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Xpert Carba-R assay for detection of carbapenemase-producing organisms in patients admitted to emergency rooms

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Abstract

Carbapenemase-producing organisms (CPO) have been identified as an urgent healthcare threat. Various methods have been used for the detection of CPO using rectal swabs. Recently, an on-demand polymerase chain reaction (PCR) assay, namely, the Xpert Carba-R assay, that requires less than an hour of turnaround time, had been developed for CPO detection in clinical samples. This study focused on the use of this assay to determine the intestinal colonization rate of CPO in patients admitted to emergency rooms (ERs).

A retrospective review of medical records was conducted at a tertiary hospital between July 2017 and June 2018. CPO screening using rectal swabs was performed for patients transferred from other hospitals or for those who tested positive in CPO culture tests in the previous three months. The Xpert Carba-R assay and culture tests were used as the CPO screening methods, and the results of both tests were compared.

Medical records of 705 patients admitted to our hospital during the study period were reviewed. Of these, 31 (4.4%) showed positive results for CPO using the Xpert Carba-R assay, and these patients were then transferred from the ERs to isolation rooms. Fifteen of the Xpert Carba-R assay-positive patients were also positive for the culture test; hence, early detection enabled the rapid isolation of CPO-infected patients and prevented the spread of the CPO.

The Xpert Carba-R assay is a rapid test to identify and guide infection control programs to contain the spread of the rectal colonization of CPO within a hospital.

Abbreviations: CP-CRE = carbapenemase-producing CRE, CPO = carbapenemase-producing organisms, CRE = carbapenem-resistant *Enterobacteriaceae,* CRO = carbapenem-resistant organisms, ER = emergency room, KCDC = Korea Center for Disease Control and Prevention, MHT = modified Hodge test, MIC = minimal inhibitory concentration, non-CP-CRE = non-carbapenemase-producing CRE, PCR = polymerase chain reaction, VRE = vancomycin-resistant *Enterococcus.*

Keywords: carbapenemase-producing organisms, enterobacteriaceae, xpert carba-r assay

1. Introduction

Multi-drug resistant bacteria have become a healthcare problem in Korea and around the world.[1–4] Recently, carbapenemase-producing organisms (CPO) such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii* have become some of the most problematic antibiotic-resistant bacteria in hospital environments.[5] Furthermore, carbapenem-resistant *Enterobacteriaceae* (CRE), including bacteria such as *Escherichia coli*, *Klebsiella pneumoniae*, and *Enterobacter cloacae*, are now commonly detected in the community.[6]

CRE can be classified into carbapenemase-producing CRE (CP-CRE) and non-carbapenemase-producing CRE (non-CP-CRE), according to the mechanisms that confer their antibiotic resistance profiles.[7] A typical resistance mechanism of CP-CRE is the production of a carbapenem-degrading enzyme, carbapenemase. Genes that produce carbapenemase are usually located in the plasmids, and therefore allow the transfer of resistance genes to other bacteria.[8] Through this mechanism, CP-CRE has been linked to outbreaks of infectious antibiotic resistance in healthcare facilities.[9]

A multi-faceted strategy is needed to minimize the worldwide spread of CPO, whereas rapid identification and isolation could help prevent their transmission.[10] Of the several CPO detection methods reported to date,[11] culture-based methods have been most frequently used; however, they have limitations with respect to sensitivity and specificity and have a long turnaround time of 24 to 48 hours.[12] Molecular tests have been developed to overcome these limitations, and the Xpert Carba-R assay (Cepheid, Sunnyvale, CA) has recently been used for CPO detection.[13] This method is based on a multiplex real-time

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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polymerase chain reaction (PCR) technique and has the advantage of detecting *bla*VIM, *bla*IMP, *bla*NDM, *bla*KPC, and *bla*OXA-48-like alleles. Furthermore, the results could be obtained within an hour.[14]

In Korea, as CRE cases have been increasing every year, mandatory surveillance has been conducted by the Korea Center for Disease Control and Prevention (KCDC).[15] According to the KCDC, there were 11,954 CRE cases in 2018, 15,265 in 2019, and 2,781 cases between January and mid-April 2020.[16] Cases were reported nationwide, although large numbers have been detected in larger cities, such as Seoul, Gyeonggi, and Busan.

