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MAJOR ARTICLE

Comparison of the Clinical Outcomes of Patients With Positive Xpert Carba-R Tests for Carbapenemase-Producing Enterobacterales According to Culture Positivity

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Background. We aimed to compare the clinical outcomes of patients with positive Xpert Carba-R assay results for carbapenemase-producing Enterobacterales (CPE) according to CPE culture positivity.

Methods. We retrospectively collected data for patients with positive CPE (positive Xpert Carba-R or culture) who underwent both tests from August 2018 to March 2021 in a 2700-bed tertiary referral hospital in Seoul, South Korea. We compared the clinical outcomes of patients positive for Xpert Carba-R according to whether they were positive (XPCP) or negative (XPCN) for CPE culture.

Results. Of 322 patients with CPE who underwent both Xpert Carba-R and culture, 313 (97%) were positive for Xpert Carba-R for CPE. Of these, 87 (28%) were XPCN, and 226 (72%) were XPCP. XPCN patients were less likely to have a history of previous antibiotic use (75.9% vs 90.3%; $P = .001$) and to have *Klebsiella pneumoniae* carbapenemase (21.8% vs 48.9%; $P < .001$). None of the XPCN patients developed infection from colonization within 6 months, whereas 13.4% (29/216) of the XPCP patients did ($P < .001$). XPCN patients had lower transmission rates than XPCP patients (3.0% [9/305] vs 6.3% [37/592]; $P = .03$). There was no significant difference in CPE clearance from positive culture results between XPCN and XPCP patients (40.0% [8/20] vs 26.7% [55/206]; $P = .21$).

Conclusions. Our study suggests that XPCN patients had lower rates of both infection and transmission than XPCP patients. The Xpert Carba-R assay is clinically useful not only for rapid identification of CPE but also for predicting risks of infection and transmission when performed along with culture.

Keywords. carbapenemase; carbapenemase-producing Enterobacterales; culture; PCR; Xpert Carba-R assay.

Carbapenem resistance is mediated by a heterogenous mechanisms, including production of carbapenemase, extended ß-lactamase, and/or AmpC cephalosporinases combined with active drug efflux or membrane impermeability [1]. Carbapenemase-producing Enterobacterales (CPE) infections have been increasing rapidly [2], causing rapid transmission and outbreaks in healthcare facilities worldwide [3]. The Xpert Carba-R assay (Cepheid, Sunnyvale, California) has been used for rapid identification of carbapenemase from clinical and surveillance specimens [4]. It is designed to detect 5 common carbapenemase genes (bla_{KPC}, bla_{NDM}, bla_{VIM}, bla_{IMP-1}, and bla_{OXA-48}) using the multiplex real-time polymerase chain reaction (PCR) technique [5], and its performance has been evaluated [4, 6–8].

Since the detection of carbapenemase genes does not indicate the presence of CPE organisms, concomitant culture is recommended to confirm the presence of these organisms [9]. The clinical implications of positive carbapenemase PCR without viable organisms have not been evaluated. In addition, there are no data on whether patients with positive PCR results without viable organisms develop positive culture conversion, defined as recovery of CPE from follow-up culture, and whether in patients with positive PCR results the clinical outcomes differ between those with positive initial concomitant culture results and those with negative initial concomitant culture results.

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This study aimed to compare the clinical outcomes of patients with positive Xpert Carba-R assay results according to the results of concomitant CPE culture.

METHODS

Study Population and Design

We retrospectively collected the data of patients with positive CPE results from either Xpert Carba-R assay or clinical and/or surveillance cultures who underwent both tests in a 2700-bed tertiary referral hospital in Seoul, South Korea, from August 2018 to March 2021. We performed active surveillance tests for CPE using both the Xpert Carba-R assay and culture when there was confirmation of an outbreak, as previously defined [10]. Routine preadmission surveillance by both Xpert Carba-R assay and culture were implemented in the liver transplantation, hematology, and hepatogastroenterology units from August 2018 due to several outbreaks and high prevalence of CPE isolates in clinical culture from these departments of our center. Also, patients exposed to CPE-positive patients by sharing a room underwent active surveillance using both the Xpert Carba-R assay and culture. Only data obtained for the first positive results for CPE are included.

