

Detection of Carbapenem-resistance in CRE by Comparative Assessment of RAPIDEC[®] CARBA NP and Xpert[™] Carba-R Assay

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Introduction: Carbapenem-resistant *Enterobacteriaceae* (CRE) infections resist nearly most available antimicrobials, resulting in poor clinical outcomes. Saudi Arabia has a relatively high CRE prevalence. This study aims to evaluate the sensitivity of Rapidec Carba NP test and GeneXpert Carba-R assay compared with conventional manners for detection of carbapenemase-producing *Enterobacteriaceae*.

Methods: This is a cross-sectional study including a total of 90 CRE isolates examined at two tertiary hospitals in KSA from October 2020 to December 2021. Gram-negative *Enterobacteriaceae* were identified by using Vitek 2 system and were furtherly tested for imipenem and meropenem susceptibility by E- test strips, followed by Rapidec Carba NP test and the Xpert[™]Carba-R assay.

Results: Carbapenem-resistant *K. pneumoniae* (78.9%) and carbapenem-resistant *E. coli* (14.4%) were the two most common isolates species. Colistin (98.9%) and tigecycline (88.9%) were the most effective antibiotics against CRE isolates, followed by amikacin (52.2%), gentamicin (33.3%), cotrimoxazole (15.6%), and ciprofloxacin (8.9%). blaOXA-48 was the predominant carbapenemase gene (44.4%), followed by blaNDM (32.2%). blaKPC gene was not detected. The Rapidec Carba NP and the Xpert[™]Carba-R demonstrated an overall sensitivity of 69.3% and 88%, respectively, in comparison to gold standard detection of meropenem and imipenem resistance by Vitek 2 system and E- test strips.

Discussion: RAPIDEC[®] CARBA NP may be a beneficial screening test for detecting CRE, but for confirmation of the results, Xpert Carba-R assay is more sensitive, significantly lowering the turnaround time compared to reference traditional methods. The information on carbapenemase genes may be used for epidemiologic purposes and outbreak management.

Keywords: CRE, carbapenemase genes, Rapidec Carba NP test, Xpert Carba-R assay

Introduction

Carbapenem-resistant *Enterobacteriaceae* (CRE) infections resist nearly most available antimicrobials, resulting in poor clinical outcomes particularly in low- and middle-income countries due to limited resources for surveillance of CRE, infection prevention and control.¹ CRE infections are mainly caused by extended-spectrum beta-lactamases (ESBLs) or AmpC enzymes joint with drug decreased permeability, because of loss of porins. Thereby pressure on carbapenems – as last option to manage infections resulting from ESBL producing bacteria – resulted in the development of isolates producing carbapenemases from Ambler Classes A, B, and D.² Risk factors related to carbapenemases producing *Enterobacteriaceae* (CPE) infection include advanced age, severity of the underlying illness, admission to intensive care unit (ICU), earlier antibiotic exposure, invasive devices, organ or stem-cell transplant, mechanical ventilation, and lengthy hospitalization. Clinical infections are typically healthcare-associated bacteraemia and ventilator-associated pneumonia, as well as surgical site sepsis and urinary tract infections.³

The rapidly increasing prevalence of Enterobacteriaceae harbouring carbapenemases is concerning and its early detection has become required. The Clinical and Laboratory Standards Institute (CLSI) previously recommended that, laboratories using Enterobacteriaceae minimum inhibitory concentration (MIC) breakpoints for carbapenems to perform the Modified Hodge when carbapenem-resistant bacteria are suspected. This procedure has a high amount of hands-on time, is difficult to do and interpret, also may elicit false-positive results.⁴ All these factors increase the need for other tests as CARBA NP test for suspected CRE isolates.⁵

After that, Cepheid Xpert Carba-R assay became available in many hospitals, and we became able to detect carbapenemase genes directly from pure colonies by an automated in vitro diagnostic test for the detection of genes associated with carbapenem resistance in Gram-negative bacteria. Moreover, it can be performed on rectal swab specimens or pure cultures of carbapenem-resistant bacterial isolates.^{6–8}

Polymyxins, tigecycline, fosfomycin, and aminoglycosides may be active against CRE infections especially when combined. It is well-known that combination therapy is associated with better clinical outcomes versus monotherapy. Other promising treatment options are recently approved β -lactam/ β -lactamases inhibitors ceftazidime-avibactam (CAZ-AVI), active only against KPC and OXA-48-producing Enterobacteriaceae, but not against metallo- β -lactamase-producing CRE.⁹