This study was conducted in a tertiary hospital located in Busan, a large city in Korea, with a high prevalence of patients harboring CPO and VRE. CPO screening was performed using the Xpert Carba-R assay and the conventional culture method, and the results of the two methods were compared. Our hospital has been conducting vancomycin-resistant *Enterococcus* (VRE) screening for 10 years; hence, VRE screening was also conducted for patients harboring CPO. Through this, we aimed to establish the effectiveness of the Xpert Carba-R assay and the prevalence of carbapenem-resistant organisms (CRO) and VRE carriage among patients on admission to the ER.

2. Methods

2.1. Study design

This was a retrospective review study based on the medical records of patients who visited the ER of a 947-bed tertiary care hospital in Busan, Korea, from July 2017 to June 2018. During that period, the total number of patients admitted to the ERs was 21,991. CPO and VRE screenings were performed for patients transferred from other hospitals or those who had been tested positive for CPO or VRE within the previous three months. Specimens were obtained through a rectal swab performed immediately upon admission to the ER, and duplicate samples from the same patient were excluded from the study. A double swab set and a transport medium (Micromedia Co. Ltd., Seoul, Korea) were used to collect and transport the rectal swabs. One swab was used for CRE culture and the other for the Xpert Carba-R assay. PCR and culture test for VRE were also performed simultaneously.

Based on the institutional review board and the approval from Kosin University Gospel Hospital, the Xpert Carba-R assay and bacterial culture tests for CRE and VRE screenings were performed as described below.

2.2. Reference culture, carbapenem susceptibility test, and PCR assay for CRE

On the day of sample collection, a swab set was shipped to a microbiological laboratory for CRE culture test. We used an automated microbiology system (BD, Phoenix, USA) for CRE screening and the modified Hodge test (MHT) for CRE confirmatory tests. MHT was also performed for strains that were sensitive to carbapenem but had a high minimal inhibitory concentration (MIC). MacConkey agar plates (Micromedia Co., Ltd., Seoul, Korea) supplemented with meropenem disks (BD, Sparks, MD) were used for MHT, in accordance with the Clinical and Laboratory Standards Institute guidelines. CRE-positive specimens were sent to KCDC, and genetic analyses were conducted using PCR targeting on genes encoding six subtypes of carbapenemases: KPC, GES, NDM, IMP, VIM, and OXA-48.

2.3. Xpert carba-R assay

This assay was performed using the GeneXpert platform (Cepheid, Sunnyvale, CA). The Xpert Carba-R assay is a qualitative in vitro real-time PCR assay designed to detect five carbapenemase gene families, including *bla*IMP, *bla*KPC, *bla*NDM, *bla*OXA-48, and *bla*VIM. In more detail, the sample from a rectal swab transport tube was transferred into the elution reagent tube and vortexed at high speed for 10 s. Following the manufacturer's instructions, the contents of the elution reagent tube were transferred using the transfer pipette provided (approximately 1.7 mL) into the specimen chamber of the Xpert Carba-R cartridge. The results were interpreted by the GeneXpert System (Cepheid, Sunnyvale, CA). All swabs were processed according to the same procedure and the run time was 47 min.

2.4. Culture test and PCR assay for VRE

Two additional perianal swab specimens were collected from the patients for the VRE culture test and PCR assay. One of the samples was transferred in the Enterococcosel broth (Micromedia Co., Ltd., Korea) containing 6 μg/mL vancomycin and incubated at 37°C. In cases without growth at 72 hours of incubation, specimens were considered to be negative for VRE. Specimens in which nigrescence was observed during incubation were further cultured in blood agar. Bacterial identification and antibiotic sensitivity tests were performed using BD Phoenix™ (BD, Sparks, MD) on the colonies obtained from overnight incubation at 37°C. For the remaining samples, RT-PCR identification for resistance genes was conducted using the AdvanSure VRE vanA/vanB real-time PCR Kit (LG Life Sciences, Seoul, Korea).