Clinical data were collected from electronic medical records and included the following: demographics, preexisting medical conditions, antibiotic use within 3 months, microbiological data, and outcomes. We analyzed the clinical outcomes of patients with positive Xpert Carba-R who were either negative for culture for CPE (XPCN) or positive for culture for CPE (XPCP).

Study Definitions

We classified initial presentation as colonization or infection. Colonization was defined as a patient having a positive result for CPE without clinical symptoms. CPE infection was identified when a patient demonstrated signs or symptoms of infection with at least 1 clinical positive result for CPE. CPE isolates were classified as nosocomial in cases where patients who had been hospitalized for 48 hours or longer. Community-onset healthcare-associated acquisition was classified as healthcare associated or community acquired according to the definition provided by Cardoso et al [11]. Immunosuppressant use was defined as described elsewhere [12]. Patients receiving immunosuppressants included those receiving cancer chemotherapy, daily corticosteroid of ≥20 mg of prednisolone or equivalent for ≥14 days, certain biologic immune modulators, and patients within 2 months of solid organ transplantation.

Positive culture conversion was defined when patients with positive Xpert Carba-R and negative culture for CPE (XPCN) gave positive results for CPE in follow-up cultures. While in hospital, patients with CPE underwent weekly follow-up culture, until clearance, but not Xpert Carba-R assay. CPE clearance was defined as 3 consecutive negative results of follow-up culture, and indeterminate was defined as 1 or 2 consecutive negative results of follow-up culture in cases where at least 3 follow-up cultures were not performed. Transmission rate was defined as the rate of CPE isolation with identical carbapenemase by Xpert Carba-R assay with or without identical organism in patients exposed to index patients. Exposed patients were defined as those who occupied the same room as an index patient with positive results for CPE.

Microbiological Data

We defined CPE as carbapenem-resistant Enterobacterales (CRE) with any carbapenemase (*Klebsiella pneumoniae* carbapenemase [KPC], New Delhi metallo-β-lactamase [NDM], imipenemase [IMP], Verona integron–encoded metallo-β-lactamase [VIM], or oxacillinase 48 [OXA-48]), and CRE as Enterobacterales isolates demonstrating resistance to any carbapenem (ertapenem, meropenem, or imipenem) based on antimicrobial susceptibility testing [13]. We introduced Xpert Carba-R assay version 2 (Cepheid) for surveillance for CPE during outbreaks, as described previously [14]. We performed Xpert Carba-R assay using stool specimen and surveillance culture mostly using stool specimens and replaced with other specimens if stool samples were unavailable. For surveillance cultures we used ChromID CARBA agar (bioMérieux, France), followed by matrix-assisted laser desorption/ionization–time of flight mass spectrometry (Bruker, Daltonics, Germany) for species identification. For clinical cultures we used blood agar (Tryptic Soy Agar with 5% sheep blood) and MacConkey agar plate. Species identification and antimicrobial susceptibilities were determined using the MicroScan WalkAway 96 plus system and Neg Combo Panel Type 72 (Beckman Coulter, Brea, California), and the standard criteria set by the Clinical and Laboratory Standards Institute [15]. The presence of carbapenemase genes was evaluated by PCR using specific primers [16].

Statistical Analysis

Student *t* test or the Mann-Whitney *U* test was used to compare differences between continuous variables, and the Pearson χ^2 test or Fisher exact test was used for the corresponding categorical variables, as appropriate. A 2-tailed *P* value of < .05 was considered statistically significant. All statistical analyses were performed with SPSS software, version 21.0 (SPSS Inc, Chicago, Illinois).

Patient Consent Statement

This observational study was approved by the Institutional Review Board of the Asan Medical Center. Informed consent was waived by the ethics committee of the Asan Medical Center because no intervention was involved and no patient-identifying information was included. To protect personal

privacy, identifying information in the electronic database was encrypted.

RESULTS

Patients and Microbiological Characteristics

A total of 37 791 surveillance cultures for CPE were performed, and 1541 patients with positive CPE results from either the Xpert Carba-R assay or culture were identified during the study period (Figure 1). Of these, 322 (20.9%) underwent both Xpert Carba-R assay and culture for CPE; 89 had an Xpert assay performed for routine preadmission surveillance, 206 for outbreak-related surveillance, 17 for exposure-related surveillance, and 10 for unknown reason. Among 313 (97%) with positive Xpert Carba-R results, 87 (28%) were XPCN and 226 (72%) were XPCP. Of 313 patients, 304 underwent surveillance culture while 9 underwent clinical culture at the time of first isolation of CPE; in XPCP patients, 217 underwent surveillance culture and 9 clinical culture, and in XPCN patients, all 87 underwent surveillance culture.

