Evaluation of the NG-Test CARBA 5 Kit for Rapid Detection of Carbapenemase Resistant *Enterobacteriaceae*

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ABSTRACT

Objective: We evaluated NG-Test CARBA 5, a new phenotypic carbapenemase detection assay, and compared it to the routine Xpert CARBA-R polymerase chain reaction assay. Furthermore, we tested the kit's performance after bacterial growth on 4 different solid media.

Methods: Seventy carbapenem resistant *Enterobacteriaceae* (CRE) isolates (60 were carbapenemase producers) were collected at the Poriya Baruch Padeh Medical Center. All isolates were grown on 4 types of agar media—BD BBL CHROMagar carbapenem resistant *Enterobacteriaceae*, BD CHROMagar Orientation, BD MacConkey II agar, and BD Trypticase Soy Agar II with 5% sheep blood—and were then subjected to NG-Test CARBA 5 kit analysis.

Results: The NG-Test CARBA 5 specificity was 100% for all 4 media. However, the sensitivity was higher when bacteria were grown on TSA with 5% sheep blood (98.3%) as compared with the Orientation medium (88.3%), the CPE medium (84.7%), and the MacConkey medium (83.6%). In addition, some of the carbapenemase mechanisms such as Verona Integron-Mediated Metallo-β-lactamase were detected with low agreement levels in specific media but higher agreement levels in the other media.

Conclusion: NG-Test CARBA 5 may enable faster detection of carbapenemase producing CRE, which will be of value for treatment adjustment and prevention control. However, the medium type on which the bacteria are grown affects kit sensitivity.

Keywords: carbapenem resistant *Enterobacteriaceae*, carbapenemase producing *Enterobacteriaceae*, NG-Test Carba 5 kit, performance, diagnostic accuracy, rapid test

Carbapenem resistant *Enterobacteriaceae* (CRE), which are common pathogens in both healthcare- and community-associated infections, have been classified by the Centers for Disease Control and Prevention as an urgent concern for world health.[1] Although they are present in the normal intestinal microbiota, *Enterobacteriaceae* cause various infections including pyelonephritis, meningitis, pneumonia, and sepsis.[2]

CRE are defined as *Enterobacteriaceae* with resistance to at least 1 of the carbapenem antibiotics (imipenem, ertepenem, meropenem, doripenem), which are currently the last-line treatment for resistant *Enterobacteriaceae.*[3] This resistance is attributed either to existence of carbapenemase, an enzyme that hydrolyzes carbapenems, or to chromosomal porin mutations in extended spectrum beta lactamase/AmpC beta lactamase producing *Enterobacteriaceae*.[4] In addition, some *Enterobacteriaceae* such as the *Proteus* species have an intrinsically reduced susceptibility to imipenem.[5]

The most troublesome type of CRE is the carbapenemase-producing CRE (CP-CRE): the genes encoded for this enzyme can be transferred to other bacteria, because they are located on mobile genetic elements.[4] Moreover, the coexistence of additional resistance genes for other antimicrobials on these mobile elements increases the probability for multidrug resistance

Abbreviations:

CP-CRE, carbapenemaseproducing CRE; CPE, carbapenem resistant *Enterobacteriaceae*; CRE, carbapenem resistant *Enterobacteriaceae*; eCIM, EDTA-modified carbapenem inactivation method; EUCAST, European committee on Antibiotic Susceptibility Testing; KPC, *Klebsiella pneumoniae* carbapenemase; mCIM, modified carbapenem inactivation method; MHT, modified Hodge test; MIC, minimum inhibitory concentration; NDM, New Delhi metallo-beta-lactamase; OXA, Oxacillinase; PCR, polymerase chain reaction; TSA, Tryptic Soy Agar; VIM, Verona Integron-Mediated Metallo-β-lactamase.

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development. These characteristics, together with the fact that CP-CRE are associated with higher mortality rates,[6] are the main factors underlying the need for a reliable and rapid detection method to immediately treat affected patients and to implement infection control activities. The identification of CP-CRE is also important for epidemiologic surveillance.[4]

Current detection assays include tests that indicate carbapenemase existence but without the capacity to identify a specific subtype. Such assays include the modified Hodge test (MHT) [7-9], the CARBA NP test,[7,10-14] and the modified carbapenem inactivation method/EDTA-modified carbapenem inactivation method.[15,16] Although these 3 assays are quite simple to perform, some of them have shown low sensitivity for specific types of carbapenemases; for example, the MHT has a low New Delhi metallo-beta-lactamase detection sensitivity.[8] Recently, Matrix Assisted Laser Desorption Ionization-Time of Flight technology has been used for the detection of CP-CRE[10,17] but has shown lower sensitivity for oxacillinase (OXA)-48.[10]

