Appropriate sites for the active surveillance of carbapenemase-producing *Enterobacteriaceae*

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Abstract

Background: Active surveillance tests for carbapenemase-producing *Enterobacteriaceae* (CPE) are recommended in patients showing risk factors for colonization by these bacteria. There are limited data however on whether surveillance tests for anatomic sites other than the stool would be useful to detect CPE colonization, and we investigated this in our present study.

Methods: Retrospective analysis was performed on cases at our tertiary care hospital during a 5-year period. Patients with CPE colonization had been admitted to our surgical intensive care unit (SICU) or sub-ICU for liver transplantation in this period and undergone surveillance tests for both the stool and other sites. Patients were grouped as stool CPE negative (but which included CPE positive cases from initial sputum and other site tests) or positive.

Results: Among the total study cohort of 158 patients, 138 (87.3%) were included in the stool CPE positive group and the remaining 20 (12.7%) in the stool CPE negative group. While the sensitivity of CPE surveillance testing of the stool was 87.3% (95% CI 81.1-92.1), the sensitivity when combining stool and sputum samples was 93.7% (88.7-96.9). The transmission rates were similar for patients showing CPE positivity in the stool, sputum and other sites, at 4.8% (27/557), 4.7% (3/64), and 6.7% (1/15), respectively ($p = 0.95$).

Conclusions: The sensitivity of CPE detection in a stool sample is suboptimal for ruling out CPE colonization and the transmission rates are similar between stool-positive or -negative cases. Thus, combining surveillance of the stool with other sites may be needed for detecting CPE.

Background

As the incidence of carbapenemase-producing *Enterobacteriaceae* (CPE) has increased worldwide, this infection is now considered to be an important public health threat because of the high transmission risk. In addition, CPE infections are troublesome to treat because of a lack of effective and safe antimicrobial agents, which has led to very high mortality rates of 40–50% [1, 2]. Hence, there have been various efforts at CPE prevention and control, such as hand hygiene, contact precaution, and active surveillance in patients who are exposed to CPE or who show risk factors for CPE colonization (e.g. residents of long-term care centers, and those with histories of treatment with antimicrobial agents or previous CPE colonization) [1, 3, 4].

Surveillance cultures are performed for the early detection of CPE colonization and to prevent additional transmission to other hospital patients. The guidelines in this regard from the World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) recommend stool, rectal swab, and perirectal swab tests (e.g. for neutropenic cases) [1, 3]. In our center, CPE surveillance culture testing is routinely done in patients admitted to our surgical intensive care unit (SICU) or sub-ICU for liver transplantation. These tests are conducted using sputum, urine, and the drained fluid from a biliary catheter or Jackson-Pratt (JP)/pigtail catheter, in addition to stool or rectal swabs. There are limited data

however on whether surveillance testing at various anatomical sites in addition to stool sampling could improve the sensitivity of CPE detection and thus assist with its prevention and control [5]. We evaluated this possibility in our present study.

Methods

Study population and study design

This study was a retrospective analysis of CPE-positive patients treated between January 2016 and January 2021 at Asan Medical Center, a 2,700-bed tertiary-care facility in Seoul, South Korea. We initially screened our hospital records for patients who had been admitted to the SICU and sub-ICU for a liver transplantation in this 5-year period and whose surveillance cultures from any specimen indicated a positive CPE result. We excluded patients who underwent this CPE surveillance test using a stool or rectal swab sample only because we aimed to investigate the usefulness of additional surveillance testing at various sites other than the stool. If CPE colonization is discovered in a patient at our center, we initiate strict contact precautions with single-room isolation and conduct detailed contact tracing in other patients who are in the same hospital room with this index patient at least one day before detection of CPE colonization. We then perform CPE surveillance on any other patients or individuals who have come into contact with the index case.