Comparisons of the clinical and microbiological characteristics of the patients with XPCP and XPCN are shown in Table 1. There were no differences in year of first isolation, days from admission to Xpert-positive day, and wards between XPCN and XPCP patients. Among XPCP patients, 217 underwent surveillance culture, and 9 underwent clinical culture at the time of first isolation of CPE. For outbreak-related surveillance, the proportion of XPCP patients was significantly higher compared to that of XPCN patients (67.7% [153/226] vs 52.9% [46/87]; $P = .02$). XPCN patients had a greater tendency to be community acquired than those with XPCP (10.3% [9/87] vs 4.0% [9/226]; $P = .053$) and were less likely to receive immunosuppressants (32.2% [28/87] vs 44.2% [100/226]; $P = .052$). They were also less likely to have a history of previous antibiotic use (75.9% [66/87] vs 90.3% [204/226]; $P = .001$), less likely to have KPC (21.8% [19/87] vs 48.9% [110/226]; $P < .001$), and more likely to have OXA-48–like carbapenemase (12.6% [11/87] vs 1.3% [3/226]; $P < .001$) and IMP carbapenemase (8.0% [7/87] vs 0.9% [2/226]; $P = .002$). The susceptibility pattern of the CPE isolates among XPCP at the time of the first clinical culture (n = 9) is shown in Supplementary Figure 1.

Clinical Outcomes

None of the XPCN patients developed infections due to colonization within 6 months, whereas 13.4% (29/216) of the XPCP patients did ($P < .001$) (Table 2). Positive culture conversion occurred in 20 of the 87 (23%) XPCN patients, after 1 (median) follow-up culture a median of 9 days from the initial positive Xpert Carba-R assay; 13 (65%) were positive for NDM-producing isolates and 7 (35%) for KPC-producing ones. There was no significant difference in CPE clearance after positive culture results between XPCN and XPCP patients (40.0% [8/20] vs 26.7% [55/206]; $P = .21$). In XPCN, 63% of patients who showed CPE clearance carried NDM, and 38% carried KPC. In XPCP, 60% of patients with CPE clearance carried NDM, 33% carried KPC, and 11% carried other types of carbapenemase. XPCN patients had a lower transmission rate (3.0% [9/305] vs 6.3% [37/592]; $P = .03$). Culture conversion occurred in 2 of the 8 XPCN patients who were responsible for transmission, but transmission took place before culture conversion. There was no significant difference in 30-day mortality between XPCN and XPCP patients (2.3% [2/87] vs 5.8% [13/226]; $P = .25$).

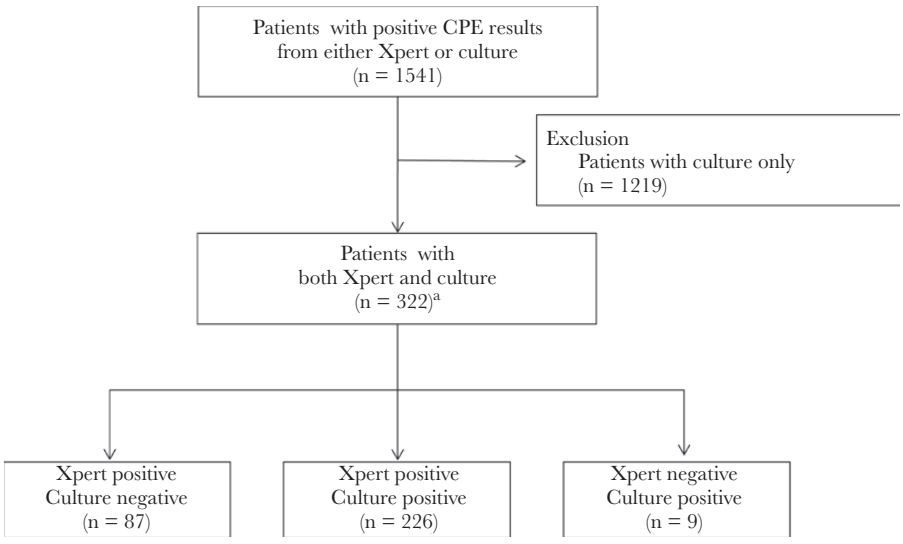

Figure 1. Flowchart of included patients with positive carbapenemase-producing Enterobacterales (CPE) results. [a]Of 322 patients, 89 underwent Xpert assay for routine preadmission surveillance, 206 for outbreak-related surveillance, 17 for exposure-related surveillance, and 10 for unknown reason.