2.5. Data analysis and resolution of discrepant results

To assess assay performance, the results of the Xpert Carba-R assay and the culture test serving as the reference method, were compared. For each specimen, results for each target gene were reported. Discrepant results were defined when different results were obtained from the Xpert Carba-R assay and the culture test performed on the same specimen. All statistical analyses were conducted with SPSS 23.0 software. Categorical variables were compared by Chi-square test or Fisher exact test, and P values $\leq .05$ were considered significant.

3. Results

3.1. Prevalence of CPO and VRE

In this study, results of 862 Xpert Carba-R assays were collected. Of these, 93 results from duplicated tests of the same patients were excluded and 64 results from patients without VRE screening were also excluded. Hence, a total of 705 specimens were included in the study, of which 31 (4.4%) were positive in the Xpert Carba-R assay and 38 (5.4%) were positive in the culture test. Among these, 148 specimens were positive for VRE (21.0%) (Table 1).

3.2. Xpert Carba-R assay results

The Xpert Carba-R assay detected 31 specimens positive for target genes namely, *bla*KPC ($n=15$), *bla*IMP-1 ($n=8$), *bla*NDM ($n=7$), and *bla*VIM ($n=1$). No specimen contained multiple

Table 1

Prevalence of CPO and VRE in clinical specimens.

Study result ($n=705$)	Xpert Carba-R assay *n* (%)	CRE culture test *n* (%)	VRE test *n* (%)
Positive	31 (4.3%)	38 (5.4%)	148 (21.0%)
Negative	674 (95.6%)	667 (94.6%)	557 (79.0%)

CPO = carbapenemase-producing organisms, CRE = carbapenem-resistant *Enterobacteriaceae*, VRE = vancomycin-resistant *Enterococcus*.

Table 3

Xpert Carba-R assay performance versus that of the carbapenem-resistant Enterobacteriaceae culture test.

	Culture-based method		
Xpert Carba-R assay	Positive	Negative	Total
Positive	15	16	31
Negative	23	651	674
Total	38	667	705

carbapenemase genes (Table 2). All results were obtained within 32 to 48 minutes.

Patients with positive results for the Xpert Carba-R assay were those transferred from other hospitals. Before transfer, 18 patients (58.1%) had been in the hospital for less than a month, and 13 (41.9%) for over a month. There was no statistical relationship between their hospital stay period before transfer and the target genes identified using the Xpert Carba-R assay ($P > .05$).

A total of 6 nursing hospitals had two or more Xpert Carba-R assay-positive patients and all the remaining patients were from different hospitals. Three of the 6 nursing hospitals had patients with a single subtype of carbapenemase, 2 with KPC, and one with NDM. None of the nursing hospitals had reported outbreaks.

Among the patients with positive results, 18 (58.1%) had a history of antibiotic use within the previous 3 months, of which 8 were for carbapenem use (25.8%), 2 for cephalosporin (6.5%), 5 for quinolone (16.1%), and 3 for ampicillin (9.7%). Subsequently, 26 (83.9%) were isolated in single rooms, 3 (9.7%) were transferred to another hospital, 1 (3.2%) was discharged, and 1 (3.2%) died in the emergency room.

3.3. Comparison between the Xpert Carba-R assay and culture test

Table 3 shows the performance of the Xpert Carba-R assay compared with that of the culture test. A specimen was considered positive in the Xpert Carba-R assay if at least one of the carbapenemase genes was detected. A specimen was considered negative when none of the target genes were detected. Of the 705 specimens, 38 were positive for CRE by the culture test. The bacteria isolated were partially or completely resistant to at least one carbapenem.

Among the 38 (5.4%) CRE-positive specimens, *Escherichia coli* was also isolated in 14 specimens, *Klebsiella pneumoniae* in 14, *Enterobacter* in 9, and one specimen contained *Citrobacter*.

Table 2

Xpert Carba-R assay results by target carbapenemase genes.

