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Assessment of the performance of CHROMagar KPC and Xpert Carba-R assay for the detection of carbapenem-resistant bacteria in rectal swabs: First comparative study from Abu Dhabi, United Arab Emirates

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ABSTRACT

Objectives: The objective of this study was to evaluate the performance of CHROMagar™ KPC compared with Xpert® Carba-R assay for the detection of carbapenem-resistant bacterial isolates from rectal swabs.
Methods: Rectal swabs were obtained from patients admitted to Cleveland Clinic Abu Dhabi (United Arab Emirates) over a period of 7 months and were screened for carbapenem resistance by either culture on CHROMagar KPC or carbapenemase production using the Xpert Carba-R molecular method. Further testing for carbapenem susceptibility of isolates recovered from CHROMagar KPC was performed using VITEK® 2.
Results: A total of 1813 rectal swabs were screened, of which 61 (3.4%) were positive for carbapenem resistance by either one or both methods. Both methods were equally efficient in detecting carbapenem resistance in 37/61 swabs (60.7%), mostly positive for *Klebsiella pneumoniae* (22 isolates), of which 40.9% (9/22) carried $bla_{\text{OXA-48-like}}$ and bla_{NDM}. Xpert Carba-R assay detected 12 additional swabs with negative CHROMagar KPC culture and revealed additional carbapenemase-producing organisms carrying $bla_{\text{OXA-48-like}}$ and/or bla_{NDM}. CHROMagar KPC recovered organisms in nine swabs not detected by the genotypic method, 44.4% of which were *K. pneumoniae*. Three swabs yielded false-positive results (carbapenem-susceptible organisms) by both methods. Sensitivity and specificity were, respectively, 75.4% and 99.8% for CHROMagar KPC and 80% and 99.8% for Xpert Carba-R.
Conclusion: This comparative study of CHROMagar KPC versus Xpert Carba-R in rectal swabs showed a slightly higher sensitivity for the PCR-based method. Whilst CHROMagar KPC provides a less expensive screening method, Xpert Carba-R may be more accurate and faster.

1. Introduction

Gram-negative bacteria increasingly harbour a wide range of acquired carbapenemases, highly versatile β-lactamase enzymes able to hydrolyse the majority of β-lactam antibiotics, including carbapenems [1]. Dissemination of carbapenemase-producing Gram-negative bacteria in hospitals, community settings and the environment has resulted in a decline in the value of carbapenems as a last-resort therapeutic option [2]. Such an increasing incidence of carbapenemases makes it imperative to optimise their detection in the clinical laboratory, and an assortment of phenotypic, molecular and biochemical methods are available for this purpose [3].

Since patients colonised by carbapenem-resistant Gram-negative bacteria remain a major transmission source of such organisms to healthcare settings [4], screening for carriage of such pathogens by rectal swabs is increasingly used [5–7]. Culture on special chromogenic media, in-house and commercial PCR assays, and carbapenem hydrolysis tests are some of the methodologies used for this purpose [8]; however, the optimal screening method remains to be determined [9].

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Cultivation techniques used to detect carbapenem-resistant bacteria from rectal swabs have long depended on in-house selective media containing imipenem, ertapenem or meropenem [4]. The in-house preparation of such media has been facilitated by the availability of ready-to-use alternatives, such as CHROMagar™ KPC. This is a commercially available solid culture medium used for the direct isolation of bacteria with reduced susceptibility to carbapenems. It is possible to directly plate a sample on this medium supplemented with agents that inhibit the growth of carbapenem-susceptible bacteria and then incubate the inoculated medium for 18–24 h. Following incubation, the chromogenic ingredients of the medium will allow colonies of Enterobacterales, *Pseudomonas* and *Acinetobacter* that are carbapenem resistant to be observed and differentiated by the variable colours of the pigments produced [10].