Table 1. Characteristics of Patients With Positive Xpert Carba-R Results for Carbapenemase at Time of First Isolation According to Culture Positivity

Variable	Culture Negative (n = 87)	Culture Positive (n = 226)	*P* Value
Year of first isolation			.09[a]
2018	19 (21.8)	35 (15.5)	
2019	13 (14.9)	39 (17.3)	
2020	44 (50.6)	97 (42.9)	
2021	11 (12.6)	55 (24.3)	
Day from admission to Xpert positive day	2 (0–9)	7 (0–13)	.68[b]
Hospital ward			
Intensive care unit	23 (26.4)	47 (20.8)	.29[c]
Medical ward	34 (39.1)	88 (38.9)	>.99[c]
Surgical ward	30 (34.5)	89 (39.4)	.44[c]
Outpatient	0	2 (0.9)	>.99[c]
Reason for Xpert Carba-R test			
Routine preadmission surveillance	34 (39.1)	53 (23.5)	.01[c]
Outbreak-related surveillance	46 (52.9)	153 (67.7)	.02[c]
Exposure-related surveillance	4 (4.6)	13 (5.8)	.79[c]
Unknown	3 (3.4)	7 (3.1)	>.99[c]
Site of acquisition			
Community acquired	9 (10.3)	9 (4.0)	.053[c]
Nosocomial	46 (52.9)	131 (58.0)	.45[c]
Community onset, healthcare associated	32 (36.8)	86 (38.1)	.90[c]
Preexisting medical condition			
Previous surgery within 6 months	36 (41.4)	117 (51.8)	.10[a]
Diabetes mellitus	19 (21.8)	66 (29.2)	.19[a]
Liver cirrhosis	41 (47.1)	129 (57.1)	.11[a]
End-stage renal disease	17 (19.5)	47 (20.8)	.81[a]
Congestive heart failure	17 (19.5)	27 (11.9)	.08[a]
Immunosuppressant use	28 (32.2)	100 (44.2)	.052[a]
Solid cancer	23 (26.4)	81 (35.8)	.11[a]
Chemotherapy within 6 months	19 (21.8)	54 (23.9)	.70[a]
Solid organ transplant	28 (32.2)	95 (42.0)	.11[a]
Hematologic malignancy	13 (14.9)	39 (17.3)	.62[a]
Neutropenia	4 (4.6)	14 (6.2)	.79[c]
Previous antibiotics within 3 months	66 (75.9)	204 (90.3)	.001[a]
Previous ß-lactam use within 3 months	66 (75.9)	199 (88.1)	.01[a]
Previous carbapenem use within 3 months	16 (18.4)	51 (22.6)	.42[a]
Meropenem MIC, μg/mL			
Surveillance culture			
>2	NA	216/217 (99.5)	
>4[d]	NA	1/217 (0.5)	
Clinical culture[e]			
8	NA	1/9 (11.1)	
>8	NA	8/9 (88.9)	
Specimen			
Stool	87 (100.0)	217 (96.0)	.07[c]
Sputum	0	10[f] (4.4)	.07[c]
Blood	0	2[g] (0.9)	>.99[c]
Urine	0	1 (0.4)	>.99[c]
Other[h]	0	2 (0.9)	>.99[c]
Type of carbapenemase			
NDM	50 (57.5)	112 (49.8)	.22[a]
KPC	19 (21.8)	110 (48.9)	<.001[a]

Table 1. Continued

Variable	Culture Negative (n = 87)	Culture Positive (n = 226)	*P* Value
OXA-48–like	11 (12.6)	3 (1.3)	<.001[c]
IMP	7 (8.0)	2 (0.9)	.002[c]
VIM	3 (3.4)	12 (5.3)	.57[c]

Data are presented as No. (%) of patients unless otherwise specified.

Abbreviations: IMP, imipenemase; KPC, *Klebsiella pneumoniae* carbapenemase; MIC, minimum inhibitory concentration; NA, non-available; NDM-1, New Delhi metallo-β-lactamase-1; OXA, oxacillinase; VIM, Verona integron–encoded metallo-β-lactamase.

