeeping genes (*gapA, infB, mgh, pgi, phoE, rpoB,* and *tonB* for *K. pneumoniae; dinB, icdA, pabB, polB, putP, trpA,* and *trpB* for *E. coli; dnaA, fusA, gyrB, leuS, pyrG, rplB,* and *rpoB* for *E. cloacae*) were chosen for MLST and several antibiotic resistance genes (KPC, OXA, CTX-M, TEM, and SHV) were used for plasmid analysis. Primers were designed for these housekeeping and resistance genes, and nested PCR assays were carried out for each gene. Amplified sequences of each gene were analyzed also by the method as explained above.

Data Collection and Statistical Analysis

Demographic and clinical information about CP-CRE index patients and contact patients were gathered from the system of electronic medical record and the reports of the SNUH infection control department. Presence of risk factors for CP-CRE acquisition clarified in previous studies such as (a) length of hospital stay, (b) previous hospitalization, (c) previous intensive care, (d) presence of indwelling catheters, (e) bed-ridden state, (f) conduction of invasive procedures, (g) immunocompromised state, and (h) use of antibiotics with broad spectrum-coverage was reviewed in the data provided.[16–20]

All the descriptive and statistical analysis were executed by Predictive Analytics SoftWare for Windows (version 25.0; SPSS Inc., Chicago, IL, USA), and p-value less than 0.05 was considered as significant.

RESULTS

A total of 66 patients were identified as possessing CP-CRE based on the results of culture studies, carbapenemase NP tests, and PCR tests for carbapenemase genes between 1 January 2017 and 31 December 2019. (**Figure 1**) Among them, 19 patients had no contact with other patients or all other patients contacted with them had been discharged from the hospital before positivity of CP-CRE in index patient was determined. Therefore, 47 patients with CP-CRE were considered as index patients, and 152 patients and 54 healthcare workers were exposed to them. Out of 152 patients, 135 (88.8%) did not have CRE, 10 (6.6%) had CNP-CRE, and 7 (4.6%) had CP-CRE. None of healthcare works had CRE. Out of 7 CP-CRE positive patients, four were in congruence of carbapenemase types with their CP-CRE index patients, and all of them were KPC.

Characteristics of CP-CRE index patients and close contact patients

The median duration of staying in the hospital of CP-CRE index patients till CP-CRE was found in their specimens was 6 days (interquartile range 2-12 days) (**Table 1**). Stool was the most common specimens where CP-CRE was detected (21, 44.7%), followed by respiratory samples (9, 19.1%), and urine (6, 12.8%). Out of 47 index patients *Klebsiella pneumoniae* was detected in 29 (61.7%) patients, and *Escherichia coli* in 7 (14.9%), and *Enterobacter* species in 7 (14.9%). KPC was the most commonly produced carbapenemase (32, 68.1%), followed by NDM (15, 31.9%) and OXA-48 (2, 4.3%). Two patients had both NDM and OXA-48 simultaneously.

The median duration of hospitalization of close contact patients until CP-CRE screening was 12 days (interquartile range 7-23 days), and the median duration of sharing rooms with their CP-CRE index patients was 3 days (interquartile range 2-7 days) (**Table 2**). Seventy eight (51.3%) close contact patients had history of previous hospitalization and 27 (17.8%) had previous intensive care within 3 months. Fifty-eight (38.2%) patients used anti-pseudomonal penicillins for more than 3 days within 1 months from CPE surveillance. 3rd or 4th generation cephalosporins, quinolones, glycopeptides, and carbapenems were also used in 56 (36.8%), 45 (29.6%), 35 (23.0%), and 30 (19.7%) patients, respectively.

Genomic evaluation in isolates from CP-CRE index patient/close contact patients

Only 7 contact patients were detected positive in CP-CRE surveillance, of which 4 were secondary patients who had the same types of carbapenemases that their CP-CRE index patients had, and there were 10 CNP-CRE detected patients as well. WGS was conducted to prove whether carbapenemase genes were transmitted between CP-CRE index patients and their secondary patients. It was also performed in the pairs of a CP-CRE index patient-a CNP-CRE detected patient to verify if transmission of CRE between CNP-CRE detected patients and CP-CRE index patients could be possible. Three CP-CRE contact patients detected positive in CP-CRE surveillance who had the different types of carbapenemases from their CP-CRE index patients were excluded from WGS analysis. Therefore, total 22 CP-CRE index patients, secondary patients, and CNP-CRE detected patients whose results of specimen culture or CP-CRE surveillance were available were gone through genomic evaluation. (**Table 3**) There were total 10 clusters and each cluster was composed of 2 or 3 patients. 4 clusters were pairs of a CP-CRE index patient-a CP-CRE-detected patient (having the same types of carbapenemases

with an index patient), and the others were pairs of a CP-CRE index patient-a CNP-CRE detected patient.