Xpert Carba-R assay results	Specimens ($n=705$)
Positive	31
KPC	15
IMP	8
NDM	7
VIM	1
OXA-48	0
Negative	674

IMP = imipenemase, KPC = *Klebsiella pneumoniae* carbapenemase, NDM = New Delhi metallo-β-lactamase, OXA-48 = oxacillinase-48, VIM = Verona integron-mediated metallo-β-lactamase.

In terms of sensitivity to carbapenems, 20 patients (52.6%) had bacteria resistant to imipenem, meropenem, and ertapenem; 4 patients had bacteria resistant to imipenem and ertapenem (10.5%); 3 patients had bacteria resistant to meropenem and ertapenem (7.9%); and 11 patients had bacteria resistant only to ertapenem (28.9%).

Of the culture-positive specimens, 35 (92.1%) were collected from patients transferred from nursing hospitals and 3 (7.9%) were re-examined patients who had positive CRE culture results when they were admitted to our hospital.

3.4. Discrepant results

There were 23 specimens that tested negative for the target genes using the Xpert Carba-R assay, but tested positive in the culture test. Of these, two specimens were positive in MHT and PCR assays as conducted by the KCDC; it was later confirmed that these were false negative results of the Xpert Carba-R assay. The PCR assays performed at KCDC revealed that one of these specimens contained KPC-2 and the other contained NDM 5.

These 23 patients were moved out from the emergency room; 4 were transferred to another hospital, 3 were discharged, 2 were transferred each in a single room, and 14 were transferred to a multi-person room. Patients in the multi-person room included the two who had false negative results from the Xpert Carba-R assay mentioned above (Table 4).

Of the culture-positive patients, the results of Xpert Carba-R assay were analyzed. The percentage of resistance to all of imipenem, ertapenem, and meropenem was higher in the assay-positive patient group (Table 5). Of the specimens resistant to all carbapenems, 93.3% were Xpert Carba-R assay-positive, but for the specimens partially resistant to carbapenems, only 6.7% were Xpert Carba-R assay-positive ($P < .001$). Sixteen specimens tested positive in the Xpert Carba-R assay but were negative in the CRE culture test (Table 6).

3.5. Comparison between the results of CRE test and VRE screening

Positive VRE screening results were confirmed in 148 out of the 705 specimens (21.0%). In 25 (46.3%) out of the 54 patients who were Xpert Carba-R assay-positive and/or CRE culture test-positive, the VRE screening results were also positive. All patients with a Van A gene-positive result from the PCR assay were also VRE culture-positive.

4. Discussion

In tertiary hospitals, such as ours, many patients are immunocompromised, and infection with these strains is fatal. Identification of patients who are colonized with CPO, as an effort to

Table 4

Discrepant results for Xpert Carba-R assay and for carbapenem-resistant Enterobacteriaceae culture test.

		Test results						
	Target detected by Xpert Carba-R Assay	Culture	MHT	Carbapenemase PCR	Resistant to specific carbapenem E I M			Patient isolation
1	None	*Escherichia coli*	Negative	None	R	R	R	M room
2	None	*Enterobacter cloacae*	Positive	KPC-2	R	R	S	M room
3	None	*Klebsiella pneumoniae*	Negative	None	R	S	S	M room
4	None	*Klebsiella pneumoniae*	Negative	None	R	S	R	transferred
5	None	*Escherichia coli*	Negative	None	R	S	I	transferred
6	None	*Enterobacter cloacae*	Positive	NDM-5	R	R	R	M room
7	None	*Klebsiella pneumoniae*	Negative	None	R	S	I	M room
8	None	*Klebsiella pneumoniae*	Negative	None	R	R	I	M room
9	None	*Enterobacter cloacae*	Negative	None	R	I	S	S room
10	None	*Enterobacter cloacae*	Negative	None	R	R	R	M room
11	None	*Escherichia coli*	Negative	None	R	S	R	transferred
12	None	*Escherichia coli*	Negative	None	R	R	S	S room
13	None	*Klebsiella pneumoniae*	Negative	None	R	I	S	discharged
14	None	*Escherichia coli*	Negative	None	R	S	I	transfer
15	None	*Escherichia coli*	Negative	None	R	S	S	M room
16	None	*Escherichia coli*	Negative	None	R	S	S	M room
17	None	*Escherichia coli*	Negative	None	R	S	S	M room
18	None	*Klebsiella pneumoniae*	Negative	None	R	I	R	M room
19	None	*Enterobacter cloacae*	Negative	None	R	S	S	discharged
20	None	*Enterobacter cloacae*	Negative	None	R	S	S	discharged
21	None	*Klebsiella pneumoniae*	Negative	None	R	R	R	M room
22	None	*Klebsiella pneumoniae*	Negative	None	R	R	R	M room
23	None	*Enterobacter cloacae*	Negative	None	R	R	R	M room

