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ORIGINAL RESEARCH

A Rapid Carbapenemase Genes Detection Method with Xpert Carba-R from Positive Blood Cultures Compared with NG-Test Carba 5 and Sequencing

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Objective: The objective of the current study was to evaluate the performance of Xpert Carba-R for the direct detection and identification of carbapenemase genes from positive blood cultures.

Methods: Pathogens which extracted from positive blood cultures and identified using MALDI-TOF MS as *Enterobacterales* were included in this study. Xpert Carba-R was used for the rapid detection of carbapenemase genes from positive blood cultures. NG-Test CARBA 5 and polymerase-chain reaction (PCR) sequencing were used for the detection of carbapenemases and carbapenemase genes in positive blood culture isolates, respectively. Finally, antibiotic susceptibility tests were conducted using the VITEK-2 Compact system.

Results: A total of 133 positive blood cultures of *Enterobacterales* were collected and 27 of them were detected to carry carbapenemase genes using Xpert Carba-R. In comparison with PCR sequencing results, the sensitivity and specificity of Xpert Carba-R and NG-Test CARBA 5 were calculated as 100%. Additionally, Xpert Carba-R could significantly shorten the turnaround time by directly detecting positive blood cultures comparing with NG-Test CARBA 5. For 27 carbapenem-producing strains, the resistance rates of carbapenems and aztreonam were 96.3% and 92.6%, respectively. Strains carrying the *bla*KPC gene were all sensitive to ceftazidime–avibactam. All strains were sensitive to tigecycline and colistin.

Conclusion: Xpert Carba-R is suitable for the rapid detection of main carbapenemase genes from positive blood cultures with high sensitivity and specificity. In comparison with NG-Test CARBA 5 and PCR sequencing methods, the timely and convenient method can be a useful test to guide optimal therapy and infection control.

Keywords: carbapenemase genes, positive blood culture, rapid detection, Xpert Carba-R

Introduction

In recent years, the emergence and widespread diffusion of antibiotic resistance has been a major public health concern, which can result in longer hospital stays, higher health care costs and mortality. It has been estimated that infections due to multidrug resistant bacteria can cause at least 700,000 deaths per year worldwide, and the number is expected to rise to 10 million by 2050.[1] Multidrug resistant gram-negative bacteria can cause a variety of infections, including bloodstream infections (BSI), pneumonia and urinary tract infections with significant implications on antibiotic consumption and patients outcome. Among these infections, BSI is associated with high mortality. Bacteria invade the blood circulation, multiply in the blood, release toxins and metabolites, which can lead to systemic multiple organ dysfunction syndrome and even death.[2]

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Approximately 71.5% of multidrug-resistant BSI pathogens are carbapenem-resistant *Enterobacterales* (CRE).[3] Mechanisms of carbapenem resistance are heterogeneous, including carbapenemases production, extended-spectrum β-lactamases and/or AmpC cephalosporinases combined with altered membrane permeability. Among these, production of carbapenemases is the main resistance mechanism,[4] and the rapid dissemination of carbapenem-producing *Enterobacterales* (CPE) throughout the world is worrisome and threatens public health. A report suggested that patients with CPE had approximately 4 times the odds of dying within 14 days compared to patients with non-CPE.[5] Early detection of CPE infection is imperative for patient treatment, infection control and epidemiological studies.[6]

Various assays have been commercialized to detect carbapenemase activity or carbapenemase genes, including PCR sequencing, carbapenem hydrolysis assays, and colorimetric-based assays. Most of these assays detect carbapenemase activity and genes in bacterial colonies, and few have been evaluated directly on biological samples. Recently, the Xpert Carba-R assay, a PCR-based test run on the GeneXpert platform, was designed for the rapid detection and differentiation of 5 carbapenemase genes (*bla*KPC, *bla*NDM, *bla*IMP, *bla*VIM, *bla*OXA-48) directly from clinical specimens.[7] In previous studies, the sensitivity and specificity of the Xpert Carba-R assay were 100% and 98%, respectively.[8] Published studies have shown that the Xpert Carba-R assay can be used to detect carbapenemase genes from strains,[9] sputum,[10] rectal swabs[11] and bronchoalveolar lavage.[12] In Aurélie Cointe's study, Xpert Carba-R was shown to be suitable for the rapid detection of carbapenemase genes on positive blood vials by inoculating isolates of several variants in blood culture bottles. Limited numbers of clinical samples were evaluated in the study and all tests were negative.[13]

NG-Test Carba 5 is another newly developed method for detecting five major carbapenemases (KPC, NDM, IMP, VIM and OXA-48).[14] Monoclonal antibodies were used for detection in bacterial colonies.