Definitions

Among our included study cases, we defined the stool CPE-positive group as patients whose initial stool surveillance testing for CPE was positive. We classified a stool CPE-negative group accordingly and divided these patients into an initial sputum CPE-positive group and initial CPE-positive from other sites group. We then compared the rate of CPE clearance between these groups, which was defined as three consecutive negative results from CPE surveillance tests within at least one week. We also investigated the transmission rate of CPE resulting from close contact with the index patients. Transmission rate was defined as the rate of contact with positive test among total contact. Close contact patients were defined as those who were in the same hospital room or same open area of the ICU with the index patient for at least one day before the confirmation of surveillance culture results. We performed CPE surveillance tests in close contact patients who were still hospitalized after the confirmation of CPE in the index patient but excluded the ones with previous CPE colonization. Transmission of CPE was confirmed when a bacterial isolate from a surveillance test showed the same CPE genotype. Also, we analyzed the transmission rate of CPE when we defined transmission of CPE as a case producing same organism and CPE genotype.

Microbiologic evaluation for CPE from surveillance tests

For microbiologic evaluation for CPE, we screened using MacConkey agar plates supplemented with imipenem (1ug/mL) and the Microscan system (Omron Microscan systems Inc., Renton, WA, USA). We performed phenotyping test of carbapenemase using the modified Hodge test (MHT),

ethylenediaminetetraacetic acid (EDTA) test, and boronic acid test [6]. We also performed PCR analysis of the CPE genotype.

Statistical analysis

Categorical variables were compared using the chi-square and Fisher's exact test, as appropriate, and continuous variables were analyzed using the Student's *t* test or the Mann-Whitney U test, as appropriate, to compare the baseline clinical characteristics of the stool CPE-positive and -negative groups. The time to CPE clearance was analyzed using a Kaplan-Meier curve and the rate of CPE clearance between groups, according to the results of the initial surveillance tests, was compared using the log-rank test. All tests of significance were two-tailed, and *p* values of < 0.05 were considered statistically significant. Statistical calculations were performed using SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY) and MedCalc for Windows, version 19.8 (MedCalc Software Ltd., Belgium).

Results

Study population

A total of 177 patients with positive CPE surveillance tests were initially enrolled but 19 of these cases were excluded from further analysis because their surveillance tests had only been performed using stool specimens. Of the remaining 158 patients in the final study cohort, 138 cases were categorized as stool CPE-positive and the remaining 20 patients as stool CPE-negative. These 20 cases showed CPE positivity from testing at other sites however, such as the sputum and urine. The median number of specimens used for CPE surveillance in our study population was 4 (interquartile range, 3–4). The clinical characteristics of the stool CPE-positive and -negative groups are compared in Table 1. The isolation of CPE from sites other than the stool was more common in the stool CPE-negative group. *Klebsiella pneumoniae* carbapenemase (KPC) was the most common CPE genotype in both groups and the in-hospital mortality were similar between the groups. In the stool CPE-negative group, CPE was positively isolated in the sputum from 9 patients, bile from 6 patients, urine from 3 patients, JP drained fluid from one patient, and both JP drained fluid and sputum from one patient. Stool or rectal swab tests were the most sensitive way to detect CPE (87.3%, 138/158, 95% confidence interval (CI) 81.1–92.1%). However, a combination of stool and sputum testing improved this sensitivity (93.7%, 148/158, 95% CI 88.7–96.9%; Table 2).

Table 1
Baseline characteristics of the study population*

	Stool CPE- positive (n = 138)	Stool CPE- negative (n = 20)	<i>p</i> value
Age, median (IQR)	57.0 (50.3–63.8)	57.0 (45.5–64.5)	0.82
Male (%)	106 (76.8)	11 (55.0)	0.04
Underlying diseases/conditions (%)			
Diabetes mellitus	36 (26.1)	8 (40.0)	0.20
Liver cirrhosis	134 (97.1)	20 (100.0)	> 0.99
End-stage renal disease	6 (4.3)	1 (5.0)	> 0.99
Solid cancer	55 (39.9)	8 (40.0)	0.99
Solid organ transplant	127 (92.0)	19 (95.0)	> 0.99
Days from liver transplantation to isolation of CPE, median (IQR)^a	6.0 (2.0–14.0)	0 (0–8.0)	0.005
Days from admission to isolation of CPE, median (IQR)	12.0 (7.0–30.3)	7.0 (3.0–27.0)	0.07
Site of CPE isolation (%)			
Urine	3/88 (3.4)	3/20 (15.0)	0.04
Sputum	16/47 (34.0)	10/14 (71.4)	0.01
Bile	5/104 (4.8)	6/17 (35.3)	< 0.001
Pigtail or JP drained fluid	1/126 (0.8)	2/19 (10.5)	0.005
Infection (%)			
Bacteremia	7 (5.1)	1 (5.0)	> 0.99
Pneumonia	10 (7.2)	0	0.36
UTI	0	0	-