WGS and MLST with plasmid analysis were done in 10 clusters to prove transmissibility of carbapenemases or CNP-CRE between CP-CRE index patients and their close contact patients. Each bacterium from 22 samples were genetically typed to all reference sequences of four bacterial species (*K. pneumoniae, K. aerogenes, E. cloacae,* and *E. coli*) (**Table 4**) and a phylogenetic tree was constructed based on the bacterial strain-typing results by *k*-mer based tree construction. (**Figure 2**) Pairs of a CP-CRE index patient-a CP-CRE-detected patient such as (I-2, C-2), (I-4, C-4), and (I-7, C-7) showed genetic distance as 0.000 from each other and it could be considered that there might be transmission of carbapenemase between CP-CRE index patients and CP-CRE contact patients. However, (I-3, C-3), another CPE index patient-CP-CRE-detected patient pair, showed genetic distance as 0.978 from each other, so there might not be transmission of carbapenemase between I-3 and C-3.

(I-5, I-10) and (I-1, C-9-1) were not related to each other in perspective of time and place, but they had genetic distance of 0.000 from each other. Also, (I-6, C-6) and (I-8, C-8) were pairs of a CP-CRE index patient-a CNP-CRE detected patient, but they were genetically related to each other. In other clusters of a CP-CRE index patient-CNP-CRE detected patients such as (I-1, C-1-1, C-1-2), (I-5, C-5), (I-9, C-9-1, C-9-2), and (I-10, C-10), there was little genetic accordance between bacteria from CP-CRE index patients and CNP-CRE detected patients. This also might suggest that CNP-CRE were not expressed by transmission of plasmids and were derived from external factors like antibiotic pressure or environmental contamination.

To prove consistency between genotyping results and phenotypic characteristics, MIC for imipenem and meropenem of each sample was remeasured. (**Table 5**) When using the

essential agreement definition of ±1 $\log_2$ dilution error, (I-2, C-2), (I-4, C-4), and (I-7, C-7) showed similar MIC results between CP-CRE index patients and CP-CRE detected patients. Other pairs did not show concordance of MIC between index patients and contacted patients.

MLST including plasmid analysis also showed similar results with WGS and results of MIC remeasurement. (I-2, C-2), (I-4, C-4), and (I-7, C-7) were in coincidence between an index patient and a contacted patient with the distribution of housekeeping genes and resistance genes in plasmids and the kinds of carrying plasmids (**Table 6**). Based on the results of WGS and MLST, the actual rate of CP-CRE transmission in CP-CRE surveillance was calculated as 1.5% (=3/206) (95% confidence interval as 0.3-4.2%).

Analysis of Risk Factors for CPE Transmission

There were only 3 CP-CRE transmission confirmed by WGS among the 206 CPE contacted patients and healthcare workers, so it was impossible to analyze risk factors for CP-CRE transmission. Instead, clinical characteristics of 3 CP-CRE transmission cases were described in detail in the separate table (**Table 7**). Median duration of overlapping periods in a same room with index patients in the CP-CRE-transmitted patients and non-transmitted patients were 4 days (interquartile range 2-4 days) and 3 days (interquartile range 2-7 days) respectively, and there was no significant difference between two groups by Mann-Whitney U test (p-value=0.857). Logistic regression test was also conducted for finding risk factors for CP-CRE transmission or acquisition, but any significant factor could not be found due to the small number of CP-CRE-transmitted patients (Data not shown).

DISCUSSION

Increasing prevalence of CP-CRE is a global concern and CPE should be controlled strictly due to its transmission by transferring plasmids to other bacteria.[21] Therefore, guidelines for controlling CP-CRE transmission and CP-CRE screening are implemented in each country. In Korea, when a CP-CRE source patient is detected, all the contacted patients and healthcare workers should go through CP-CRE screening tests.[11] However, the positivity rate in CP-CRE screening tests is not well clarified and only a few studies reported it as 2.0-3.2%.[12,13]

In this study, the actual CP-CRE transmission rate was investigated using WGS with remeasurement of MIC. The CP-CRE transmission rate was calculated as 2.0% (=3/152) (95% confidence interval as 0.4-5.6%) in close contact patients in a shared room. Fifty-four close contact healthcare workers were all negative in CP-CRE screening tests. The calculated rate of CP-CRE transmission is relatively low, so the efficiency and profitability of CP-CRE screening may be not high. Considering the rate of CP-CRE transmission was zero in healthcare workers, it can be inferred that not all CP-CRE contacted healthcare workers have to go through CP-CRE screening. Moreover, three CP-CRE-transmitted cases showed similar MIC results between CP-CRE index patients and CP-CRE detected patients. This might suggest that genotypic identity imply accordance of phenotypic traits such as antibiotic resistance and transmission of carbapenemases between index patients and contacted patients existed.

The rate of CP-CRE transmission could be influenced by standard measurements for infection control implemented in the hospital, and hand hygiene is an integral factor for infection control.[22] Poor hand hygiene among healthcare workers could promote CP-CRE transmission significantly and increase the rate of CP-CRE transmission,[22] so the compliance

rate for hand hygiene among medical staff in hospital should be reviewed. From 2017 to 2019, the rate of observation for hand hygiene among healthcare workers in each year was around 95.0% steadily in SNUH. Medical staff in SNUH complied highly with rules for hand hygiene, and the rates of keeping hand hygiene were maintained similarly for 3 years.