Whilst culture-based methods such as CHROMagar KPC are simple and inexpensive, they are time consuming and labour intensive and have questionable accuracy that is dependent on the bacterial load in rectal swabs [5]. For such reasons, molecular assays that claim to resolve these shortcomings of conventional culture have been developed. The Cepheid Xpert® Carba-R assay is a genotypic cartridge-based test that can, in <1 h, detect and differentiate genes encoding KPC, NDM, VIM, IMP and OXA-48 β-lactamases in the aforementioned groups of organisms using rectal swabs. Cepheid Xpert Carba-R applies automated, qualitative real-time PCR and is a rapid and accurate assay for the detection of carbapenemase-encoding genes [11].

In Abu Dhabi, like other areas of the Arabian Gulf region, reports of carbapenemase-producing bacterial isolates are currently accumulating, although they are still limited to isolated case series of isolates producing OXA-181 [12] and other undetermined OXA-48-like enzymes [13]. Abu Dhabi, the capital and the largest by area of the seven United Arab Emirates (UAE), exemplifies a major commercial and cultural centre and harbours a diverse population where interchange with expatriates may form a favourable background for transfer of resistant bacteria, including carbapenemase-producers [14,15]. Hence, screening for carriage of these organisms by an appropriate methodology is crucial. The aim of the current study was to compare the chromogenic CHROMagar KPC with the Xpert Carba-R method for the detection of carbapenem-resistant Gram-negative bacteria in rectal swabs obtained from patients admitted to Cleveland Clinic Abu Dhabi, a quaternary-care hospital in the UAE. The hospital is owned by Mubadala Development Company and is managed and operated by US-based Cleveland Clinic in Ohio. It is a 364 (expandable to 490)-bed facility and has five centres of excellence in the following specialties: heart and vascular; neurological; digestive diseases; eye; and respiratory and critical care.

2. Materials and methods

2.1. Collection of rectal swabs

Rectal swabs were collected from patients admitted to the Cleveland Clinic Abu Dhabi from September 2017 through March 2018. Screening of patients for the collection of rectal swabs was targeted so that samples were collected from patients satisfying one of the following criteria: previous admission to a healthcare facility in the last 3 months; transfer from another healthcare facility to Cleveland Clinic Abu Dhabi; admission to the intensive care unit; organ transplant recipients; cancer patients; cystic fibrosis patients; patients on haemodialysis; and patients with a positive history of isolation of a multidrug-resistant organism in the last 6 months. Duplicate swabs were obtained from each patient.

2.2. Screening by CHROMagar KPC and carbapenem susceptibility testing

One swab of each duplicate set was used for plating on commercially available CHROMagar™ KPC (CHROMagar, Paris, France). Plates were incubated at 37 °C and were examined for growth at 24 h and 48 h. All suspicious coloured colonies obtained on CHROMagar KPC (dark pink, metallic blue, cream to blue, or opaque) according to the manufacturer's recommendations were subcultured for purity and were then subjected to identification and susceptibility testing to ertapenem and meropenem using a VITEK®2 automated system (bioMérieux, Craponne, France). VITEK®2 was also used to identify extended-spectrum β-lactamase (ESBL)-producing isolates. Results of antimicrobial susceptibility testing, as minimum inhibitory concentration (MIC) estimates, were interpreted using the breakpoints and interpretations of the Clinical and Laboratory Standards Institute (CLSI), M100S, 27th ed.

2.3. Xpert Carba-R assay

The second swab was screened for carbapenemases using the Cepheid Xpert® platform with the Xpert® Carba-R assay (Cepheid, Sunnyvale, CA) according to the manufacturer's package insert, within 24–48 h of collection. For this assay, the swab was placed directly into the sample reagent vial and was vortexed for ~10 s to mix. Then, ~1.7 mL of each vial was transferred into the sample chamber of the Carba-R assay cartridge and was placed onto the instrument, where the assay had a run time of ~48 min. A Carba-R assay positive result was defined as detection of at least one carbapenemase gene (i.e. bla_{KPC}, bla_{NDM}, $bla_{OXA\text{-}48\text{-}type}$, $bla_{IMP\text{-}1}$ and bla_{VIM}) from a rectal swab.