E = ertapenem, I = imipenem, I = intermediate resistance, KPC = Klebsiella pneumoniae carbapenemase, M room = multi-patient room, M = meropenem, MHT = modified Hodge test, NDM = New Delhi metallo-β-lactamase, PCR = polymerase chain reaction, R = fully resistant, S room = single-patient room, S = susceptible.

control the spread of infection and as recommended by public health organizations, such as KCDC,[17] is becoming increasingly important, especially in regions with a high prevalence of the infection. It is thought that there will be differences in the setting up of targets for conducting CRO tests by country and by hospital; nevertheless, molecular techniques have been increasingly favored due to their rapid turnaround times combined with higher sensitivity and specificity. By using the Xpert Carba-R assay for a group of patients with high CRO risk, it is possible to prevent the unnecessary use of single-person rooms while awaiting the results of the CRO test per conventional testing as well as to avoid the risk of CRO outbreaks due to the use of multi-person rooms.

In this study, we evaluated the performance of the Xpert Carba-R assay for the detection of carbapenemase genes directly from rectal swabs. The Xpert Carba-R assay positivity rate was 4.4%, with KPC as the most common carbapenem-resistant gene. Similar results were also observed in the study conducted by KCDC, based on the 2018 data.[16]

Table 5

Susceptibility to carbapenems detected using Xpert Carba-R assay for culture positive specimens.

	Xpert Carba-R-negative ($n=23$)	Xpert Carba-R-positive ($n=15$)	*P* value
Resistance to carbapenem			<.001
Partial resistance to I, E, M	17 (73.9%)	1 (6.7%)	
Full resistance to I, E, M	6 (26.0%)	14 (93.3%)	

E = ertapenem, I = imipenem, M = meropenem.

There are several causes for the increase in carbapenem-resistant strains, among which are carbapenem overuse, abuse, and the propagation of carbapenemase-expressing genes through plasmids.[18–20] We examined the effects of antibiotic use in patients three months prior to the Xpert Carba-R assay, and 41.9% did not use any antibiotics. From this, it can be considered that the dissemination of CPO via plasmids accounts for a large proportion of the resistant strains detected. Therefore, transmission control is important for CPO infection control. Results from the Xpert Carba-R assays were confirmed within one hour, except for in one case; all patients with positive results were isolated in single-patient rooms at the point of admission. As a result, we were able to prevent the possibility of CPO spread much earlier compared to the time that would have been taken using the conventional culture test method.

However, there were some patients who tested CPO-negative in the Xpert Carba-R assay but tested positive in the culture test. Some studies have reported that the Xpert Carba-R assay might generate a negative IMP result when the same sample also contains IMP-7, -13, or -14, and a recent report showed that the Xpert Carba-R assay is not reliable for the detection of OXA-48-like genes.[21,22] In this study, 23 specimens were Xpert Carba-R assay-negative, but culture test-positive. Of these, two specimens were positive for MHT and PCR assay, indicating that one possessed KPC-2 and the other possessed NDM 5, respectively. This result was a confirmed false negative of the Xpert Carba-R assay. In these two cases, the negative results were not associated with a specific carbapenemase and may have been associated with low bacterial load in the rectal swab specimens. Due to their false negative results, patients who should have been immediately isolated were not; instead, they were only isolated when the

Table 6

Discrepant results showing isolates positive for Xpert Carba-R assay but negative for CRE culture test.