Moreover, each 3 CP-CRE transmitted cases occurred in May, August, and October in 2018, respectively. They happened in similar periods of 2018, but were not linked epidemiologically with one another, because they did not share the pathways where each CP-CRE index patient-CP-CRE contact patient pair had gone through. Consequently, they were not considered as CP-CRE outbreak.

WGS analysis showed that CP-CRE from 75% (=3/4) of the secondary patients were in accordance with CP-CRE from their index patients. So, there might be transmission of plasmids carrying carbapenemase genes between the secondary patients who have the same type of carbapenemases with their CP-CRE index patients and their index patients. Moreover, most strains of CNP-CRE from CRE detected patients were genetically distant from those of CP-CRE from their index patients. It was compatible with the finding that CNP-CRE is usually not transferable and arises from environmental colonization or porin deficiency and overexpression of efflux pumps derived from antibiotic pressure. Also, some pairs on the phylogenetic tree were not related to each other in perspective of time and place, but they showed genetic identity with each other. This phenomenon indicated that some bacterial strains might colonize in general environment of the hospital and might be transmitted to inpatients.

Several studies identified risk factors for acquisition of CP-CRE in a single patient. One matched case-control study investigated 58 CP-CRE patients among 621,623 admitted patients from 2011 to 2016, and revealed the risk factors for acquiring CP-CRE as the length of hospital

admission more than 20 days, hospital admission within 1 year, and use of antibiotics more than 10 days.[16] Other retrospective study analyzed 303 CP-CRE patients and 5,929 control patients, and found the risk factors of obtaining CP-CRE as longer inpatient stay, mechanical ventilation, dialysis, and exposure to broad-spectrum antibiotics.[20] However, few researches investigated about risk factors for transmission of CP-CRE in a shared room and factors precipitating CP-CRE transmission is not clarified yet. Risk factors for transmission of multidrug-resistant bacteria were reported in several studies and duration of staying in a same room and environmental contamination could influence possibility of transmission of multidrug-resistant bacteria[12,23–26]. One prospective study was conducted for 29 methicillin-resistant *Staphylococcus aureus* (MRSA) index patients and 84 household contacts between 2005 and 2007, and it proposed that prolonged exposure time to MRSA index patients at home was the significant risk factor for MRSA transmission.[23] In this study duration of staying in a same room was not significantly different between close contact patients with and without transmission of CP-CRE. Other studies revealed that contaminated environment of a shared room could influence CP-CRE transmission in a hospital.[24,26]

This study has several limitations. First, there were only a few CP-CRE-transmitted cases, so it was impossible to find significant risk factors for CP-CRE transmission. Second, environmental cultures around places where CP-CRE index patients stayed had not been carried out, so information about environmental contamination in CP-CRE index cases could not be investigated. Moreover, several factors that could affect the rate of CP-CRE spread in a hospital, such as the number of antibiotics stewardship cases per 1000 patient-days, the ratio of caregivers to patients, and the amount of used hydro-alcoholic products were not investigated also.[22] Further studies should be conducted with information about environmental

culture studies, enforcement rate of antibiotic stewardship, or ratio of caregivers to patients, and more CP-CRE transmitted cases.

CONCLUSION

The rate of CP-CRE transmission in CP-CRE screening was calculated as 2.0% based on WGS analysis in the tertiary teaching hospital, and CP-CRE contacted healthcare workers were all negative in CP-CRE screening tests. Transmission of CP-CRE in shared rooms between CP-CRE index patients and close contact patients was not common, so CPE surveillance should be implemented in more selective and specific ways.

TABLES

Table 1. Demographic and clinical characteristics of CP-CRE index patients

Characteristics	CP-CRE index patients (N=47) (%)
Age (median) (years, IQR)	64 (52-73)
Sex	
Male	22 (46.8)
Female	25 (53.2)
Admitted department	
Emergency medicine	15 (31.9)
Internal medicine	9 (19.1)
General surgery	9 (19.1)
Neurology	7 (14.9)
Others	7 (14.9)
Duration of hospitalization till CP-CRE was detected (median) (days, IQR)	6 (2-12)
Underlying diseases	
Hematologic diseases or solid malignancy	20 (42.6)
Chronic kidney diseases	10 (21.3)
Chronic heart diseases	9 (19.1)
Chronic liver diseases	5 (10.6)
Chronic pulmonary diseases	3 (6.4)
Diabetes mellitus	6 (12.8)
Stroke	6 (12.8)
Organ transplantation	4 (8.5)
Bacterial species	
Klebsiella pneumoniae	29 (61.7)
Escherichia coli	7 (14.9)
Enterobacter species	7 (14.9)
Others	4 (8.5)
Types of carbapenemases	
KPC	32 (68.1)
NDM	15 (31.9)
OXA-48	2 (4.3)

Abbreviation: IQR, interquartile range; CP-CRE, carbapenemase-producing carbapenem-resistant Enterobacteriaceae; KPC, *Klebsiella pneumoniae* carbapenemase; NDM, New Delhi metallo-beta-lactamase

Table 2. Demographic and clinical characteristics of CP-CRE close contact patients

