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Diagnostic Accuracy of BD Phoenix CPO Detect for Carbapenemase Production in 190 *Enterobacteriaceae* Isolates

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ABSTRACT The rapid and accurate detection of carbapenemase-producing *Enterobacteriaceae* (CPE) is necessary for patient management and infection control measures. We compared the performance of the BD Phoenix CPO Detect with that of a homemade Carba NP assay and a modified carbapenem inactivation method (mCIM) by challenging all 3 assays with 190 isolates of *Enterobacteriaceae* with meropenem MICs of >0.125 mg/liter. A total of 160 isolates produced KPC-, IMI-1-, NDM-, IMP-, and OXA-type carbapenemases, while 30 isolates were negative for carbapenemase production. The sensitivity and specificity were 90.6% (95% confidence interval [CI], 85.0% to 94.7%) and 100.0% (95% CI, 88.4% to 100.0%), respectively, for the Carba NP; 100.0% (95% CI, 97.7% to 100.0%) and 96.7% (95% CI, 82.7% to 99.9%), respectively, for the mCIM; and 89.4% (95% CI, 83.5% to 93.7%) and 66.7% (95% CI, 47.2% to 82.7%), respectively, for the BD Phoenix CPO Detect. In particular, the BD CPO Detect failed to detect a significant number of CPE with IMI-1. While the BD Phoenix CPO Detect is able to classify carbapenemases and is built into routine susceptibility testing with the potential to reduce the time to CPE detection, its low specificity means that a positive result will need confirmatory testing by another method.

KEYWORDS CPO Detect, Carba NP, Phoenix, carbapenemase, mCIM

Among the limited armamentarium of antibiotics available to clinicians, the carbapenems have long been regarded as the last effective line of defense against infections caused by Gram-negative bacteria. However, their effectiveness is being increasingly threatened by the emergence of multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii* bacteria, and, more recently, carbapenem-resistant *Enterobacteriaceae* (CRE) (1). Carbapenem resistance in *Enterobacteriaceae* can be mediated by extended-spectrum β-lactamase (ESBL) or AmpC β-lactamase production in combination with decreased permeability due to the alteration or downregulation of porins or by enzymatic hydrolysis of carbapenems by carbapenemases (carbapenemase-producing *Enterobacteriaceae* [CPE]) (2, 3). The latter mechanism is predominantly plasmid encoded and associated with mobile genetic elements. This allows for the efficient transmissibility of resistance between *Enterobacteriaceae* and is of great public health concern (4, 5).

Carbapenemases are categorized according to the Ambler classification scheme. Plasmid-mediated class A carbapenemases in *Enterobacteriaceae* are also called serine carbapenemases, and they include KPC, IMI-2, IMI-3, and GES (6). Class B carbapenemases are metallo-β-lactamases and include NDM, IMP, and VIM, with NDM being the most prevalent. Metallo-β-lactamases confer resistance to all β-lactam antibiotics except for aztreonam. Class D carbapenemases in *Enterobacteriaceae* belong mainly to the OXA-48 subgroup and its variants (7).

In 2017, the World Health Organization (WHO) recognized CPE as a global threat and

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listed it as a pathogen on the priority list to be supported in research and the development of new and effective drugs against them (8). An observational study comparing 14-day mortality between patients with CPE and non-CPE bacteremia found that patients with CPE bacteremia had 4 times the odds of dying within 14 days than those with non-CPE bacteremia (9). These results highlight the importance of detecting the underlying mechanism of carbapenem resistance to contribute to patient management.

Given the therapeutic and infection control implications of CPE, their accurate and timely detection is vital for patient management as well as implementation of containment measures. Phenotypic methods for CPE detection have included combination disk testing (MAST, UK; Rosco, Denmark); biochemical colorimetric tests, such as the Carba NP (10, 11); and lateral flow assays, such as the Carba5 (12). A recent modification of the carbapenem inactivation method (mCIM) was reported to have a sensitivity of 99% and specificity of 100% for CPE detection (13). In 2017, BD launched the BD Phoenix CPO Detect panels. They are a series of antibiotic panels used for susceptibility testing and are also equipped with the capacity for carbapenemase detection and classification according to their Ambler classes. The panels utilize nine wells containing meropenem, doripenem, temocillin, and cloxacillin, either alone or in combination with various chelators and β-lactamase inhibitors required for the detection and classification of carbapenemases. A recent study that evaluated the BD Phoenix CPO Detect panel against 294 carbapenem-resistant isolates of *Enterobacteriaceae* spp., *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* reported that it had an overall sensitivity of 97.1% and specificity of 68.6% for carbapenemase detection (14).