The only methods that enable specific carbapenemase detection are molecular-based, including polymerase chain reaction (PCR),[18,19] microarrays,[20,21] and whole genome sequencing.[22] Because molecular tests do not require an isolated bacterial colony, they can be performed directly on stool and rectal swabs and even on positive blood cultures. The subsequently shortened time-to-result is critical in life-threatening infections such as sepsis. However, in contrast to phenotypic tests, genotypic tests will not recognize a CP-CRE isolate that has gained a new resistance gene.[4]

In the current study, we present the evaluation of the NG-Test CARBA 5 (NG Biotech, Guipry, France), a new phenotypic assay designed to detect carbapenemases, and its comparison to our routine PCR method, the Xpert Carba-R assay (Cepheid, Sunnyvale, CA). In addition, we evaluated the kit's performance after bacterial growth on 4 different solid media: 3 that are not recommended by the manufacturer (BD MacConkey II agar, BD BBL CHROMagar CPE, and BD CHROMagar Orientation) and 1 that is recommended (BD Trypticase Soy Agar II with 5% sheep blood).

Materials and Methods

Bacterial Isolates

The study was performed at the clinical microbiology laboratory at the Poriya Baruch Padeh Medical Center. We collected 70 bacterial isolates that were identified by Matrix Assisted Laser Desorption Ionization-Time of Flight technology (version 4.1; Bruker Daltonics, Bremen, Germany), as bacteria that belong to the *Enterobacteriaceae* family and were found to be resistant to carbapenems by our routine methods.

Briefly, specimens were inoculated in a brain-heart infusion medium and enriched with a meropenem disk. After a 48-hour incubation, the specimens were cultured on selective BD BBL CHROMagar carbapenem-resistant *Enterobacteriaceae* (CPE) media (BD Diagnostics, Sparks, MD) and incubated (36°C, 5% CO_2) for 24 hours. Then a β CARBA kit (Bio-Rad Laboratories Ltd, Rishon Lezion, Israel) was used to detect strains with a decreased susceptibility to carbapenems. Colonies that gave a positive result were further analyzed using the Xpert Carba-R (Cepheid, Sunnyvale, CA) PCR assay, which detects the genes encoding the 5 most prevalent carbapenemases (*Klebsiella pneumoniae* carbapenemase [KPC], NDM, VIM, OXA-48, and imipenemase [IMP]). Isolates with a positive β CARBA result and a negative Xpert Carba-R result were not included in the study. Bacteria that were negative in Xpert Carba-R and CARBA testing but were resistant to carbapenem antibiotics, as determined by minimum inhibitory concentration (MIC) testing (European committee on Antibiotic Susceptibility Testing [EUCAST] criteria), were considered non-CP-CRE.

Out of the 70 isolates that we collected for this study, 10 were non-CP-CRE and 60 were carbapenemase producers: 4 IMP, 13 NDM, 10 OXA-48, 11 VIM, and 22 KPC. All isolates were stored at −80°C until further analysis. Before analysis, all isolates were grown on selective BD BBL CHROMagar CPE media (BD Diagnostics, Sparks, MD).

Detection of Carbapenemases Using the NG-Test CARBA 5 Kit

All isolates were grown on 4 different agar media: the BD BBL CHROMagar CPE (BD Diagnostics, Sparks, MD), the BD CHROMagar Orientation medium (BD Diagnostics, Sparks, MD), the BD Trypticase Soy Agar II with 5% sheep blood (BD Diagnostics, Sparks, MD), and the BD MacConkey II agar medium (BD Diagnostics, Sparks, MD). Each isolate was then tested using the NG-Test CARBA 5 kit (NG Biotech, Guipry, France), a qualitative rapid lateral flow assay, in which mouse monoclonal antibodies directed against KPC (K), OXA (O), VIM (V), IMP (I), and NDM (N) are immobilized on the nitrocellulose membrane test zones K, O, V, I, and N. The suspected colony is mixed with a 150 µL extraction buffer, after which 100 µL of this mixture is dispensed in the cassette well and allowed to migrate

toward the conjugate pad. If a carbapenemase is present in the bacterial colony, then it reacts with labeled anti-carbapenemase monoclonal antibodies. The carbapenemase-antibody complex migrates through the nitrocellulose membrane and is 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. If the control line does not appear, then the test result is invalid.