Characteristics	CP-CRE contact patients (N=152) (%)
Age (median) (years, IQR)	63.0 (49.5-72.0)
Sex	
Male	104 (68.4)
Female	48 (31.6)
Contacted department	
Emergency medicine	53 (34.9)
Internal medicine	28 (18.4)
General surgery	25 (16.4)
Neurology	18 (11.8)
Orthopedics	12 (7.9)
Neurosurgery	9 (5.9)
Others	7 (4.6)
Duration of hospitalization until CP-CRE surveillance (median) (days, IQR)	12 (7-23)
Duration of sharing a room with CP-CRE index patients (median) (days, IQR)	3 (2-7)
Underlying diseases	
Hematologic diseases or solid malignancy	66 (43.4)
Chronic kidney diseases	26 (17.1)
Chronic heart diseases	20 (13.2)
Chronic liver diseases	27 (17.8)
Chronic pulmonary diseases	16 (10.5)
Diabetes mellitus	43 (28.3)
Stroke	21 (13.8)
Organ transplantation	10 (6.6)
Previous hospitalization within 3 months	78 (51.3)
Previous intensive care within 3 months	27 (17.8)
Invasive procedure during the hospital course*	103 (67.8)
Use of broad spectrum antibiotics**	
Anti-pseudomonal penicillins	58 (38.2)
3rd or 4th generation cephalosporins	56 (36.8)
Quinolones	45 (29.6)
Carbapenems	30 (19.7)
Colistin	5 (3.3)
Tigecycline	2 (1.3)
Glycopeptides	35 (23.0)

Abbreviation: IQR, interquartile range

*Any type of percutaneous drainages and transfemoral interventions, central line insertion,

intracardiac device implantation, intubation or tracheostomy, endoscopic evaluation, biopsy or centesis, and surgery were included.

[**]Used in more than 3 days within 1 month

Table 3. Clusters of CP-CRE index patients, secondary patients, and CNP-CRE detected patients gone through WGS analysis

Number of cluster	Number of colony	Sex	Age	Specimen	Bacterial species	Types of carbapenemases
2017-6	**I-1**	**F**	**71**	**Sputum**	***Klebsiella pneumoniae***	**NDM-5, OXA-181**
	C-1-1	F	65	Rectal	*Klebsiella aerogenes*	negative
	C-1-2	F	72	Rectal	*Klebsiella aerogenes*	negative
2018-3	**I-2**	**M**	**72**	Rectal	***Klebsiella pneumoniae***	**KPC**
	C-2	F	78	Rectal	*Klebsiella pneumoniae*	KPC
2018-5	**I-3**	**F**	**78**	**Urine**	***Escherichia coli***	**KPC**
	C-3	F	55	Rectal	*Klebsiella pneumoniae*	KPC
2018-8	**I-4**	**M**	**66**	**TTA**	***Klebsiella pneumoniae***	**KPC**
	C-4	M	81	Rectal	*Klebsiella pneumoniae*	KPC
2018-11	**I-5**	**M**	**59**	**Sputum**	***Klebsiella pneumoniae***	**NDM**
	C-5	M	23	Rectal	*Klebsiella pneumoniae*	Negative
2018-13	**I-6**	**M**	**50**	**TTA**	***Enterobacter cloacae***	**NDM**
	C-6	M	70	Rectal	*Enterobacter cloacae*	Negative
2018-14	**I-7**	**M**	**70**	**sputum**	***Klebsiella pneumoniae***	**KPC**
	C-7	M	38	rectal	*Klebsiella pneumoniae*	KPC
2018-19	**I-8**	**M**	**23**	**urine**	***Klebsiella pneumoniae***	**KPC**
	C-8	M	23	rectal	*Klebsiella pneumoniae*	negative
2018-20	**I-9**	**M**	**56**	**BAL**	***Klebsiella pneumoniae***	**KPC**
	C-9-1	M	71	rectal	*Klebsiella pneumoniae*	negative
	C-9-2	M	94	rectal	*Klebsiella pneumoniae*	negative
2019-3	**I-10**	**M**	**83**	**rectal**	***Klebsiella pneumoniae***	**KPC**
	C-10	M	63	rectal	*Klebsiella pneumoniae*	negative

Abbreviation: I, index; C, colony; TTA, transtracheal aspiration; BAL, bronchoalveolar lavage

Table 4. Results of bacterial strain-typing by using WGS and matching to reference sequences