The aim of this study was to evaluate the clinical usefulness of Xpert Carba-R for the rapid detection of carbapenemase genes in positive blood cultures. The performance of the Xpert Carba-R assay and NG-Test CARBA 5 was compared for the detection of five carbapenemase genes or carbapenemases in positive blood culture broth or isolates.

Materials and Methods

Specimen Preparation

Blood cultures were processed according to routine methods using BD BACTEC™ FX blood culture system (Becton-Dickinson, Sparks, MD, USA). Once blood culture bottles were positive, gram staining was used for microscopic examination. Patients were included only one time when they happened BSI at the first time. If Gram stain showed a single form of gram-negative bacilli, pathogens would be enriched from positive blood culture fluid and directly identified by MALDI-TOF MS (BioMérieux, France). The specific methods for isolation and identification for pathogens were referred to the "in-house" MALI-TOF MS protocol for direct identification of GN bacteria from positive blood cultures described in the literature of Menglan Zhou et al.[15] *Enterobacterales* isolated and identified in positive blood cultures were considered "potential carbapenemase producers" and included in the study. For positive blood cultures, isolates were inoculated onto blood agar plates (Antobiology, China). Blood agar plates were incubated at 35 °C overnight. To evaluate the accuracy of pathogens extracted from positive blood culture bottles, identification was carried out after colonies were grown on blood agar plates.

Xpert Carba-R

As blood cultures were positive, the Xpert Carba-R assay (Cepheid, Sunnyvale, CA, USA) was used to detect the carbapenemase genes in a cartridge. In brief, 40μL aliquot was directly mixed with Sample Reagent Buffer and vortexed. Then, 1.7mL of this sample reagent was transferred to an Xpert cartridge which was detected on the GeneXpert platform. *Klebsiella pneumoniae* ATCC BAA-1705 (*bla*KPC positive strain) and *Escherichia coli* ATCC 25922 (carbapenem-susceptible strain) were used as positive and negative controls.

PCR Sequencing Analysis

DNA was extracted from purified bacterial isolates using a TIANamp Bacteria DNA Kit (Tiagen, China) and tested by PCR with primers specific to five carbapenemase genes (*bla*KPC, *bla*NDM, blaVIM, *bla*OXA-48, *bla*IMP). A volume of

12.5μL of PCR Master Mix (Vazyme, USA) was mixed with 2μL of forward and reverse primers in a 25μL reaction. Reactions were amplified on the Applied Biosystems 2720 Thermal Cycler (ThermoFisher Scientific, USA) using following the cycling conditions: an initial 94°C 2 min hold, followed by 36 cycles at 94°C for 30s, 60°C for 40s and 72°C for 1 min, followed 72°C for 5 min. The appropriately sized PCR products were confirmed by DNA sequence analysis.[16] A positive result means that at least one carbapenemase gene was detected in this specimen. The negative result means that there were no *bla*KPC, *bla*NDM, blaVIM, *bla*OXA-48 or *bla*IMP carbapenemase genes detected by the PCR-based DNA sequence analysis. *K. pneumoniae* ATCC 2146 (*bla*NDM positive) and *K. pneumoniae* ATCC BAA-1705 (*bla*KPC positive) were used as positive controls. *E. coli* ATCC 25922 was used as a negative control.

NG-Test CARBA 5

Bacterial isolates were tested using the NG-Test CRABA 5 kit (Fosun Diagnostics, China) simultaneously. The NG-Test CRABA 5 is a qualitative rapid lateral flow assay with mouse monoclonal antibodies against KPC, NDM, IMP, VIM and OXA-48, which are immobilized on nitrocellulose membrane test zones. The suspected colony was mixed with 150 µL extraction buffer, and then 100 µL of this mixture was dispensed into the cassette well and allowed to migrate toward the conjugate pad. The carbapenemase-antibody complexes migrated through the nitrocellulose membrane and were captured by corresponding anti-carbapenemase monoclonal antibodies immobilized on the membrane, resulting in a red line (or lines) on the test zone(s) and on the control zone.

Antibiotic Sensitivity Test

Antibiotic susceptibility tests were conducted using the VITEK-2 Compact system (BioMérieux, France) according to the Clinical and Laboratory Standards Institute (CLSI) guidelines (CLSI 2020, version M100-S30). Ceftazidime–avibactam (Oxoid, England) were tested using Kirby–Bauer method.

Data Analysis and Statistics Analysis

We calculated the sensitivity and specificity of the Xpert Carba-R and NG-Test CARBA 5 when compared with the PCR sequencing. Antibiotic sensitivity analyses were performed using Whonet (version 5.6).