*Excluded patients who underwent a liver transplantation after a positive isolation of CPE or who did not undergo a liver transplantation

CPE, carbapenemase-producing *Enterobacteriaceae*; IQR, interquartile range; JP, Jackson-Pratt pigtail catheter; UTI, urinary tract infection; KPC, *Klebsiella pneumoniae* carbapenemase; NDM-1, New Delhi metallo-beta-lactamase-1

	Stool CPE- positive (n = 138)	Stool CPE- negative (n = 20)	<i>p</i> value
Intraabdominal infection	3 (2.2)	0	> 0.99
Others	1 (0.7)	0	> 0.99
CPE genotype (%)			0.01
KPC	97 (70.2)	18 (90.0)	
NDM-1	36 (26.1)	0	
KPC and NDM-1	1 (0.7)	1 (5.0)	
CPE clearance (%)	24 (17.4)	8 (40.0)	0.03
Days from isolation to CPE clearance, median (IQR)	14.5 (8.0–32.0)	6.0 (4.0–17.0)	0.04
Rates of CPE isolation from transmission cases (%)	46/557 (8.3)	4/79 (5.1)	0.32
In-hospital mortalities (%)	14 (10.1)	2 (10.0)	> 0.99
*Excluded patients who underwent a liver transplantation after a positive isolation of CPE or who did not undergo a liver transplantation			
CPE, carbapenemase-producing <i>Enterobacteriaceae</i> ; IQR, interquartile range; JP, Jackson-Pratt pigtail catheter; UTI, urinary tract infection; KPC, <i>Klebsiella pneumoniae</i> carbapenemase; NDM-1, New Delhi metallo-beta-lactamase-1			

Table 2
CPE surveillance culture results for various anatomical sites among the study population

Surveillance site	Sensitivity (n/N, 95% CI)
Stool/rectal swabs	87.3% (138/158, 81.1–92.1)
Urine	5.6% (6/108, 2.1–11.7)
Sputum	42.6% (26/61, 30.0–55.9)
Bile	9.1% (11/121, 4.6–15.7)
Pigtail/JP drained fluid	2.1% (3/145, 0.4–5.9)
Stool/rectal swabs or urine	89.2% (141/158, 83.3–93.6)
Stool/rectal swabs or sputum	93.7% (148/158, 88.7–96.9)
Stool/rectal swabs or bile	91.1% (144/158, 85.6–95.1)
Stool/rectal swabs or pigtail/JP drained fluid	88.6% (140/158, 82.6–93.1)
CPE, carbapenemase-producing <i>Enterobacteriaceae</i> ; CI, confidence interval; JP, Jackson-Pratt pigtail catheter	

Of the 20 patients in the stool CPE-negative group, 10 cases showed a positive conversion in subsequent stool CPE surveillance tests at a median of 6.0 days after the initial negative stool results. Nine of these 10 patients showed initial positive results from a sputum test, and did not show CPE clearance in subsequent surveillance. The remaining 10 patients still showed a negative result from subsequent stool specimens and CPE clearance was revealed at a median of 4.5 days from the same sites that initially showed positive CPE results (urine in 2 patients, JP drained fluid in one patient from, bile in 6 patients, and JP drained fluid and sputum in one patient). The clinical characteristics of these 20 patients are provided in Supplemental Table 1.