Number of colony	Best reference	Reads best reference (%)	Reads other references (%)
I-1	*K. pneumoniae* JM45	73.3	5.4
C-1-1	*K. aerogenes* KCTC2190	90.8	0.0
C-1-2	*K. aerogenes* KCTC2190	91.7	0.0
I-2	*K. pneumoniae* CG43	79.1	4.2
C-2	*K. pneumoniae* CG43	80.9	1.9
I-3	*E. coli* UMN026	63.4	3.6
C-3	*K. pneumoniae* CG43	21.4	5.3
I-4	*K. pneumoniae* CG43	84.8	3.5
C-4	*K. pneumoniae* CG43	84.6	3.6
I-5	*K. pneumoniae* HS11286	68.5	0.6
C-5	*K. pneumoniae* CG43	69.0	2.7
I-6	*E. cloacae* ATCC13047	68.7	0.0
C-6	*E. cloacae* ATCC13047	68.3	0.0
I-7	*K. pneumoniae* CG43	76.3	2.2
C-7	*K. pneumoniae* CG43	83.7	3.3
I-8	*K. pneumoniae* CG43	85.8	2.9
C-8	*K. pneumoniae* CG43	85.2	3.2
I-9	*K. pneumoniae* CG43	82.3	2.8
C-9-1	*K. pneumoniae* JM45	72.6	2.4
C-9-2	*K. pneumoniae* MGH78578	65.4	0.8
I-10	*K. pneumoniae* HS11286	70.2	2.3
C-10	*K. pneumoniae* CG43	83.4	3.8

Table 5. Results of remeasurement of MIC for imipenem and meropenem

Number of colony	Bacterial species	Imipenem MIC (μg/ml)	Meropenem MIC (μg/ml)
I-1	*K. pneumoniae*	32 (R)	128 (R)
C-1-1	*K. aerogenes*	4 (R)	1 (S)
C-1-2	*K. aerogenes*	4 (R)	2 (I)
I-2	*K. pneumoniae*	8 (R)	16 (R)
C-2	*K. pneumoniae*	16 (R)	8 (R)
I-3	*E. coli*	2 (I)	2 (I)
C-3	*K. pneumoniae*	16 (R)	32 (R)
I-4	*K. Pneumoniae*	4 (R)	2 (I)
C-4	*K. Pneumoniae*	4 (R)	2 (I)
I-5	*K. Pneumoniae*	64 (R)	128 (R)
C-5	*K. Pneumoniae*	≤0.5 (S)	2 (I)
I-6	*E. cloacae*	4 (R)	2 (I)
C-6	*E. cloacae*	≤0.5 (S)	≤0.5 (S)
I-7	*K. pneumoniae*	8 (R)	8 (R)
C-7	*K. pneumoniae*	8 (R)	8 (R)
I-8	*K. pneumoniae*	32 (R)	64 (R)
C-8	*K. pneumoniae*	2 (I)	16 (R)
I-9	*K. pneumoniae*	8 (R)	4 (R)
C-9-1	*K. pneumoniae*	4 (R)	8 (R)
C-9-2	*K. pneumoniae*	≤0.5 (S)	4 (R)
I-10	*K. pneumoniae*	128 (R)	≥256 (R)
C-10	*K. pneumoniae*	4 (R)	4 (R)

Table 6. Results of MLST including plasmid analysis in CP-CRE index patients and close contact patients who had CRE

(a) Pairs with concordance in distribution of housekeeping and resistance genes and plasmids

	Housekeeping genes							Resistance genes	Plasmids
	gapA	**infB**	**Mdh**	**pgi**	**phoE**	**rpoB**	**tonB**		
I-2 (*K. pneumoniae*)	4	1	2	52	1	1	7	KPC-2, OXA-1, TEM-104 (fragment), SHV-11 (fragment)	IncFIB(K)_1 & IncFIB(K)_1, IncFIB(pQil)_1, IncFII(K)_1, IncX3_1
C-2 (*K. pneumoniae*)	4	1	2	52, 52	1	1	7	KPC-2, OXA-1, TEM-1D, SHV-11 (fragment), CTX-M-15	IncFIB(K)_1, IncFII(K)_1, IncX3_1
I-4 (*K. pneumoniae*)	4	1, 1	2	52	1	1	7	KPC-2, OXA-1, TEM-1D, SHV-11, CTX-M-15	IncFIB(K)_1 & IncFIB(K)_1, IncFII(K)_1, IncX3_1, Col440I_1
C-4 (*K. pneumoniae*)	4	1	2	52	1	?	7	KPC-2, OXA-1, TEM-1D, CTX-M-15	IncFIB(K)_1 & IncFIB(K)_1, IncFII(K)_1, IncX3_1
I-7 (*K. pneumoniae*)	4	1, 1	2	52	1	1	7	KPC-2, OXA-1, TEM-1D, SHV-11, CTX-M-15	IncFIB(K)_1 & IncFIB(K)_1, IncFII(K)_1, IncX3_1, Col440I_1
C-7 (*K. pneumoniae*)	4	1	2	52	1	?	7	KPC-2, OXA-1, TEM-1D, CTX-M-15	IncFIB(K)_1 & IncFIB(K)_1, IncFII(K)_1, IncX3_1

(b) Pairs with discordance in distribution of housekeeping and resistance genes and plasmids

	Housekeeping genes							Resistance genes	Plasmids
	gapA	**infB**	**Mdh**	**Pgi**	**phoE**	**rpoB**	**tonB**		