Gulf countries, including Saudi Arabia, are challenged by multi-drug resistant strains spread such as CRE. The first documented outbreak of carbapenem-resistant *K. pneumoniae* in Saudi Arabia was reported in Riyadh in 2010 and involved 20 patients.¹⁰

As many studies defining molecular characterization of CPE in Medina and Jeddah cities, we planned this study to evaluate the reliability of both RAPIDEC[®] CARBA NP test and the Xpert Carba-R assay compared to the gold standard VITEK 2 system for detection of meropenem and imipenem resistance using pure colonies and to figure out the frequency of CRE in our hospitals.

Methods

We conducted this research at Clinical Microbiology Laboratories of King Fahad Hospital, Madinah, and King Abdulaziz University Hospital, Jeddah, Saudi Arabia. The study was approved by the Research Ethics Committee at both corresponding hospitals. The patient consent to review their medical records and samples was not required by the approving ethics committees. The research involves no more than minimal risk to subjects (45 CFR 46.116). The patient data confidentiality and compliance with the following declaration of Helsinki.

Inpatients with CRE from clinical samples were identified by daily microbiological work. During the period of October 2020 to September 2021, a prospective chart review was carried out utilizing the patient data from hospitals and laboratories computerized data or papers created by physicians. We used hospitals' epidemiologic databases to record demographic data of inpatients with positive cultures for CRE.

According to the Centers for Disease Control and Prevention's Specimen Collection Guidelines, clinical samples were taken from patients (CDCP, 2013) including respiratory, urinary, wound swap, blood cultures, sterile body fluids, and tissue samples. Clinical samples have been sent to the lab to undergo routine microbiological cultures processing. Using the VITEK-2 system at Clinical and Molecular Microbiology Laboratory, King Abdulaziz University Hospital and The Phoenix automated microbiology 100 ID/AST system at Clinical Microbiology Laboratory, King Fahad Hospital, Gram-negative Enterobacteriaceae were detected. According to CLSI recommendations, breakpoints for imipenem and meropenem were established. All chosen isolates were determined to be carbapenem-resistant using the automated systems, and their sensitivity to imipenem and meropenem was then confirmed using E-test strips (bioMérieux, France). The Phoenix automated microbiology 100 ID/AST system was used to assess the organisms' susceptibility to antimicrobial agents (Becton Dickinson Company, Sparks, Md.). Also, VITEK-2 system with AST-GN292 cards and 04.02 PC software (bioMérieux, France) was used depending on the routine in the respective laboratory and in agreement with CLSI guidelines. Ceftriaxone, Ceftazidime, Cefepime, amoxicillin/clavulanate, gentamicin, cotrimoxazole, amikacin, ceftazidime, imipenem, ciprofloxacin, meropenem, piperacillin tazobactam, and nitrofurantoin were utilised as antimicrobial agents, all strains were further confirmed for meropenem and imipenem resistance by using E-test strips (bioMérieux, France). So, carbapenem resistance was suspected when the minimum inhibitory concentration (MIC) was greater than 1 mg/L for imipenem and/or meropenem utilising

automated testing methods and confirmed by E test strips. Isolates suspected of carrying carbapenemase genes were tested by GeneXpert system using Xpert® Carba-R assay.

RAPIDEC CARBA NP is ready to use strips test based on detecting carbapenem hydrolysis by carbapenemase-producing gram-negative bacilli. After incubating for a maximum of 2 hours, we compared visually a control well, without imipenem, to the reaction well containing imipenem.⁵ The test was deemed positive once we observed a significant colour variation between the two wells.