Statistical analysis was used as follows:

[a]Pearson χ^2 test;

[b]Student *t* test;

[c]Fisher exact test.

[d]One patient performed sputum surveillance culture.

[e]Of 9 patients who performed clinical culture, 4 performed sputum culture, 2 performed blood culture, 2 performed clinical culture from pigtail catheter for intra-abdominal fluid collection, and 1 performed urine culture.

[f]Of 10 patients, 5 performed both sputum culture and stool surveillance culture.

[g]Of 2 patients, 1 performed both blood culture and stool surveillance culture.

[h]Two isolates were collected at clinical culture from pigtail catheter for intra-abdominal fluid collection.

DISCUSSION

In this study, we found that CPE culture was negative in more than a quarter of patients with CPE when the Xpert Carba-R assay and culture were performed concurrently. In addition, XPCN patients were less likely to develop infection and transmit the CPE to others.

In the present study, of the patients with positive results for the Xpert Carba-R assay, 28% (87/313) were negative for CPE

Table 2. Clinical Outcomes of Patients With Positive Xpert Carba-R Results for Carbapenemase at Time of First Isolation According to Culture Positivity

Variable	Culture Negative (n = 87)	Culture Positive (n = 226)	*P* Value
Initial presentation			.07
Colonization	87 (100.0)	216 (95.6)	
Infection	0	10 (4.4)	
Development of infection from colonization within 6 months	0	29/216 (13.4)	<.001
Days from development of infection from colonization	NA	24 (13–60)	NA
Positive culture conversion	20 (23.0)	NA	NA
NDM	13/20 (65.0)		
KPC	7/20 (35.0)		
Days from positive Xpert Carba-R assay to culture conversion	9 (7–45)	NA	NA
No. of follow-up cultures to positive conversion, median (IQR)	1 (1–2)	…	NA
CPE clearance after positive culture results			
CPE clearance[a]	8/20 (40.0)	55/206[b] (26.7)	.21
NDM	5/8 (62.5)	33/55 (60.0)	
KPC	3/8 (37.5)	18/55 (32.7)	
VIM	0	3/55 (5.5)	
IMP	0	2/55 (3.6)	
OXA-48–like	0	1/55 (1.8)	
Indeterminate[c]	4/20 (20.0)	39/206 (18.9)	.91
NDM	4/4 (100.0)	24/39 (61.5)	
KPC	0	16/39 (41.0)	
VIM	0	5/39 (12.8)	
Transmission rate[d]	9/305 (3.0)	37/592 (6.3)	.03
30-day mortality from initial isolation	2 (2.3)	13 (5.8)	.25
90-day mortality from initial isolation	6 (6.9)	19 (8.4)	.66

Data are presented as No. (%) of patients unless otherwise specified.

Abbreviations: CPE, carbapenemase-producing Enterobacterales; IMP, imipenemase; IQR, interquartile range; KPC, *Klebsiella pneumoniae* carbapenemase; NA, non-available; NDM-1, New Delhi metallo-β-lactamase-1; OXA, oxacillinase; VIM, Verona integron–encoded metallo-β-lactamase.

[a]CPE clearance was defined as 3 consecutive negative results of follow-up culture.

[b]Of 226 patients with positive culture results, 206 patients underwent follow-up culture.

[c]Indeterminate was defined as 1 or 2 consecutive negative results of follow-up cultures in cases where at least 3 follow-up cultures were not performed.

[d]Rate of CPE isolation in exposed patients exposed to the index patient.

culture. Both false-positive result of Carba-R Xpert assay and false-negative result of CPE culture could be associated with this finding. Patients with XPCN might have carbapenemase-producing organisms (including *Pseudomonas aeruginosa* or *Acinetobacter baumannii*) other than Enterobacterales [4, 17] or false-negative of culture for CPE. We could not differentiate these in this study. A possible reason for negative results of CPE culture is low sensitivity of the ChromID CARBA for detecting OXA-48–like producers [9, 18], but the prevalence of OXA-48–like producers is very low in our center. Therefore, our results imply that ChromID CARBA may demonstrate low sensitivity for NDM- or KPC-producing Enterobacterales, especially when the burden of bacteria is low. Furthermore, at least 23% of XPCN patients developed positive conversion for CPE in follow-up cultures (All were NDM- and KPC-producing Enterobacterales). Therefore, about one-fourth of patients with XPCN may carry CPE and can transmit to others. Further study is needed to validate our finding.