I-1 (***K. pneumoniae***)	3	3, 3	1	1	1	1	4		
C-1-1 (***K. aerogenes***)	- (dnaA)	- (fusA)	5 (gyrB)	8 (leuS)	5 (pryG)	1 (rplB)	5 (rpoB)		
C-1-2 (***K. aerogenes***)	10 (dnaA)	- (fusA)	17 (gyrB)	3 (leuS)	- (pryG)	1 (rplB)	(rpoB)		
I-3 (*E. coli*)	23 (dinB)	9 (icdA)	8, 8 (pabB)	12 (polB)	9 (putP)	11 (trpA)	7 (trpB)	-	IncB/O/K/Z_1, IncFIA_1, IncFIB(AP001918)_1, IncFII(pRSB107)_1, IncFII(pSE11)_1, IncX3_1, Col156_1
C-3 (unidentified)	-	-	-	-	-	-	-	-	-
I-5 (unidentified)	-	-	-	-	-	-	-	-	-
C-5 (*K. pneumoniae*)	4	1	2	52	1	1	7	SHV-28, CTX-M-15	IncFIB(K)_1
I-6 (*E. cloacae*)	-	-	-	-	-	-	-	-	IncFIB(pHCM2)_1
C-6 (*E. cloacae*)	-	-	-	-	-	-	-	-	IncFIB(pHCM2)_1
I-8 (*K. pneumoniae*)	4	1	2	52	1	1	7	KPC-2 (fragment), OXA-1, TEM-1D, SHV-11 (fragment), CTX-M-15	IncFIB(K)_1, IncFII(K)_1, IncX3_1
C-8 (*K. pneumoniae*)	4	1	2	52, 52	1	1	7	SHV-28, CTX-M-15	IncFIB(K)_1 & IncFIB(K)_1
I-9 (*K. pneumoniae*)	4	1	2	52	1	1	7	KPC-2, OXA-9 (fragment), SHV-28	IncFIB(Mar)_1, IncFIB(pQil)_1, IncFII(K)_1, IncHI1B_1, Col440I_1

C-9-1 (Failed)	-	-	-	-	-	-	-	-	-
C-9-2 (*K. pneumoniae*)	3	4	6	1	7	4	40	OXA-1, SHV-11, CTX-M-15	IncFIB(K)_1 & IncFIB(K)_1, IncFII(K)_1
I-10 (*K. pneumoniae*)	25	10	1	1	20	1	22	KPC-2, SHV-25	IncFIA(HI1)_1, IncFIB(K)_1, IncFIB(pKPHS1)_1, IncFII(K)_1, IncFII(Yp)_1, IncX3_1, Col440I_1
C-10 (*K. pneumoniae*)	4	1	2	52	1	1	7	SHV-28, CTX-M-15	IncFIB(K)_1 & IncFIB(K)_1, IncFIB(pQil)_1, IncFII(K)_1 & IncFII(K)_1

Table 7. Description of 3 CP-CRE transmitted cases

Cluster number	2018-3		2018-8		2018-14	
Colony number	**I-2**	**C-2**	**I-4**	**C-4**	**I-7**	**C-7**
Sex/Age	M/72	F/78	M/66	M/81	M/70	M/38
Bacterial species/Carbapenemase type	*K. pneumoniae*/KPC	*K. pneumoniae*/KPC	*K. pneumoniae*/KPC	*K. pneumoniae*/KPC	*K. pneumoniae*/KPC	*K. pneumoniae*/KPC
Diagnosis	SFTS	Peripheral T cell lymphoma	Sick sinus syndrome	Dilated cardiomyopathy	Rectal cancer	IPMN of pancreas
Department of Wards	Emergency medicine, internal medicine	Internal medicine	Emergency medicine, internal medicine	Internal medicine	General surgery	General surgery
General condition*	Bed-ridden	Bed-ridden	Bed-ridden	Ambulatory	Bed-ridden	Ambulatory
Presence of invasive catheters	No	No	No	Pacemaker	Percutaneous nephrostomy, Pelvic percutaneous drainage	No
Duration of hospitalization till detection of CP-CRE (days)	5	10	2	11	5	24
Duration of sharing room (days)	2		4		4	
Invasive procedure during hospitalization**	Cerebrospinal fluid tapping	Chemoport insertion, axillary aspiration, bone marrow biopsy	Intubation	Pacemaker removal, Peripherally inserted central catheter insertion	No	Laparoscopic distal pancreatectomy & splenectomy
Use of broad spectrum antibiotics***	No	No	No	Vancomycin	Ertapenem, Vancomycin	Moxifloxacin
Previous hospitalization within 3 months	No	No	Yes	No	Yes	No
Previous intensive care within 3 months	No	No	No	No	No	No

Previous surgery within 3 months	No	No	No	No	No	Laparoscopic distal pancreatectomy & splenectomy
Previous immunosuppressive therapy within 3 months	No	No	No	No	Chemotherapy	No

Abbreviation: I, index; C, colony; SFTS, severe fever with thrombocytopenia syndrome; IPMN, intraductal papillary mucinous neoplasm;

*General condition at the moment of CP-CRE screening test was reviewed in nursing records.

**Any type of percutaneous drainages and transfemoral interventions, central line insertion, intracardiac device implantation, intubation or tracheostomy, endoscopic evaluation, biopsy or centesis, and surgery were included.