CPE clearance according to the initial surveillance results

We compared the rate of CPE clearance between the stool CPE-positive and -negative groups using Kaplan-Meier curves, as shown in Fig. 1. The rate of CPE clearance in the stool CPE-positive group was significantly lower than that of the negative group (17.4% vs 40.0%, Log-rank $p = 0.006$). The time from initial isolation to CPE clearance was also longer in the stool CPE-positive group (median 14.5 vs 6.0 days, $p = 0.04$). In addition, we compared the rate of CPE clearance among the cases that were initial stool CPE-positive, initial sputum CPE-positive and the initial CPE-positive at other sites (Fig. 2). This rate was found to be the highest in the initial CPE-positive at other sites group (stool, 17.4% vs sputum, 10.0% vs other sites, 70.0%, Log-rank $p < 0.001$). We also compared the rate of CPE clearance between the initial stool or sputum CPE-positive and the initial CPE-positive at other sites groups (stool or sputum, 16.9% vs other sites, 70.0%, $p < 0.001$; Supplemental Fig. 1).

CPE transmission rate

We further performed CPE surveillance tests in 557 close contact subjects for 82 of our 138 index patients in the stool CPE-positive group and in 79 such subjects for 18 of our 20 index patients in the stool CPE-negative group. The transmission rates were measured at 4.8% (27/557) and 5.1% (4/79) in the stool CPE-positive and -negative groups, respectively ($p = 0.93$). In terms of acquisition of the same CPE genotype and organism, the transmission rate was 4.1% (23/557) and 3.8% (3/79), respectively ($p = 0.89$). These transmission rates were not significantly different between the three index groups (i.e. initial stool positive, initial sputum positive, initial other site positive; 4.8% vs 4.7% vs 6.7%, $p = 0.95$; Table 3).

Table 3
The transmission rate of CPE from close contact with an index patient

	Initial stool CPE-positive group	Initial stool CPE-negative group		p value
		Initial sputum CPE-positive group	Initial CPE-positive from other sites	
Same genotype	4.8% (27/557)	4.7% (3/64)	6.7% (1/15)	0.95
Same genotype and organism	4.1% (23/557)	3.1% (2/64)	6.7% (1/15)	0.82
CPE, carbapenemase-producing <i>Enterobacteriaceae</i>				

Discussion

The sensitivity of CPE surveillance tests from stool or rectal swabs was found to be 87.3% in our present study. That is, 12.7% of patients with CPE colonization would be missed if only stool surveillance tests were used. The CPE clearance rate was shown in our present analysis to be lower in the stool CPE-positive group than the stool CPE-negative group. The transmission rates were similar however when compared according to the results of the initial surveillance tests for CPE.

Because of the high morbidity and mortality associated with CPE infection, multimodal interventions for infection control and prevention in relation to this pathogen are strictly recommended in many countries [4]. In addition to hand hygiene, contact precautions, environmental cleaning, and antimicrobial stewardship, active surveillance can also be performed to control transmission in patients at a high risk of CPE colonization [7, 8]. However, the optimal anatomic sites for CPE surveillance in addition to stool sampling have not yet been determined [9, 10]. WHO and CDC guidelines currently recommend CPE surveillance testing using stools or rectal swabs. However, as indicated in a previous study, the sensitivity for detecting CPE in this way is still only about 88% (95% CI 68–97), which will lead to a relatively high proportion of false-negative test results [5]. In our current study, we confirmed this sensitivity level (87.3%), and that it is suboptimal for definitively ruling out CPE colonization. Notably however, we found

that a combination of stool and sputum testing will detect CPE colonization with a better sensitivity of 93.7%.