Prior to the introduction of the BD Phoenix CPO Detect panel, the microbiology laboratory in Ng Teng Fong General Hospital (NTFGH) routinely employed a homemade Carba NP test for the detection of carbapenemase production in CRE isolated from both clinical and screening specimens. In this study, we compared the performance of the BD Phoenix CPO Detect panel with those of the mCIM and Carba NP tests for CPE detection.

MATERIALS AND METHODS

The EUCAST methodology recommends a meropenem MIC of greater than 0.125 mg/liter for CPE screening (15). Clinical isolates obtained from 2012 to 2018 which fulfilled this criteria were selected for inclusion in this study. These isolates were subcultured onto tryptic soy agar (TSA) with 5% sheep blood. The strains were then incubated overnight in ambient air at 35°C ± 2°C. A second subculture was performed before testing. Isolates were identified by mass spectrometry using matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS; Bruker Daltonics, Germany).

Carba NP test. A sterile loop was used to pick 10 μl of the test organism growing adjacent to the meropenem disk or Etest and emulsified into B-PER II solution (bacterial protein extraction reagent; Thermo Scientific Pierce, Rockford, IL, USA). After incubation for 30 min, the bacterial suspension was centrifuged at 10,000 × *g* for 5 min. In a 96-well microtiter plate, 30 μl of supernatant was added to 100 μl of imipenem working solution that contained 6 mg/ml imipenem-cilastatin powder (Facta Farmaceutici, San Nicolò a Tordino, Italy), phenol red working solution, and 100 mM $ZnSO_4$ (Sigma-Aldrich, St. Louis, MO). The phenol red working solution was prepared by mixing 2 ml of a 0.5% (wt/vol) phenol red solution (Sigma-Aldrich) with 16.6 ml of distilled water, and the solution was adjusted to pH 7.8 with either diluted NaOH or diluted HCl. The microtiter plate was then incubated at 37°C for 2 h. Carbapenemase production was interpreted as positive when the color of the reaction well changed from red to orange (10, 11).

Modified carbapenem inactivation method. A sterile loop was used to add 1 μl of the test organism into 2 ml of tryptic soy broth (TSB; BD Diagnostic Systems, Sparks, MD). After vortexing the bacterial suspension for 10 to 15 s, a 10-μg meropenem disk (Oxoid, Basingstoke, Hampshire, UK) was added to the bacterial suspension, and the tube was incubated for 4 h ± 15 min at 35°C ± 2°C in ambient air. A 0.5 McFarland standard suspension of *Escherichia coli* ATCC 25922 (mCIM indicator organism, a carbapenem-susceptible strain) was prepared just prior to the completion of the 4-h incubation. This was used to lawn the surface of a Mueller-Hinton agar (MHA) plate (BD Diagnostic Systems) using the procedure for standard disk diffusion susceptibility testing. The meropenem disk was then removed from the TSB suspension, placed onto the inoculated MHA plate, incubated for 18 to 24 h at 35°C ± 2°C in ambient air. Carbapenemase production was determined by measuring the zone of inhibition around the meropenem disk after overnight incubation for 18 to 24 h. A zone diameter measuring 6 to 15 mm was considered positive for carbapenemase production, a diameter of 16 to 18 mm was considered indeterminate, and a diameter of ≥19 mm was considered negative (13).

Isolate preparation for BD Phoenix CPO Detect. Bacterial suspensions of all test isolates were prepared from colonies grown on tryptic soy agar (TSA) with a sheep blood plate (BD Diagnostic Systems,

TABLE 1 Distribution of selected CRE test isolates by carbapenemase genotype and species[a]

Bacterial species	KPC	IMI type	NDM	IMP1	OXA48 type	NDM+ OXA48	PCR negative	Total
Citrobacter amalonaticus			1					1
C. fameri			1					1
C. freundii	1		11					12
E. aerogenes							5	5
E. cloacae	2	23	21		4	1	4	55
E. coli	3		24		6	1	3	37
K. pneumoniae	1		41	1	16		18	77
K. georgiana			1					1
Leclercia adecarboxylata			1					1
Total	7	23	101	1	26	2	30	190

[a]Isolates had meropenem MICs of >0.125mg/L (as per EUCAST screening guidelines).