***Used in more than 3 days within 1 month

FIGURES

Figure 1. Flow of screening study objects

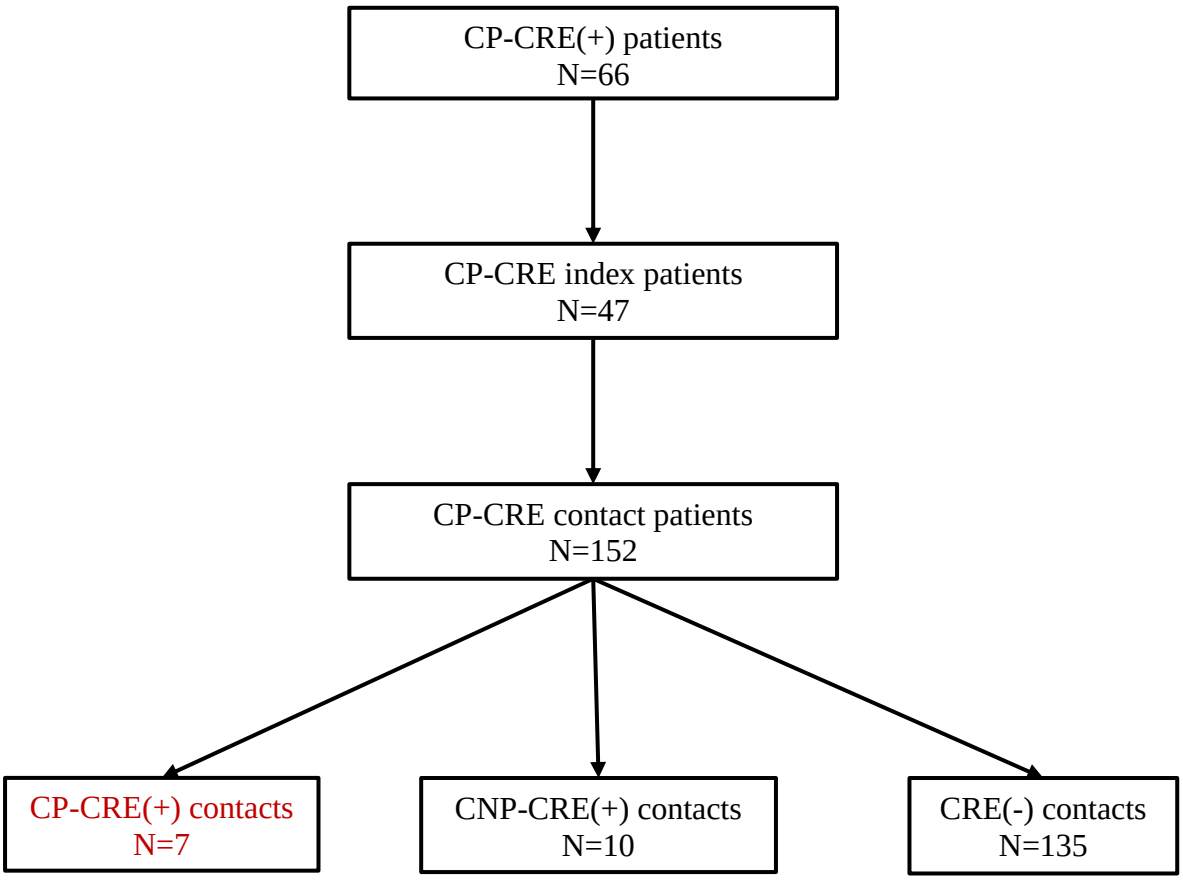
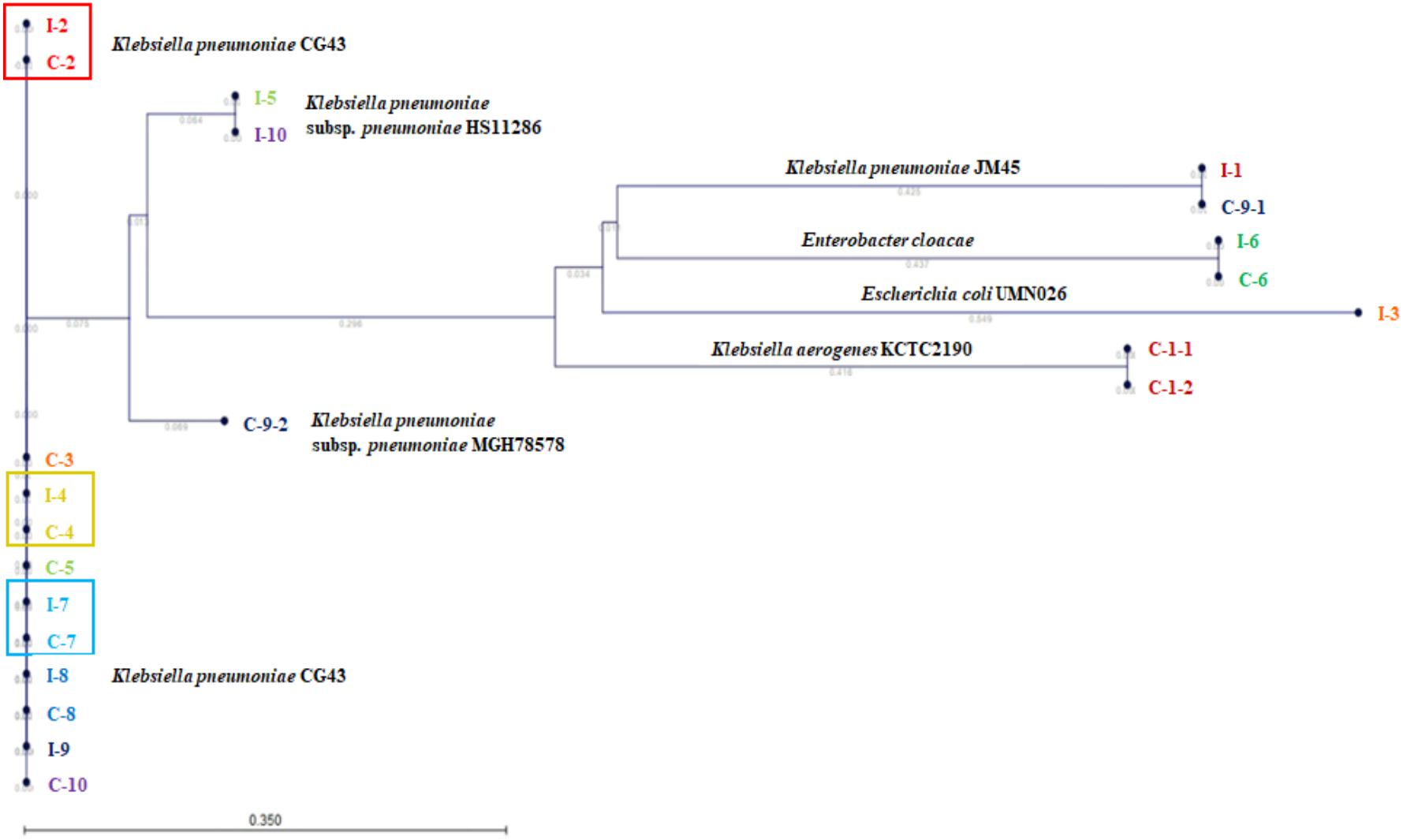