A quick, automated, qualitative Real-Time PCR test called the GeneXpert system integrates sample preparation, nucleic acid extraction, amplification, and target sequence identification using a straightforward procedure with little chance of errors or contamination. Each strain was examined for the presence of the carbapenemase genes KPC, OXA-48, NDM, VIM, and IMP using a small sample.¹¹

Statistical Analysis

The χ^2 test was used to compare categorical variables. We considered a P-value <0.05 as statistically significant. We calculated sensitivity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of detecting a carbapenem resistance by Xpert Carba R and RAPIDEC CARPA NP test when compared to microbiological culture and antimicrobial susceptibility testing by VITEK or Phoenix were selected for further testing for meropenem and imipenem susceptibility using E- test strips (bioMérieux, France). Sensitivity was true-positive/(true positive + false negatives) \times 100. Specificity was “true negative/(true negative + false positive) \times 100. Positive Predictive Value was true positive/(true positive + false positive) \times 100. Negative Predictive Value was true negative/(true negative + false negative) \times 100. Accuracy was (True Positive + True Negative)/(True Positive + True Negative + False Positive + False Negative) \times 100. Data were analysed using Statistical Package for Social Sciences (SPSS) software, version 19.

Results

Between October 2020 and December 2021, a total of non-duplicate 90 CRE strains were isolated from King Fahad Hospital, Madinah, and King Abdulaziz University Hospital, Jeddah, Saudi Arabia. Table 1 illustrates the demographic data of patients included in the study and isolates' characteristics. Thirty-nine (43.3%) were females and 51 (56.7%) were males. The (mean \pm SD) of age of the patients was 51.14 \pm 23.8 years, and the age range was from 1 to 88 years. Regarding nationality, 40% of patients infected with CRE strains were Saudi and 60% were non-Saudi.

Ninety isolates were identified as CRE. The two most prevalent species were carbapenem-resistant *K. pneumoniae* (CRKP) and carbapenem-resistant *E. coli* (CREC), which together accounted for 78.9% and 14.4% of the total number of CRE isolates, respectively (Table 1). Other forms of CRE, such as *Klebsiella oxytoca*, *Serratia marcescens*, and *Citrobacter freundii*, have prevalence rates that are given *Enterobacter aerogenes* in (Table 1).

Overall, the most frequent source of CRE isolation was from UTIs (28.9%) followed by wound swab samples (26.7%), then respiratory tract infections (RTIs) and blood stream infections (BSI) were 22.2% and 13.3%, respectively (Table 1). Figure 1 details the occurrence of different carbapenem-resistant Enterobacteriaceae as per source of clinical samples.

The antibiotic susceptibility results showed colistin (98.9%) and tigecycline (88.9%) as the most effective antibiotics against CRE isolates. All the recovered CRE isolates were resistant to imipenem and meropenem. Details of antimicrobial resistance to individual CRE are shown in Figure 2.

Among 90 CRE isolates, *bla*OXA-48 was the most predominant carbapenemase gene 44.4%, followed by *bla*NDM 32.2%. Over the study period, 43.7%, 38%, and 12.7% of *K. pneumoniae* and 38.5%, 15.3%, and 30.8% of *E. coli* isolates were found to carry *bla*OXA gene, *bla*NDM gene, and both genes, respectively. No *bla*KPC gene was detected from all bacterial isolates during the study (Table 2).

Compared to meropenem and imipenem resistance by VITEK 2 system and Phoenix and E- test strips both The Xpert™Carba-R assay demonstrated an overall sensitivity, specificity, PPV, NPV and accuracy of 88%, 100%, 100%, 100%, and 100%, respectively. Meanwhile, RAPIDEC CARBA NP test showed an overall sensitivity, specificity, PPV, NPV and accuracy of 69.3%, 100%, 100%, 6.9%, and 70%, respectively (Table 2). We noticed no statistically significant difference between both tests in detecting individual carbapenemase genes (Table 3).

Table 1 Patients' Demographics and Isolates' Characteristics

	Number (%)
Age in years	
Mean (\pm SD)	51.14 (\pm 23.8)
Range	1–88
Gender	
Male	51 (56.7)
Female	39 (43.3)
Nationality	
Saudi	36 (40.0)
Non-Saudi	54 (60.0)
Hospital units	
ICU	52 (57.8)
Non-ICU	38 (42.2)
Source of Isolate	
Urine	26 (28.9)
Wound Swab	24 (26.7)
Respiratory	20 (22.2)
Blood Sample	12 (13.3)
Sterile Body Fluid	6 (6.7)
Tissue	2 (2.2)
Organism Isolated	
<i>K. pneumoniae</i>	71 (78.9)
<i>K. oxytoca</i>	2 (2.2)
<i>E. coli</i>	13 (14.4)
<i>E. aerogenes</i>	2 (2.2)
<i>S. marcescens</i>	1 (1.1)
<i>C. freundii</i>	1 (1.1)
Patient Outcome	
Deceased	44 (48.9)
Survived	46 (51.1)

Abbreviations: SD, Standard Deviation; ICU, Intensive Care Unit; *K. pneumoniae*, *Klebsiella pneumoniae*; *K. oxytoca*, *Klebsiella oxytoca*; *E. coli*, *Escherichia coli*; *E. aerogenes*, *Enterobacter aerogenes*; *S. marcescens*, *Serratia marcescens*; *C. freundii*, *Citrobacter freundii*.