Sample	Target detected by Xpert Carba-R assay	Culture, Species of CRO	Specimen	Antibiotics used in previous three months	Previous hospitalisation period
1	IMP	No isolate		None	7 days
2	KPC	No isolate		None	3 days
3	IMP	No isolate		None	3 months
4	IMP	*Pseudomonas aeruginosa*	Blood	Quinolone	5 months
5	IMP	*Pseudomonas aeruginosa*	Sputum	Quinolone	2 months
6	VIM	No isolate		Carbapenem	4 months
7	IMP	No isolate		None	6 months
8	IMP	No isolate		Ampicillin	1 month
9	KPC	No isolate		None	7 months
10	KPC	No isolate		None	1 month
11	NDM	No isolate		Quinolone	2 weeks
12	KPC	No isolate		None	5 years
13	NDM	No isolate		Quinolone	1 month
14	IMP	No isolate		Carbapenem	1 month
15	NDM	No isolate		Ampicillin	4 months
16	IMP	*Pseudomonas aeruginosa*	Sputum	Carbapenem	7 days

CRE = carbapenem-resistant Enterobacteriaceae, CRO = carbapenem-resistant organism, IMP = imipenemase-metallo-β-lactamase, KPC = *Klebsiella pneumoniae* carbapenemase, NDM = New Delhi metallo-β-lactamase, VIM = Verona integron-mediated metallo-β-lactamase.

results were confirmed using a culture test three days later. For patients with Xpert Carba-R assay-negative but culture test-positive results, the possibilities of non-CP- or specific carbapenemase series-CRE, and low bacterial load in the rectal swabs must be considered.

Culture test-positive patients were subdivided into cases showing resistance to all carbapenems and cases showing partial resistance. The Xpert Carba-R assay-positive rate was 93.3% for strains showing resistance to all carbapenems, but only 6.7% for cases of partial carbapenem resistance. To overcome this limitation, it may be necessary to improve the sensitivity of the Xpert Carba-R assay for each carbapenemase gene as well as the gene families.

There were 16 specimens that tested positive in the Xpert Carba-R assay but negative in the culture test. Here, we suggest some possible causes for these results. First, due to the increased sensitivity of NAAT (nucleic acid amplification technique), not all positive Xpert Carba-R assay results could be confirmed by the culture test. We followed the carbapenem resistance cut-off value for *Enterobacteriaceae* stated in the CLSI guidelines; however, this cut-off value can cause low levels of CPO resistance to be missed. Second, the possibility that some strains resistant to carbapenem did not grow well during culturing must be considered. Culture results for specimens taken from other parts of the patient were examined in cases who were Xpert Carba-R assay-positive and culture-negative. In three of the 16 cases, carbapenem-resistant *Pseudomonas aeruginosa* was detected in the blood and sputum specimens (Table 6).

Positive VRE screening results were detected in 148 patients (21.0%), whereas 54 (7.7%) showed a positive CPO test, regardless of the use of the Xpert Carba-R assay and/or the culture test. Statistics from KCDC and other studies also showed higher VRE colonization compared to CPO.[23,24] In particular, of the patients who tested positive for CPO, the proportion of positive VRE screening results was also relatively higher, at 46.3%, as compared to only 18.9% of the CPO-negative group tested positive for VRE. This seems to be indicative of hospital-acquired infections, because most of the CPO-positive patients had been initially admitted to other hospitals before being transferred to ours.

There are some limitations in this study. This is a retrospective study covering only a single healthcare facility. Further, additional analysis on the discrepant results due to the inconsistencies between the culture test and the Xpert Carba-R assay is crucial. As for the setback due to false negative results, additional research is required to improve the accuracy of the Xpert Carba-R assay for infection control.

In conclusion, the Xpert Carba-R assay is a reliable and accurate multiplex qualitative assay suitable for the rapid detection of CPO among patients on admission to the ER. Compared to culture-based methods, direct testing on samples using the Xpert Carba-R assay reduces the turnaround time. This allows clinicians and infection control personnel to make accurate and rapid decisions to reduce the transmission of these antibiotic resistance organisms within healthcare facilities. Further research on modalities to prevent the spread of hospital-acquired antibiotic resistance should continue not only for VRE, but also for CPO.

Author contributions

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