Statistical Analysis

We used the Xpert Carba-R as the reference method for calculating sensitivity and specificity. Specimens that were found positive or negative by the Xpert Carba-R were defined as "true positive" or "true negative," respectively.

Agreement levels between the Xpert Carba-R and the NG-Test CARBA 5 kit were calculated as the percentage of specimens that had the same results out of the total number of tested specimens (excluding invalid results). Data were analyzed using SAS version 9.3 (SAS Institute, Cary, NC).

Results

The distribution of the different bacterial isolates according to their carbapenem resistance mechanism and antimicrobial susceptibility is presented in **Table 1**. Note that this distribution does not represent the prevalence of the different carbapenemases.

Identification of Isolates Grown on MacConkey Medium

The NG-Test CARBA 5 correctly detected 54 (77.1%) of the 70 isolates when grown on the MacConkey agar medium. Seven (10%) isolates had an invalid result. More specifically, 21 of the 22 KPC-positive isolates (95.5%) were successfully detected. Among the 13 NDM-positive isolates, 8 (61.5%) were accurately detected, and 2 (15.4%) had an invalid result. Testing the 10 OXA-48-positive isolates yielded 8 (80%) correct identifications and 2 (20%) invalid results. Out of the 11 VIM-positive isolates, 7 (63.6%) were positive and 1 (9.1%) had an invalid result. The kit detected 50% of the 4 IMP-positive isolates. Among the non-CP-CRE isolates, 8 (80%) were correctly detected as carbapenemase-negative and 2 (20%) isolates yielded an invalid result. **Table 2** summarizes the results.

Table 1. Distribution of the Different Bacterial Isolates, Antimicrobial Susceptibility, and Carbapenemases

Non-CP	IMP	VIM	KPC	OXA	NDM	MIC (µg/mL)																Bacterial Isolates
						Meropenem				Imipenem				Ertapenem								
						256	128	64	32	16	256	128	64	32	16	256	128	64	32	16		
…	…	…	3	…	…	…	…	1	…	2	…	…	2	…	1	…	…	1	2	…		*Citrobacter spp.*
1	…	3	5	…	8	…	5	6	6	…	…	9	4	4	…	…	7	5	5	…		*Enterobacter cloaca* complex
1	4	3	5	5	…	5	2	4	7	…	5	1	6	6	…	2	5	5	5	1		*Escherichia coli*
…	…	…	3	…	…	…	2	1	…	…	…	3	…	…	…	…	…	2	1	…		*Klebsiella oxytoca*
8	…	5	5	5	4	11	11	5	…	…	6	16	5	…	…	4	17	6	…	…		*Klebsiella pneumoniae*
…	…	…	1	…	1	…	…	1	1	…	…	…	1	1	…	…	…	…	1	1		Other[a]
10	4	11	22	10	13	16	20	16	14	2	11	29	18	11	1	6	29	19	14	2		Total

EUCAST, European committee on Antibiotic Susceptibility Testing; KPC, Klebsiella pneumoniae *carbapenemase; MIC, minimum inhibitory concentration; NDM, New Delhi metallo-beta-lactamase; non-CP, non-carbapenemase producing; OXA, Oxacillinase; VIM, Verona Integron-Mediated Metallo-β-lactamase.*
[a]Providencia stuartii *and* Escherichia hermannii.

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Identification of Isolates Grown on CPE Medium

When inoculated on the CPE medium, 1 VIM-positive isolate failed to grow. Of the other 69 isolates, the NG-Test CARBA 5 correctly detected 60 (86.9%). No invalid results were obtained. Among the 22 KPC-positive isolates, 21 (95.45%) were correctly detected. Among the 13 NDM-positive isolates, 9 (69.2%) were positive. Out of the 10 OXA-48-positive isolates, 8 (80%) were accurately detected. Out of the 10 VIM-positive isolates, 8 (80%) proved positive. The kit successfully detected the 4 IMP-positive isolates. All 10 non-CP-CRE specimens were correctly detected as being carbapenemase-free. **Table 3** summarizes the results.

Identification of Isolates Grown on Orientation Medium

The NG-Test CARBA 5 performance with the isolates grown on the Orientation medium were better compared with its performance with isolates grown on the other 2 media; 63 (90%) of the 70 isolates were correctly detected. None of the test results were invalid. Among the 22 KPC-positive isolates, 21 (95.5%) were correctly detected. Out of the 13 NDM-positive isolates, 11 (84.6%) were accurately detected. All 10 (100%) OXA-48-positive isolates came up as positive. Out of the 11 VIM-positive isolates, 7 (63.6%) were detected. The kit successfully detected all the IMP-positive isolates. All 10 (100%) non-CP-CRE isolates were correctly detected as being carbapenemase-negative. **Table 4** summarizes the results.