Results

A total of 300 blood vials were collected in Jiangsu Province Hospital from May 2020 to June 2021 (Figure 1). Through rapid identification, 133 positive blood cultures of *Enterobacterales* were detected by Xpert Carba-R for carbapenemase genes and 27 CPE were obtained (Table 1). The most common pathogenic bacteria identified among those CPE was *K. pneumoniae* (92.6%), followed by *E. coli* (3.7%) and *Citrobacter freundii* (3.7%). Using the Xpert Carba-R, the *bla*KPC gene was identified in 24 strains of *K. pneumoniae*, and the *bla*NDM gene was identified in 2 strains of *K. pneumoniae*, 1 strain of *E. coli* and 1 strain of *C. freundii*. The results of PCR sequencing and NG-Test CARBA 5 are also displayed in Table 1. All results obtained by using the commercial kits were consistent with the PCR sequencing results, and the sensitivity and specificity of Xpert Carba-R and the NG-Test CARBA 5 were calculated as 100%.

Table 2 shows the characteristics of Xpert Carba-R and NG-Test CARBA 5. The specimens of Xpert Carba-R were positive blood culture, so the setup time of Xpert Carba-R was only 3–5 min. But for NG-Test CARBA 5, the setup time was significantly increased to 16 h due to the second incubation required for the assay. As to the testing cost, the Xpert Carba-R was higher than the NG-Test CARBA 5.

Results of antibiotic sensitivity tests are shown in Table 3. All 27 CPE isolates were resistant to cephalosporin, piperacillin–tazobactam and ampicillin–sulbactam. The resistance rates of carbapenem and aztreonam were 96.3% and 92.6%, respectively. Strains carrying *bla*KPC gene were sensitive to ceftazidime–avibactam. No isolates were resistant to tigecycline or colistin. Among the 27 CPE patients, 10 patients were treated with monotherapy including tigecycline, polymyxin B and carbapenems. The remaining 17 patients were treated with two or more antibiotics, and the main combination regimen was carbapenems combined with tigecycline or polymyxin

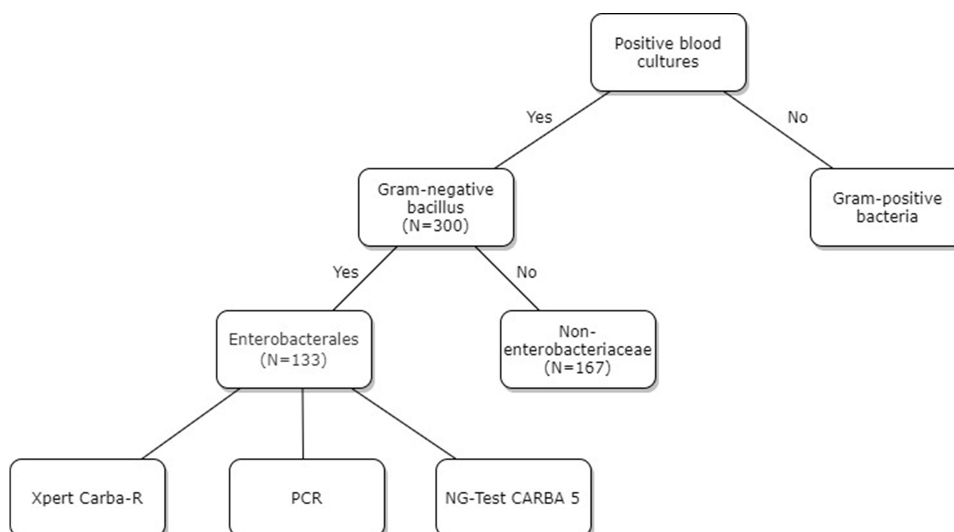

Figure 1 Detect flow of positive blood cultures.

B. When the patients were discharged from the hospital, 18 patients recovered, 9 patients did not recover and two patients were died in hospital.

Discussion

Since the early 2000s, CRE isolates have emerged worldwide and these isolates are mainly due to acquired carbapenemases.[10] CRE infections have been a significant hospital threat and an emerging public-health problem. Reports from the China CRE Network showed that the overall CRE infection rates varied significantly by region, and

Table 1 Results of the Xpert Carba-R and the NG-Test Carba 5

Species (n=27)	No. of Isolates	Xpert Carba-R (n)	NG-Test CARBA 5 (n)	PCR Sequencing (n)	Consistent Rate (%)
K. pneumoniae	25	*bla*KPC (23)	KPC (23)	*bla*KPC (23)	100
		*bla*NDM (1)	NDM (1)	*bla*NDM (1)	100
		*bla*KPC and *bla*NDM (1)	KPC and NDM (1)	*bla*KPC and *bla*NDM (1)	100
E. coli	1	*bla*NDM (1)	NDM (1)	*bla*NDM (1)	100
C. freundii	1	*bla*NDM (1)	NDM (1)	*bla*NDM (1)	100