2.4. Analysis of the results

Samples were classified into five categories based upon agreement or discrepancy between findings of the CHROMagar KPC culture and Xpert Carba-R assay, as follows: (1) samples with perfect match of positive growth on CHROMagar KPC, positive Xpert Carba-R assay and carbapenem-resistant phenotype on antimicrobial susceptibility testing; (2) samples with negative growth on CHROMagar KPC but positive Xpert Carba-R assay; (3) samples with positive growth on CHROMagar KPC but negative Xpert Carba-R assay; (4) samples with positive growth on CHROMagar KPC and positive Xpert Carba-R assay but carbapenem-susceptible phenotype on antimicrobial susceptibility testing; and (5) samples with negative growth on CHROMagar KPC and negative Xpert Carba-R assay. Analysis of sensitivity and specificity of both methods was performed following the Standards for Reporting of Diagnostic Accuracy Studies (STARD) guidelines [16], where the index method was considered as either of the two methods, and the error-free reference standard was assumed to be a combined standard for true-positive samples that yielded a positive result with either one or both assays.

3. Results

3.1. Studied samples and results of CHROMagar KPC and Xpert Carba-R assay

A total of 1813 rectal swabs was screened by both CHROMagar KPC and Xpert Carba-R assay, of which 61 (3.4%) were associated with positive results revealing the presence of carbapenem-non-susceptible organisms by culture and/or detection of carbapenemase genes by PCR. CHROMagar KPC was positive for 49/61 swabs (80.3%) and allowed the detection of 54 carbapenem-non-susceptible isolates; of note, 5 swabs yielded positive cultures

Table 1
Organisms detected in rectal swabs according to the results of CHROMagar™ KPC.

Species	No. of positive cultures
Klebsiella oxytoca	1
Klebsiella pneumoniae[a]	26
Escherichia coli	12
Citrobacter freundii	1
Enterobacter cloacae	1
Pseudomonas aeruginosa	7
Pseudomonas fluorescens	1
Acinetobacter baumannii complex	5
Total isolates	54

[a] Five swabs showed *K. pneumoniae* in combination with another organism (two with *E. coli*, one with *C. freundii*, one with *P. aeruginosa* and one with *A. baumannii* complex).

for two different organisms. All of the recovered organisms using CHROMagar KPC are shown in Table 1. The isolates consisted of 41 Enterobacterales, 8 *Pseudomonas* spp. and 5 *Acinetobacter baumannii* complex. Twelve swabs positive by Xpert Carba-R assay yielded negative culture by CHROMagar KPC.

On the other hand, PCR by Xpert Carba-R assay was positive for 52/61 swabs (85.2%). The detected genetic profiles were heterogeneous and included bla_{KPC}, bla_{NDM}, bla_{VIM} and bla_{OXA-48}. Of the 52 swabs with positive PCR, 14 (26.9%) yielded two carbapenemase-encoding genes. The different detected carbapenemase genes using Xpert Carba-R assay with corresponding CHROMagar KPC culture results are shown in Table 2. The assay performance of CHROMagar KPC revealed the lowest percentage for bla_{OXA-48}.

Three swabs yielded false-positive results (carbapenem-susceptible organisms) by both methods.

3.2. Categorisation of studied samples with respect to performance of CHROMagar KPC and Xpert Carba-R assay

The five categories of samples are shown in Table 3, with the MICs of ertapenem and meropenem and the results of both assays. In brief, 37/61 swabs (60.7%) belonged to category 1 where the results of the two assays were in accordance. In these 37 swabs, the predominant organism was *Klebsiella pneumoniae*, with 22 isolates yielding carbapenemases of class A (KPC), B (NDM or VIM) or D (OXA-48), of which 40.9% co-produced OXA-48 and NDM. Moreover, in the 37 swabs there was only one meropenem-susceptible and five meropenem-intermediate isolates, whilst all other isolates were resistant to both ertapenem and meropenem.