Identification of Isolates Grown on TSA with 5% Sheep Blood

Sixty-nine (98.6%) of the carbapenemase-positive isolates and all the non-CP-CRE (100%) isolates were correctly detected by the kit after growth on the TSA medium (**Table 5**). All (100%) of the KPC-, NDM-, OXA-48-, and IMP-positive isolates were accurately detected by the kit. For the 11 VIM-positive isolates, the kit gave a positive result for 10 (90.9%).

Table 2. Identification Results of Isolates Grown on MacConkey Medium

Carbapenemase Type (n)	Correct Identification n (%)	False Negative n (%)	Invalid n (%)	Agreement Level (%)
KPC (22)	21 (95.5)	1 (4.5)	0 (0)	95.5
NDM (13)	8 (61.5)	3 (23.1)	2 (15.4)	88.9
OXA-48 (10)	8 (80)	0 (0)	2 (20)	80
VIM (11)	7 (63.6)	3 (27.3)	1 (9.1)	70
IMP (4)	2 (50)	2 (50)	0	50
Non-CP (10)	8 (80)	0 (0)	2 (20)	100
Total (70)	54 (77.1)	9 (12.8)	7 (10)	83.1

KPC, Klebsiella pneumoniae *carbapenemase; NDM, New Delhi metallo-beta-lactamase; non-CP, non-carbapenemase producing; OXA, Oxacillinase; VIM, Verona Integron-Mediated Metallo-β-lactamase.*

Table 3. Identification Results of Isolates Grown on CPE Medium

Carbapenemase Type (n)	Correct Identification n (%)	False Negative n (%)	Invalid n (%)	Agreement Level (%)
KPC (22)	21 (95.5)	1 (4.5)	0 (0)	95
NDM (13)	9 (69.2)	4 (30.8)	0 (0)	69.2
OXA-48 (10)	8 (80)	2 (20)	0 (0)	80
VIM (10)[a]	8 (80)	2 (20)	0 (0)	80
IMP (4)	4 (100)	0 (0)	0 (0)	100
Non-CP (10)	10 (100)	0 (0)	0 (0)	100
Total (69)	60 (86.9)	9 (13.1)	0 (0)	86.9

CPE, carbapenem-resistant Enterobacteriaceae; *KPC,* Klebsiella pneumoniae *carbapenemase; NDM, New Delhi metallo-beta-lactamase; non-CP, non-carbapenemase producing. OXA, Oxacillinase; VIM, Verona Integron-Mediated Metallo-β-lactamase.*
[a]*One VIM isolate did not grow on this medium.*

Table 4. Identification Results of Isolates Grown on Orientation Medium

Carbapenemase Type (n)	Correct Identification n (%)	False Negative n (%)	Invalid n (%)	Agreement Level (%)
KPC (22)	21 (95.5)	1 (4.5)	0 (0)	95.5
NDM (13)	11 (84.6)	2 (15.4)	0 (0)	84.6
OXA-48 (10)	10 (100)	0 (0)	0 (0)	100
VIM (11)	7 (63.6)	4 (36.4)	0 (0)	63.6
IMP (4)	4 (100)	0 (0)	0 (0)	100
Non-CP (10)	10 (100)	0 (0)	0 (0)	100
Total (70)	63 (90)	7 (10)	0 (0)	90

KPC, Klebsiella pneumoniae *carbapenemase; NDM, New Delhi metallo-beta-lactamase; non-CP, non-carbapenemase producing; OXA, Oxacillinase; VIM, Verona Integron-Mediated Metallo-β-lactamase.*

Table 5. Identification Results of Isolates Grown on TSA Medium

Carbapenemase Type (n)	Correct Identification n (%)	False Negative n (%)	Invalid n (%)	Agreement Level (%)
KPC (22)	22 (100)	0 (0)	0 (0)	100
NDM (13)	13 (100)	0 (0)	0 (0)	100
OXA-48 (10)	10 (100)	0 (0)	0 (0)	100
VIM (11)	10 (90.9)	1 (9.1)	0 (0)	90.9
IMP (4)	4 (100)	0 (0)	0 (0)	100
Non-CP (10)	10 (100)	0 (0)	0 (0)	100
Total (70)	69 (98.6)	1 (1.4)	0 (0)	98.6

KPC, Klebsiella pneumoniae *carbapenemase; NDM, New Delhi metallo-beta-lactamase; non-CP, non-carbapenemase producing; OXA, Oxacillinase; TSA, Tryptic Soy Agar; VIM, Verona Integron-Mediated Metallo-β-lactamase.*