Regarding the isolated genes from each organism, overall 30-day mortality was 48.9% (44 out of 90 patients died). On the other hand, none of the detected carbapenemase genes was identified as an independent predictor of mortality. Furthermore, the mortality rates among patients infected with CRE isolates carrying *bla*OXA, *bla*NDM, *bla*OXA, and *bla*NDM, *bla*VIM and *bla*IMP showed no significant difference (Table 4).

Discussion

Due to ESBL or plasmid mediated AmpC producers of the Enterobacteriaceae family, carbapenems are the antimicrobials of last resort to treat the infections.¹² Carbapenemases were increasingly reported in Enterobacteriaceae in the past 10 years. To prevent their spread, detection of infected patients and carriers with carbapenemase producers is necessary.¹³

There are more than 53.3% of our patients were hospitalized in ICU (Table 1). This is consistent with the study of Alotaibi et al, 2017¹⁴ conducted at the King Khalid University Hospital and reported that admission to ICU has been associated with the acquisition of CRE.

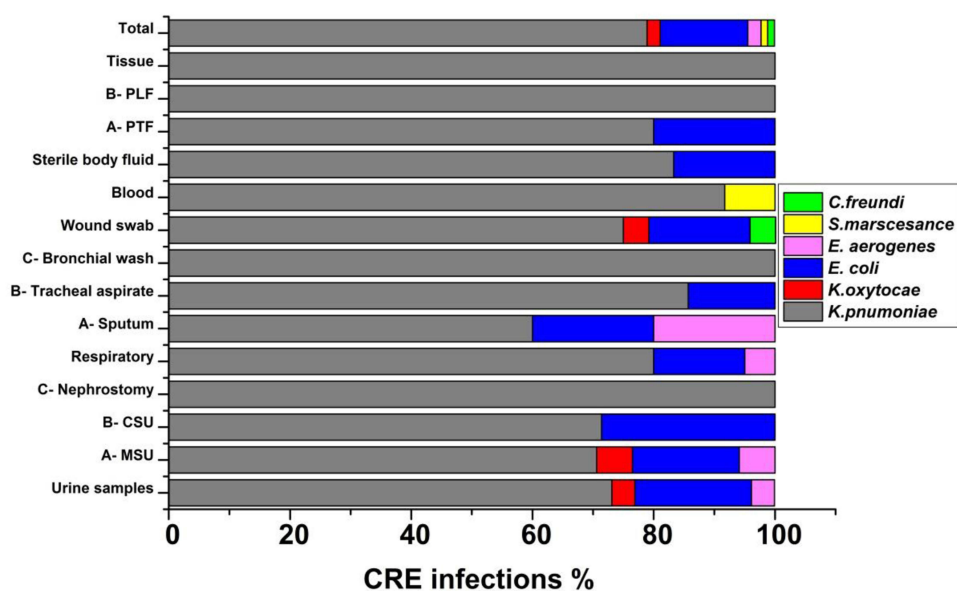


Figure 1 Carbapenem-resistant enterobacteriaceae in different clinical samples.

Abbreviations: CSU, Catheter specimen of urine; MSU, midstream urine.

Antimicrobials	Organisms					
	<i>K. pneumoniae</i> (n=71)	<i>K. oxytoca</i> (n=2)	<i>E. coli</i> (n=13)	<i>E. aerogenes</i> (n=2)	<i>S. marcescens</i> (n=1)	<i>C. freundii</i> (n=1)
Ceftriaxone	99%	100%	92%	50%	0%	0%
Ceftazidime	99%	100%	92%	50%	0%	0%
Cefepime	99%	100%	92%	50%	0%	0%
Amoxicillin-clavulanate	100%	100%	100%	100%	100%	
Piperacillin-tazobactam	100%	100%	100%	100%	100%	
Imipenem	100%	100%	100%	100%	100%	
Meropenem	100%	100%	100%	100%	100%	
Gentamycin	68%	100%	69%	50%	0%	0%
Amikacin	48%	100%	46%	50%	0%	0%
Ciprofloxacin	95%	100%	69%	50%	100%	100%
Trimethoprim/Sulfamethoxazole	85%	100%	77%	100%	100%	100%
Nitrofurantoin*	84%	0%	40%	100%		
Tigecycline	9%	0%	23%	0%	100%	0%