Twelve swabs (19.7%) belonged to category 2, with Xpert Carba-R detecting either bla_{OXA-48} or bla_{NDM} or a combination of both and with a negative CHROMagar KPC culture. On the other hand, 9/61 swabs (14.8%) belonged to category 3, again with *K. pneumoniae* being the predominant isolated organism. Intermediate susceptibility to ertapenem was observed in one of the nine isolates, and susceptibly to meropenem was observed in two isolates. The remaining 3/61 swabs (4.9%) belonged to category 4, where three organisms that produced colonies on CHROMagar KPC and yielded positive Xpert Carba-R results turned out to be carbapenem-susceptible by VITEK®2 with meropenem MIC estimates of 1–2 μg/mL. Category 5 comprised 1752 rectal swabs that did not show evidence of carbapenem non-susceptibility by any of the two techniques.

The sensitivity and specificity of both assays relative to the combined error-free reference are shown in Table 4. Overall, the sensitivity of CHROMagar KPC (75.4%) was slightly lower than the sensitivity of the Xpert Carba-R assay (80.3%), whilst the specificities of both methods were 99.8%.

Table 2
Carbapenemase genes detected using Xpert® Carba-R assay, with corresponding CHROMagar™ KPC culture results, and assay performance of Xpert Carba-R assay for each carbapenemase profile.

Xpert Carba-R result	Corresponding organism detected by CHROMagar KPC, with assay performance of CHROMagar KPC[a]	No. of samples
bla_{KPC}	*Klebsiella pneumoniae*	1
	Assay performance 100%	
bla_{NDM}	*Acinetobacter baumannii* complex	2
	Pseudomonas spp.	2
	Enterobacter cloacae	1
	Escherichia coli	5
	K. pneumoniae	1
	Negative	3
	Total	14
	Assay performance 78.57%	
bla_{VIM}	*A. baumannii* complex	1
	Pseudomonas spp.	2
	Total	3
	Assay performance 100%	
bla_{OXA-48}	*Klebsiella oxytoca*	1
	K. pneumoniae	9
	E. coli	4
	Pseudomonas spp.	2
	Negative	7
	Total	22
	Assay performance 68.18%	
bla_{NDM} + bla_{OXA-48}	*K. pneumoniae*	9
	E. coli	2
	Negative	2
	Total	13
	Assay performance 84.62%	
bla_{VIM} + bla_{OXA-48}	*K. pneumoniae*	2
	Citrobacter freundii	1
	Total	3
	Assay performance 100%	
Negative	*A. baumannii* complex	2
	Pseudomonas spp.	2
	K. pneumoniae	4
	E. coli	1
	Total	9

[a] Assay performance was defined as the number of positive cultures with respect to the total number of carbapenemases of each type detected by Xpert Carba-R assay multiplied by 100.

4. Discussion

Active surveillance for faecal carriage of carbapenem-resistant Gram-negative organisms has become a routine laboratory practice and is recommended by public-health organisations in order to limit the spread of such challenging pathogens [17,18]. To this end, the availability of chromogenic culture media, as well as advanced molecular diagnostics to support such a screening process, is convenient for the clinical microbiology laboratory workflow. This prospective study revealed the extent of dissemination of carbapenem resistance in a hospital setting in Abu Dhabi and compared culture- and molecular-based surveillance methods available in the UAE for the detection of carbapenem-resistant Gram-negative bacteria in rectal swabs.

From an epidemiological perspective, the study showed a 3.4% rate of faecal carriage of carbapenem-resistant organisms. This is low compared with other studies on rectal surveillance that reported a rate of 10% carbapenem resistance in the USA [19], 13% in Morocco [20] and 38% in Iran [21]. This might be related not only to the different patient populations studied but also to the variability in rectal surveillance methods used for screening, the extent of spread of carbapenemase-producing isolates, and diverse containment measures applied in these countries.

The specificity and sensitivity of CHROMagar KPC and Xpert Carba-R for detecting carbapenem-resistant isolates are similar. Such comparable performance indicates that some level of

Table 3
Five categories of rectal swabs showing the results of culture using CHROMagar™ KPC, with ertapenem and meropenem minimum inhibitory concentrations (MICs), and genetic profile using Xpert® Carba-R assay.