Although culture-based detection is recommended as the standard method of CPE screening [19], PCR-based detection using the Xpert Carba-R assay has been introduced in clinical fields because it provides reliable results in 1 hour whereas culture-based methods require 48 hours [9, 20]. High rates of XPCN in our study raise concerns on false-negative results of CPE screening using only culture method and supports the previous recommendation of the combined use of PCR and culture for CPE screening [4, 7–9, 21, 22]. Furthermore, our findings implicate the need for improvement of culture medium and supplement with an enrichment method for the screening of CPE to avoid the lack of detection. In addition, the importance of follow-up surveillance culture in XPCN patients should not be underestimated as more than one-fifth of these patients underwent positive conversion after a median of 9 days of follow-up.

XPCN patients were less likely to have KPC. As KPC is frequently carried by CPE compared to carbapenemase-producing non-Enterobacterales organisms [23], it is less likely that KPC had false-negative culture results due to organisms other than Enterobacterales.

Hoyos et al evaluated the performance of the Xpert Carba-R assay and reported that 14.2% (2/14) of positive Xpert Carba-R patients gave negative culture results [22]. As the number of patients included in the previous study was small, the clinical outcome of the XPCN patients as well as rates of transmission and colonization by CPE could not be determined [22]. In our study, XPCN patients had lower transmission rates than XPCP patients, and none developed infection from colonization over 6 months. Due to limited resources, infection control including contact precautions and cohorting of patients should be reinforced in patients at high risk of transmitting CPE, and the results of our study suggest that infection control strategies should prioritize XPCP patients rather than XPCN.

XPCN patients showed a tendency to arise by community acquisition and to receive fewer immunosuppressants and antibiotics than XPCP patients. A possible explanation for this result is that patients with community-acquired CPE may have low levels of bacteria that may have been detected by high cycle threshold values for PCR and showing negative culture results, and since they have had less exposure to immunosuppressants and antibiotics, CPE clearance may have occurred spontaneously. However, we could not analyze the cycle threshold values of Xpert Carba-R assay as there were no electronic medical records. Further study is warranted to validate our findings.

Although there was no significant difference in CPE clearance between XPCN and XPCP patients in our study, among patients who showed CPE clearance, about 60% carried NDM, and >30% carried KPC in both groups. This result is in line with a previous study that reported patients carrying KPC had a significantly lower probability of clearance compared to NDM [24].

Our study has several limitations. First, as we performed the Xpert Carba-R assay only once, the number of patients with positive PCR results could have been underestimated. However, several studies have evaluated the performance of the Xpert Carba-R assay [7–9, 16, 22] and report its sensitivity and specificity as 100% and 96.7%, respectively [8]. Second, false-negative results of culture using ChromID CARBA agar due to weak hydrolysis by metallo-β-lactamase carbapenemase [8] and low sensitivity for OXA-48–like producers cannot be excluded as we did not perform further direct PCR sequencing of carbapenemase genes in patients with negative culture results. Third, as we defined transmission as the presence of identical genotypes in index and exposed patients, and we did not perform preadmission testing in all departments, exposed patients with identical CPE genotypes might have acquired CPE from other sources. Therefore, the transmission rates may be overestimated. Fourth, there is a potential for selection bias as we performed the Xpert Carba-R assay in only 322 of 1451 patients with positive CPE results, and this study includes patients from a single tertiary center in South Korea. Further multicenter studies are needed to validate our findings.

In conclusion, our study suggests that XPCN patients have lower rates of both infection and transmission than XPCP patients. Culture conversion occurred in about a quarter of XPCN patients who had positive results. The Xpert Carba-R assay has clinical use for rapid identification of CPE and also for predicting infection and transmission when used along with culture.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. Conceptualization, methodology, and writing–original draft: H. S., J. J. Data curation: H. S., J.-Y. L., S. H. R., S. H. K., E. O. K. Software, formal analysis: H. S. Supervision: S. B., M. J. K., Y. P. C., S.-H. K., S.-O. L., S.-H. C., H. S., M.-N. K., Y. S. K.

Potential conflicts of interest. All authors: No potential conflicts of interest.

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