Table 2 Testing Parameters of the Xpert Carba-R and NG-Test CARBA 5

Paramenter	Xpert Carba-R	NG-Test CARBA 5
Principle	Real-time PCR assay	Lateral flow immunoassay
Specimen	Blood culture broth	Strain
Sensitivity	100%	100%
Specificity	100%	100%
Setup time	3–5 min	16h
Testing time	50 min	15min
Cost (CNY/assay)	1170	140
Internal control	Sample processing control, probe check control	Control line
Materials not provided in the assay	GeneXpert System, vortex mixer	Inoculation loop, vortex mixer

Table 3 Sensitivity and Resistance of 27 CPE

Antibiotics	Sensitivity (%)	Resistant (%)
Ceftazidime	0	100.0
Ceftriaxone	0	100.0
Cefepime	0	100.0
Cefotetan	0	100.0
Meropenem	3.7	96.3
Imipenem	3.7	96.3
Piperacillin–tazobactam	0	100.0
Ampicillin–sulbactam	0	100.0
Aztreonam	7.4	92.6
Tigecycline	100.0	0
Colistin	100.0	0
Ceftazidime–avibactam	88.2	11.8

the rate in Jiangsu was the highest.[17] Approximately 32% of patients with BSI caused by CRE die within 14 days.[5] Hence, early detection of patients carrying and/or CPE infection in positive blood cultures is essential.

Rapid methods, including Xpert Carba-R and Carba-NP[18] have been proposed for the rapid detection of CPE from positive blood cultures. Carba-NP detect CPE basing on acid production during imipenem hydrolysis.[19] Unfortunately, Carba-NP cannot detect the type of carbapenemase. It is capable detecting carbapenemase from *Enterobacterale*-positive blood cultures, but in cannot differentiate CPE expressing serine carbapenemases from those expressing metallo-β-lactamase.[20] To date, two reports on rapid carbapenemase genes detection with Xpert Carba-R directly from positive blood cultures have been published in PubMed. Jaureguy et al reported good performance of this test on aerobic vials inoculated with isolates, but that did not contain blood.[21] Aurélie Cointe et al focused on assessing the influence of the patient's blood on the performance of the test, but only a few assays worked directly on positive blood cultures.[13] In our study, the sensitivity and specificity of Xpert Carba-R were 100% compared with the PCR sequencing method. Of 133 positive blood cultures, 27 CPE were obtained. *K. pneumoniae* accounted for the majority of carbapenemase-producing isolates among *Enterobacterales*, which was the consistent with previous studies.[17] Ninety-six percent of *K. pneumoniae* carried *bla*KPC gene, suggesting that *bla*KPC remains the main genotype of *K. pneumoniae*.

In our study, we compared two rapid tests for the five carbapenemase genes or carbapenemases, namely the Xpert Carba-R and NG-Test CARBA 5. Both of them showed excellent performance with the sensitivity and specificity of 100%. These two accurate assays can also shorten the testing time to within 2 h, but PCR sequencing needed 54–86 h. However, Xpert Carba-R could directly detect carbapenemase genes in positive vials, which could significantly reduce the setup time. No culture-based methods may reduce the time needed to get the antibiotic resistance data, leading to an earlier institution of effective antimicrobial treatment. In previous studies, neither assays could detect specific *bla*IMP subtypes,[14] and no isolate producing IMP was detected in this study.

The results of antibiotic sensitivity tests showed that 27 CPE were all sensitive to tigecycline and colistin. Qureshi et al evaluated a cohort study on patients with CRE infection and the results showed that in patients who received combination therapy with carbapenem/tigecycline or carbapenem/colistin, 28-day survival was significantly higher than in those on monotherapy.[22] Strains carrying *bla*KPC gene were sensitive to ceftazidime–avibactam. Ceftazidime–avibactam, a novel β-lactam combination, has been demonstrated to have a higher rate of clinical success than other antimicrobial regimens for BSI.[23]

This study has some limitations. First, our convenience sample size was relatively small due to our limited available resources for this study. However, this was the first attempt to study the performance of Xpert Carba-R in positive blood cultures from clinical samples. Another limitation may be due to the limited variety of carbapenemase genes. Due to local epidemiology, *bla*IMP, *bla*VIM and *bla*OXA-48 were not detected in our study.

Conclusion

Xpert Carba-R is suitable for the rapid detection of main carbapenemase genes from positive blood cultures with high sensitivity and specificity. In comparison with NG-Test CARBA 5 and PCR sequencing methods, the timely and convenient method can be a useful test to guide optimal therapy and infection control.

Ethics and Consent Statement

This work was approved by the Ethics Committee at Jiangsu Province Hospital and complied with the Declaration of Helsinki. Written informed consent and confidentiality agreements were obtained from the patient.

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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