To the best of our knowledge, there remains little available evidence whether additional surveillance tests at sites other than stool could usefully improve the sensitivity of CPE detection [5]. In our current study cohort, 10 patients in the initial stool CPE-negative group showed a conversion to CPE positivity in a subsequent stool sample at a median of 6.0 days, and 9 of these patients had initial CPE-positive results from a sputum test. Although these patients would still have been confirmed with a CPE infection after about one week if surveillance tests had not been conducted at other sites, the transmission rate from close contact with other individuals was not significantly different among our initial stool CPE-positive, the initial sputum CPE-positive, and the initial CPE-positive from other sites groups. Hence, the risk of CPE transmission might be increased in situations where only stool testing is done and contact precautions are not taken in the period before the index patient is confirmed as being positive. Additional surveillance tests at sites other than the stool would thus have value in terms of control and prevention of CPE transmission. However, this would necessarily increase medical costs and the clinical burden in hospitals. We thus suggest that stool and sputum testing for CPE may be reasonable in resource-limited settings and that additional sites such as sputum, urine, and drained fluid can be tested in more well-resourced settings. Because of the small sample sizes of the close contacts with our index patients in the initial CPE-positive at other sites group, further studies with a larger cohort are needed to evaluate the transmission profile for cases such as these.

We found from our present analysis that the clearance of CPE was more common among the initial stool CPE-negative cases that had a positive isolation of these bacteria from urine, bile, and JP or pigtail drained fluid than from the sputum (9/10 vs 1/10 patients). We speculated that a subsequent CPE positive result from a stool sample would be likely in the patients who showed a positive result in an initial sputum sample because sputum can be ingested into the gastrointestinal tract if swallowed. Conversely, this may be less likely in patients showing CPE positivity at other sites such as urine that are not directly connected with the gastrointestinal tract.

This study had some limitations of note. First, the analysis was performed in a single tertiary care hospital, and most of the enrolled patients had undergone a liver transplantation. Because such cases involve the use of several different medical devices, require mechanical ventilation, and have a higher risk of exposure to antimicrobial agents and thus they have a greater risk of CPE colonization than the general population [11, 12]. Second, we did not perform genetic analyses of the CPE strains to compare the isolates from close contact patients and index cases. In the absence of any bacterial sequencing data, and given that the prevalence of CPE colonization has been increasing in both hospital and community settings [13], it was therefore not definitive that all of the transmission cases we examined had arisen due to exposure to one of our index patients. Third, because we defined CPE clearance as three consecutive negative surveillance tests in one week, patients who did not complete this rate of testing could not be regarded as cleared and this may have biased our data. Finally, a substantial portion

of the close contact hospital patients had already been discharged and did not undergo surveillance testing for CPE.

Conclusions

The sensitivity of CPE detection in a stool sample is suboptimal for definitively ruling out infection and colonization with this pathogen, and the transmission rate appears to be similar if the patient shows a negative stool sample but is found to be positive in another test. A combination of CPE surveillance testing of the stool and sputum in resource-limited settings may be a feasible way of achieving a higher sensitivity. Further studies are needed to investigate the usefulness and cost-effectiveness of this combination testing in a larger study population.

Abbreviations

CPE, carbapenemase-producing Enterobacteriaceae; WHO, World Health Organization; CDC, Centers for Disease Control and Prevention; SICU, surgical intensive care unit; JP, Jackson-Pratt, MHT, modified Hodge test; EDTA, ethylenediaminetetraacetic acid; KPC, Klebsiella pneumoniae carbapenemase; CI confidence interval

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Institutional Review Board of Asan Medical Center. Informed consent was waived because of the nature of this study.

Consent for publication

All the authors gave final approval of the version to be published.

Availability of data and material

Please contact authors for data requests.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

JH Park, S-H Kim and J Jung designed the study and JH Park have drafted the word. JH Park, H-S Choi, H Yang, SH Kwak, EO Kim, H Sung, M-N Kim, S-H Kim and J Jung collected and analyzed data. YP Chong, S-H Choi, S-O Lee, YS Kim, H Sung, M-N Kim, S-H Kim and J Jung reviewed the draft and substantively revised it.

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Figures

Figure 1

Kaplan-Meier curve analysis of CPE clearance in the stool CPE-negative and -positive groups

Figure 2

Kaplan-Meier curve analysis of CPE clearance in the initial stool, sputum, and other testing site surveillance-positive cases

Supplementary Files

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