Sparks, MD) after 18 to 24 h of incubation. The colonies were suspended in Phoenix ID broth, and the McFarland standard was adjusted to 0.25 using the Phoenix AP. The bacterial suspension was then inoculated into the BD Phoenix CPO Detect susceptibility panel (BD Diagnostic Systems). Antimicrobial susceptibility testing results and carbapenemase-producer classification were interpreted using EpiCenter S/W version 6.21A, with reference breakpoints from the European Committee on Antimicrobial Susceptibility Testing (16). Quality control for the panel was performed following the manufacturer's recommendations.

PCR testing for the bla_{KPC}, bla_{NDM}, $bla_{OXA-48-like}$, and bla_{OXA-23} carbapenemase genes was performed on all isolates by the National Public Health Laboratory (NPHL). For isolates negative for the abovementioned targets, a KPC-metallo-β-lactamase confirmation kit (Rosco Diagnostica A/S, Taastrup, Denmark) was used to detect the mechanism for carbapenemase production. Isolates detected as having KPC-class A were further screened by PCR for bla_{GES}, bla_{NMC-A}, and bla_{IMI}, and isolates detected as having metallo-β-lactamase were additionally screened by PCR for bla_{VIM} and bla_{IMP}. Isolates with inhibition zones suggestive of AmpC hyperproduction plus porin loss and/or efflux pumps were not further investigated. In total, 160 strains which were positive by PCR for the carbapenemase gene (CPE) and 30 strains which were negative by PCR for the carbapenemase gene (non-CPE) were used for this evaluation. Table 1 shows the distribution of the 190 isolates by genotype and species.

RESULTS

The mCIM was positive for all 160 CPE strains tested. Of the 30 non-CPE isolates, the mCIM gave a false-positive result for 1 isolate of *Klebsiella pneumoniae*. In this evaluation, the mCIM produced a sensitivity of 100%, which was superior to the Carba NP test, with a sensitivity of 90.6% (Table 2).

The performance of the BD Phoenix CPO Detect gave an overall sensitivity of 89.4% and specificity of 66.7% for carbapenemase detection (Table 2).

Among the 7 KPC isolates, the BD Phoenix CPO Detect correctly identified 6 of them as harboring class A carbapenemase but failed to detect any carbapenemase in 1 isolate. Of 23 IMI-type isolates, the BD Phoenix CPO Detect correctly identified 7 of them as harboring class A carbapenemases and failed to detect carbapenemase in the rest of the isolates.

Among the 101 NDM strains and 1 IMP strain, BD Phoenix CPO Detect correctly

TABLE 2 Performance of CarbaNP, mCIM, and BD Phoenix CPO Detect

Carbapenemase genotype	CarbaNP positive	mCIM positive	BD Phoenix CPO Detect positive
IMI (n = 23)	22	23	7
KPC (n = 7)	6	7	6
NDM (n = 101)	96	101	101
IMP (n = 1)	1	1	1
OXA (n = 26)	18	26	26
NDM+OXA (n = 2)	2	2	2
PCR negative (n = 30)	0	1	10
Sensitivity, % (95% CI)	90.6 (85.0–94.7)	100.0 (97.7–100.0)	89.4 (83.5–93.7)
Specificity, % (95% CI)	100.0 (88.4–100.0)	96.7 (82.7–99.9)	66.7 (47.2–82.7)

TABLE 3 Performance of the BD Phoenix CPO Detect[a]

CPE class	Genotype	MIC (mg/liter)	Test no.	Positive by BD Phoenix CPO Detect	Sensitivity (%)	Specificity (%)
A	KPC	>0.125–2	0	0	43.3	
		>2	7	6		
	IMI	>0.125–2	3	0		
		>2	20	7		
B	NDM	>0.125–2	4	4	100.0	
		>2	97	97		
	IMP	0.125–2	0	0		
		>2	1	1		
D	OXA	>0.125–2	11	11	100.0	
		>2	15	15		
Non-CPE		>0.125–2	15	3		66.7
		>2	15	7		

[a]Dual producer not included in the table.

identified 92 isolates as harboring class B carbapenemase. Eight isolates of *K. pneumoniae* (7 NDM and 1 IMP) were identified as unclassified carbapenemase producers. Two NDM-positive *Enterobacter cloacae* strains were incorrectly classified as class D carbapenemase producers.