* only 26 urinary isolates

> 50% resistance

10% to 50% Resistance

tn

No Data

Figure 2 The antimicrobial resistance pattern of each isolated organism *Klebsiella pneumoniae* *K. Oxytoca*; *Klebsiella Oxytoca*; *E. coli*: *Escherichia coli*; *E. aerogenes*: *Enterobacter aerogenes*; *S. marcescens*: *Serratia marcescens*; *C. Freundii*: *Citrobacter Freundii*.

Herein, the overall 30-day mortality was 48.9%, as shown in Table 1. These results align with the results of another study, which demonstrated a 2-fold increase in mortality among the CRE group relative to the Carbapenem-sensitive Enterobacteriaceae (CSE) group.¹⁵ In a recent study, 11 (28.9%) of 38 colonized patients developed CPE BSIs, and 7 (63.6%) of those died due to infection.¹⁶

Table 2 Sensitivity, Accuracy, PPV and NPV of GeneXpert and CARBA NP Test in Comparison to Gold Standard Detection of Meropenem and Imipenem Resistance by Vitek 2 System and E-Test

90 Samples	Sensitivity	Specificity	Positive Predictive value	Negative Predictive value	Accuracy
GeneXpert	88%	100%	100%	100%	100%
Carba Test	69.3%	100%	100%	6.9%	70%

Abbreviations: PPV, Positive predictive value; NPV, Negative predictive value.

Table 3 Comparison Between Results of Both CARPA NP Test and Xpert™ Carba-R Assay

Carbapenemase Detected by Xpert™ Carba-R Assay	Carba Test Positive Number (%)	Carba Test Negative Number (%)	Carba Test Equivocal Result Number (%)	X ²	P- value
OXA-48 (n.=40).	23 (57.5)	9 (22.5)	8 (20)	5.378	0.068
NDM (n.=29)	22 (75.9)	3 (10.3)	4 (13.8)	0.969	0.616
OXA 48 + NDM (n.=14)	12 (85.7)	1 (7.1)	1 (7.1)	1.951	0.377
VIM (n.=3)	2 (66.7)	1 (33.3)	0 (0.0)	1.084	0.582
IMP (n.=2)	2 (100)	0 (0.0)	0 (0.0)	0.877	0.645
No genes (n.=2)	0 (0.0)	2 (100)	0 (0.0)	0.877	0.645

Abbreviations: OXA-48, Oxacillinase-48; NDM, New Delhi Metallo-beta-lactamase; VIM, Verona Integron-Encoded Metallo-beta-lactamase; IMP, Imipenemase.

Table 4 Outcome of Patients Regarding the Isolated Genes from Each Organism

	N/90 (%)	Deceased	Survived	X ²	P- value	Significance
OXA-48	40 (44.4%)	19/40 (47.5%)	21/40 (52.5%)	0.056	0.835	NS
NDM	29 (32.2%)	14/29 (48.3%)	15/29 (51.7%)	0.006	1	NS
OXA 48+NDM:	14 (15.6%)	7/14 (50%)	7/14 (50%)	0.008	1	NS
VIM:	3 (3.3%)	1/3 (33.3%)	2/3 (66.7%)	0.301	1	NS
IMP:	2 (2.2%)	1/1 (50%)	1/1 (50%)	0.001	1	NS
No genes:	2 (2.2%)	2/2 (100%)	0/2 (0%)	2.138	0.236	NS

Abbreviations: OXA-48, Oxacillinase-48; NDM, New Delhi Metallo-beta-lactamase; VIM, Verona Integron-Encoded Metallo-beta-lactamase; IMP, Imipenemase.