Figure 2. Phylogenetic trees of CP-CRE index patients and close contact patients who had CRE



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요약 (국문 초록)

밀접 접촉 환자 및 의료진을 대상으로 염기서열분석을 이용한 카바페넴분해효소 생성 장내세균속 전파율 조사

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장 의 진

서론: 카바페넴분해효소 생성 카바페넴 내성 장내세균속의 (carbapenemase-producing carbapenem-resistant Enterobacteriaceae, CP-CRE) 전파를 줄이기 위해 CP-CRE가 확인된 환자와 동실에 재원했던 환자들과 해당 환자를 돌보았던 의료진들에 대해 CRE 감시 검사를 하는 것이 추천된다. 본 연구의 목적은 CRE 감시 검사에서 CP-CRE 전파로 확인되는 경우의 분율을 파악하고 CP-CRE 전파의 위험인자를 밝히는 것이다.

방법: 본 연구는 2017년 1월부터 2019년 12월까지 1,751 병상의 3차 병원에서 후향적으로 진행됐다. 기준 환자는 입원 기간 동안 감염 부위나 집락 부위에서 CP-CRE 양성으로 확인되는 경우였다. 다인실에서 CP-CRE 기준 환자가 나왔을 경우 최소 1일 이상 동실에 재원했던 환자들과 기준 환자와 최소 1회 이상 접촉했던 의료진들에 대해 CRE 감시 검사를 시행했다. 감시 검사에서 CRE가 검출되면 다중연쇄반응 검사를 이용해 카바페넴분해효소의 유무를 확인했다. 또 염기서열 분석법과 카바페넴 최소억제농도 재측정, 다좌위 형별 분석을 통해 기준 환자와 접촉 환자 사이에 CP-CRE를 비롯한 CRE 전파가 있었는지 살펴보았다.

결과: 총 47명의 CP-CRE 기준 환자가 있었고, 206명의 환자와 의료진이 이 환자들과 접촉했다. 이들 중 14명의 환자들에서 CRE가 검출됐고 여기서 4명만이 CPE 기준 환자와 같은 종류의 카바페넴분해효소를 보유하고 있었다. 염기서열 분석법과 카바페넴 최소억제농도 재측정을 이용해서 이 4명 중 3명에서 CP-CRE 기준 환자와 접촉 환자 사이에 카바페넴분해효소 전파가 있었을 가능성을 보였다. 54명의 의료진에서는 CRE가 검출되지 않았다. 따라서 동실 재원 환자를 대상으로 한 CRE 감시 검사에서의 CP-

CRE 전파율은 2.0%로 계산됐다. CP-CRE 전파 사례 수가 적어 CP-CRE 전파의 위험인자는 분석하지 못했다.

결론: 동실 재원 환자를 대상으로 한 CRE 감시 검사에서의 CP-CRE 전파율은 2.0%였다. 의료진에서는 CRE가 검출되지 않았다.

주요어 : 카바페넴 분해 효소 생성 장내세균속; 전파; 감염 관리; 염기서열 분석법

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