Among the 26 OXA-48 strains, BD Phoenix CPO Detect correctly identified 24 strains as harboring class D carbapenemase, while 2 *E. coli* isolates were identified as unclassified carbapenemase producers.

Two CPE strains (1 *E. coli* and 1 *E. cloacae* strain), each harboring dual carbapenemase genes of NDM and OXA-48, were included in this study. The *E. coli* dual producer was identified as producing only a class D carbapenemase, while the *E. cloacae* dual producer was identified as producing a class B carbapenemase only.

Among the 30 non-CPE isolates tested, BD Phoenix CPO Detect correctly identified 20 isolates as carbapenemase negative. However, it incorrectly classified 10 of them as being CPE (Table 3). Out of the 10 isolates incorrectly classified as CPE, follow-up testing with the KPC-metallo-β-lactamase confirmation kit (Rosco Diagnostica A/S, Taastrup, Denmark) found 4 isolates (2 *E. cloacae*, 1 *Enterobacter aerogenes*, and 1 *E. coli* strain) displaying a pattern consistent with AmpC hyperproduction plus porin loss and/or efflux pumps. Five isolates (4 *K. pneumoniae* strains and 1 *E. aerogenes* strain) showed no synergy by combination disk testing. One isolate (*K. pneumoniae*) which the BD Phoenix CPO Detect wrongly identified as a class B carbapenemase producer showed KPC-class A activity by combination disk testing; however, PCRs for all additional carbapenemase genes (bla_{GES}, bla_{NMC-A}, bla_{IMI}, bla_{IMP}, and bla_{VIM}) were negative.

DISCUSSION

The accurate detection of CPE is essential for the appropriate management of patients with infections caused by these organisms, as well as for timely implementation of infection control measures. Since 2010, the number of CPE in Singapore has been increasing. The quarterly incidence of unique subjects with positive cultures for clinical and surveillance CRE cultures was reported to range from 7.73 to 10.32 per 100,000 patient-days and an average of 16.0 per 100,000 patient-days, respectively, between 2013 and 2015, with the 3 dominant carbapenemases in circulation identified as NDM, KPC, and OXA-48-like (17). However, it is important to note that differences do exist between institutions. In our institution, IMI-1 surpassed KPC as the dominant class A carbapenemase. Unlike the plasmid-mediated IMI-2 and IMI-3, IMI-1 in *E. cloacae* is chromosomally encoded (18).

We expect the BD Phoenix CPO Detect to be used mainly for isolates obtained from clinical specimens requiring susceptibility testing. It is unlikely to be used routinely for CPE screening given the cost of each panel. Most laboratories in Singapore use a

combination of selective chromogenic media (e.g., chromID Carba Smart), followed by either combination disk testing (e.g., Rosco, Denmark), Carba NP, or mCIM to screen for CPE. This is both cost-effective and appropriate, especially in the case of the mCIM, given its sensitivity of 100%. We also found mCIM to be superior to Carba NP test in terms of ease of interpretation. The Carba NP being a colorimetric test is known to have different shades of color change which could be challenging for laboratory staff to interpret. Both mCIM and the Carba NP test are unable to classify the different carbapenemase types; hence, further testing either by phenotypic or molecular means will be needed in the event of outbreak investigation and contact tracing.