The two most frequent species among our 90 isolates that were classified as CRE were carbapenem-resistant *K. pneumoniae* (CRKP) and carbapenem-resistant *E. coli* (CREC) (Table 1). Similar findings were made by Chen et al, who discovered that *K. pneumoniae* made up 76.4% (323/423) and *E. coli* made up 8.3% (35/423) of the 423 CRE isolates.¹⁷

Overall, the most frequent source of bacterial isolation was from UTIs followed by skin and soft tissue infections, respiratory tract infections, and bloodstream infections (Table 1). A study conducted in Malaysia revealed similar results in which CRE, in addition to those isolated from rectal swabs, urine (31.4%); blood (19%), and tracheal aspirate (14%) were all detected.¹⁸

The antibiotic susceptibility results showed as the most effective antibiotics toward CRE isolates, followed by amikacin, gentamicin, cotrimoxazole, ciprofloxacin, and ceftriaxone (Figure 2). Our results match the findings of Renteria et al, who found that tigecycline had a 95.3% overall susceptibility among CRE, much greater than amikacin's 48.7%, levofloxacin's 11.5%, and ceftriaxone's 4.2%.¹⁹ Concerningly, many CRE isolates are resistant to practically all current medicines in a variety of contexts.^{20,21}

In the present study, carbapenemase genes (namely OXA-48, NDM or both) were detected in the majority of our CRE isolates. KPC is the renowned to be observed carbapenemase in Enterobacteriaceae with KPC-2 and KPC-3 as the most predominant alleles.²² No *bla* KPC gene was detected from all the bacterial isolates during our study. This finding corroborated several other studies proving that KPC carbapenemase is rarely detected in Asia.²³ KPCs are most

commonly detected in *K. pneumoniae* from the US, China, Colombia, Israel, Greece, and Italy, according to Miao et al, whereas NDMs are mostly discovered in *K. pneumoniae*, *E. coli*, and *Enterobacter* spp.^{24,25}

We detected either OXA-48 and NDM genes or both together. Our results were matched with that of Pevoric et al, who found that the commonest carbapenemase genes were *bla*-OXA-48 (52%) and *bla*-NDM (34%).²⁶ NDM is the most common carbapenemase in the Indian subcontinent while *CRE* with OXA-48 is endemic in Turkey.²⁷ Although the lack of information on the patients' travel histories prevents any clear conclusions from being reached, a high frequency of population mobility between Saudi Arabia and both India and Turkey may explain the high prevalence of isolates with this resistance gene in our settings.²⁸

Seventy-one *K. pneumoniae* isolates were identified and confirmed to be carbapenemase-producers. The carbapenemase gene OXA-48 was the most detected followed by NDM-1 and VIM. In the study of Alizadeh et al, the most common carbapenemase gene was *bla*-OXA-48-like followed by *bla*-NDM, *bla*-IMP, *bla*-VIM, and *bla*-KPC.²⁹

The RAPIDEC CARBA NP test demonstrated an overall sensitivity of 69.3% in comparison to gold standard detection of meropenem and imipenem resistance by VITEK 2 system and E-test (Table 2 and Table 3). Our results were less than that reported by other studies^{22,29,30} which estimated the sensitivity of the RAPIDEC CARBA NP test for detecting *CRE* to be 89.8%, 93.9%, and 98.8%, respectively. The type of beta-lactamase enzymes carried by *CRE* isolates contributes to the variations in sensitivity and specificity of this test.

We also attempted to evaluate the performance of the GeneXpert Carba-R assay for rapid detection of *bla*-KPC, *bla*-NDM, *bla*-VIM, *bla*-IMP, and *bla*-OXA-48 carbapenem resistance genes from bacterial isolates grown on blood agar or MacConkey agar with a positive screen test for carbapenemase production, ie, with a meropenem MIC > 0.25 mg using E-test and VITEK 2 system. Xpert Carba-R assay showed 88% sensitivity (Tables 2–4). This result was comparable to the results of Khalifa et al and Cury et al who reported sensitivity 94% and 95.7% of the Xpert Carba-R assay, respectively.^{31,32}

Conclusion

RAPIDEC[®] CARBA NP may be a beneficial screening test for detecting *CRE*, but for confirmation of the results, Xpert Carba-R assay is more sensitive, significantly lowering the turnaround time compared to reference traditional methods. The information on carbapenemase genes may be used for epidemiologic purposes and outbreak management.

Access to Data

Supporting data is available on request.

Consent

All representatives from the anonymous hospitals have agreed to participate in the paper.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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