Table 6. Performance of the NG-Test CARBA 5 Kit

Medium Type	Agreement Level (%)	Sensitivity, % (95% CI)	Specificity, % (95 % CI)
MacConkey	85.7	83.6 (71.2–92.2)	100 (63.1–100)
CPE	86.9	84.7 (73–92.8)	100 (69.1–100)
Orientation	90	88.3 (77.43–95.2)	100 (69.1–100)
TSA	98.6	98.3 (91.16–99.9)	100 (69.1–100)

CI, 95% confidence interval; CPE, carbapenem-resistant Enterobacteriaceae; TSA, Tryptic Soy Agar.

Performance of the NG-Test CARBA 5 Kit

Overall agreement levels between the Xpert Carba-R and the NG-test CARBA 5 kit were quite similar for isolates cultured on the MacConkey vs the CPE medium, with 85.7% and 86.9% agreement, respectively. The agreement level increased to 90% and 98.6% when the bacteria were grown on the Orientation and TSA media, respectively (**Table 6**). Analysis of the agreement levels by carbapenemase type revealed that KPC and non-CP-CRE were detected by the NG-Test CARBA 5 kit with high agreement levels; KPC and non-CP-CRE had agreement levels of 95.5% to 100% and 100%, respectively. The other carbapenemases had agreement levels that varied by medium type (**Tables 1–5**); for example, for the OXA-48-positive isolates, agreement levels were 80% when they were grown on the MacConkey and CPE media and 100% when they were grown on the Orientation and TSA media. The specificity of the kit was 100% for all 3 medium types. However, the sensitivity was higher when bacteria were grown on the TSA medium (98.3%) as compared to the other media types: 83.6% (MacConkey), 84.7% (CPE), and 88.3% (Orientation) (**Table 6**).

Discussion

The goal of this study was to evaluate the diagnostic performance and accuracy of the NG-Test CARBA 5 kit, a new phenotypic assay for the detection of carbapenemases in *Enterobacteriaceae* bacteria. In addition, we sought to test whether the culture medium affected assay results. The NG-Test CARBA 5 kit is easy to use and requires no special expertise of the laboratory staff. It also has the advantage of showing results within less than 30 minutes. For comparison, the minimum turnaround time of the available PCR assays for the detection of CRE mechanisms is 50 minutes.

Overall, the sensitivity (83.6%–98.3%) and specificity (100%) of this kit were quite high. Only 2 recent publications have investigated the performance of this kit. The first paper described the kit validation process, which involved 296 bacterial isolates and reported a sensitivity and specificity of 100% and 95.3% for retrospectively tested isolates and 100% and 100%, respectively, for prospectively tested isolates.[23] The strains were grown on URISelect 4 or on Mueller-Hinton agar plates, and the reference method was PCR, in contrast to our study. The second publication regarding the NG-Test CARBA 5 kit reported on an evaluation of the kit with 197 bacterial isolates[24] and found an overall sensitivity and specificity of 97.3% and 99.7%, respectively. The lower sensitivity in the current study may have been a result of the small sample size. However, the results of our study indicated that the medium type on which the bacteria are grown impacts the performance of the kit. It is interesting that of the 4 tested media, a low sensitivity (84.7%) was obtained when bacteria were grown on the CPE medium, which is a selective medium for CRE and is our routine medium for culturing rectal swabs for CRE detection. Thus, a laboratory must consider this aspect when choosing to implement the NG-Test CARBA 5 kit. The highest sensitivity (98.3%) in our study was actually obtained from the TSA medium, which is not a selective agar but is recommended for use by the manufacturer.

The current study showed low agreement levels between the NG-Test CARBA 5 kit and the Xpert Carba-R results for both the VIM and NDM carbapenemases when the bacteria were grown on selective media. This finding has not been previously reported. Thus, future research on strains with such mechanisms of resistance is still required to ascertain whether the kit is adequate for the identification of VIM and NDM.

Another aspect that may interest a laboratory is the kit's cost, which is lower than that of the available PCR assays. In addition, it does not require dedicated equipment, which again impacts the costs of CRE detection.

It is important to emphasize the great clinical value in using the kit. Rapid identification of CRE bacteria will allow antibiotic treatment to be adjusted and measures to be taken to prevent infections such as patient isolation.

Conclusion

In summary, implementation of the NG-Test CARBA 5 in the clinical microbiology laboratory may enable faster detection

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of CP-CRE, which will be of value for treatment adjustment and prevention control. LM

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