The sensitivity of 89.4% in the BD Phoenix CPO Detect in our evaluation is in contrast to that found by Thomson et al., who reported a sensitivity of 97.1% (14). The poor performance of the BD Phoenix CPO Detect in detecting IMI-1 carbapenemase in our study could account for this difference, as Thomson et al. only included 1 IMI isolate in their evaluation. Despite being chromosomally encoded, IMI-1 carbapenemase-producing colistin-resistant *E. cloacae* has caused one outbreak on the French island of Mayotte (19). Previous studies have shown that IMI carbapenemase enzyme production can be induced when these isolates are challenged with imipenem (20, 21). Therefore, failure in identifying IMI-producing *Enterobacteriaceae* could potentially result in treatment failure if clinicians prescribe carbapenems, particularly imipenem. Hence, while BD Phoenix CPO Detect is sensitive for KPC detection, laboratories in the areas where IMI carbapenemases are in circulation need to be aware that it may not reliably detect this particular class A CPE.

Consistent with what was reported by Thomson et al., we found the BD Phoenix CPO Detect to have a low specificity of 66.7% for CPE (14). This was especially marked for isolates with a meropenem MIC of >2 mg/liter, as almost half (7 out of 15) of such isolates were reported falsely as being CPE. False-positive carbapenemase reporting by the BD Phoenix CPO Detect is concerning, as it could potentially lead to either unnecessary isolation of patients, which adds pressure on the limited number of isolation rooms, or to inappropriate cohorting that would potentially put patients at risk of acquiring CPE. Given this low specificity, it would be prudent for laboratories to perform a confirmatory test for cases that are flagged as carbapenemase positive by the BD Phoenix CPO Detect.

We also found that the BD Phoenix CPO Detect failed to simultaneously report both classes of carbapenemases in 2 isolates with dual OXA and NDM carbapenemase gene carriage. This was a similar finding in the Thomson et al. study (14). While molecular assays, such as the Xpert Carba-R, can report multiple carbapenemase genes in a single test, they tend to be costly. Recently, Carba5, a multiplex lateral flow immunoassay for the detection of NDM-, KPC-, IMP-, and VIM-type and OXA-48-like carbapenemases, not only had a reported sensitivity and specificity of 100% and 95.3%, respectively, but also was demonstrated to be capable of detecting the simultaneous production of several of the five main carbapenemases by one strain (12).

All CPE were ertapenem resistant (MIC, >1 mg/liter). However, there were 18 isolates (3 IMI, 4 NDM, and 11 OXA types) with meropenem MICs of <2 mg/liter by Etest; these would be considered susceptible by EUCAST criteria (16). The BD Phoenix CPO Detect correctly identified 15 of these isolates as harboring carbapenemases. The question of whether one can safely treat infections caused by these isolates with carbapenem monotherapy or whether combination therapy is always required is unanswered. Clinicians working in institutions whose laboratories use susceptibility panels equipped with the BD Phoenix CPO Detect will undoubtedly see more reports of CPE with carbapenem MICs falling within the susceptible range. By building carbapenemase detection into routine susceptibility testing, the BD Phoenix CPO Detect offers valuable support for clinical studies to look into different therapeutic strategies for infections caused by such organisms.

Our study had several limitations. First, our Carba NP was a homemade assay, which may explain a lower sensitivity of 90.6% compared with that of commercial biochemical kits, such as the Rapidec Carba NP, which has a reported sensitivity in the range of 96% (22) to 99% (23). Second, while all isolates were primarily screened for common carbapenemase

genes, such as bla_{KPC}, bla_{NDM}, $bla_{OXA-48-like}$, and bla_{OXA-23}, additional gene testing for bla_{GES}, bla_{NMC-A}, bla_{IMI}, bla_{VIM}, and bla_{IMP} was performed selectively only for isolates that were negative by the primary PCR screen. Therefore, there may be more isolates harboring dual carbapenemase genes for which only a single class was reported by BD Phoenix CPO Detect. Finally, our study included only a limited repertoire of CPE in our evaluation. For example, strains with SME, NMC-A, VIM, and SPM enzymes were lacking. Also, of the 23 IMI CPE isolates, only 1 was IMI-7, while the rest were IMI-1. Plasmid-encoded IMI-2 or IMI-3 CPE strains were not available for inclusion in the study.

In conclusion, the BD Phoenix CPO Detect had a low sensitivity for CPE detection, especially in the case of IMI-1 carbapenemase production, and poor specificity in comparison with that of either the Carba NP test or mCIM. Confirmatory testing by an alternative method is recommended for CPE-positive cases reported by BD Phoenix CPO Detect.

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