Category	No. of swabs	CHROMagar KPC results		MIC (μg/mL) [susceptibility interpretation]		Genetic profile by Xpert Carba-R	
		Cultured species	No. of isolates	Ertapenem	Meropenem	Carbapenemase(s)	No.
1	37[a]	*Escherichia coli*	11	≥8 [R]	2 [I] to ≥16 [R]	OXA-48	4
				≥8 [R]	2 [I] to ≥16 [R]	NDM	5
				≥8 [R]	2 [I] to ≥8 [R]	OXA-48 + NDM	2
		Klebsiella pneumoniae	22	2 [R]	1 [S]	OXA-48 (with ESBL)	1
				≥8 [R]	≥16 [R]	NDM	1
				4 [R] to ≥8 [R]	4 [R] to ≥16 [R]	OXA-48	8
				≥8 [R]	≥16 [R]	KPC	1
				≥8 [R]	≥16 [R]	OXA-48 + NDM	9
				≥8 [R]	≥16 [R]	OXA-48 + VIM	2
		Klebsiella oxytoca	1	4 [R]	2 [I]	OXA-48 (with ESBL)	1
		Citrobacter freundii	1	≥8 [R]	≥16 [R]	OXA-48 + VIM	1
		Enterobacter cloacae	1	≥8 [R]	≥16 [R]	NDM	1
		Pseudomonas aeruginosa	4	–	8 [R] to ≥16 [R]	NDM	2
				–	≥16 [R] to 32 [R]	VIM	2
		Acinetobacter baumannii complex	2	–	≥16 [R]	NDM	2
2	12	Negative	12	–	–	OXA-48	7
				–	–	NDM	3
				–	–	OXA-48 + NDM	2
3	9	*K. pneumoniae*	4 (one with ESBL)	1 [I] to ≥8 [R]	1 [S] to ≥16 [R]	Negative	9
		E. coli	1 (with ESBL)	4 [R]	2 [S]		
		P. aeruginosa	2	–	8 [R] to ≥16 [R]		
		A. baumannii complex	2	–	≥16 [R]		
4	3	*P. aeruginosa*	1	–	2 [S]	OXA-48	1
		Pseudomonas fluorescens	1	–	2 [S]	OXA-48	1
		A. baumannii complex	1	–	1 [S]	VIM	1
5	1752	Negative	1752	–	–	Negative	1752

R, resistant; I, intermediate; S, susceptible; ESBL, extended-spectrum β-lactamase.
[a] Results of 37 swabs of category 1 are shown; however, 5 swabs yielded positive CHROMagar KPC culture for two organisms.

Table 4
Overall performance of CHROMagar™ KPC and Xpert® Carba-R assay compared with the error-free combined standard of positive samples with either one or both methods.

Sample	Combined error-free reference	CHROMagar KPC	Xpert Carba-R
Positive	61	46	49
Negative	1752	12	9
False-positive (category 4)	0	3	3
Sensitivity		46/61 (75.4%)	49/61 (80.3%)
Specificity		1752/1755 (99.8%)	1752/1755 (99.8%)

versatility is available for the clinical laboratory in selecting a suitable method. In a resource-limited setting, CHROMagar KPC is an inexpensive method that still offers a convenient means to avoid missing a good proportion of carriers of carbapenem-resistant isolates. Analysis using CHROMagar KPC for one strain costs US$11 versus US$87 for Xpert Carba-R assay if time and personnel costs are not considered. It is noteworthy that the similar rate at which the two methods detected carbapenem resistance was observed for a variety of carbapenemases, including OXA-48, NDM, KPC, VIM and combinations of these carbapenemases. Initial reports regarding CHROMagar KPC indicated its applicability to recover isolates carrying bla_{KPC} with high sensitivity [22,23], and this was evident in the only KPC-producing *K. pneumoniae* from the current collection that was recovered on this medium and confirmed by Xpert Carba-R assay. Similarly, the performance of CHROMagar KPC was 100% equal to Xpert Carba-R method in detecting isolates with VIM with or without OXA-48 (Table 2). Although such data may support the use of either of the two methods for screening of rectal swabs, an indication for a desirable choice is required in the context of a probable epidemic or while investigating asymptomatic carriage of carbapenem-resistant organisms [24]. As the first marketed screening medium, CHROMagar KPC is able to detect bacteria mostly with high-level resistance to carbapenems, but not those with low-level resistance. Meanwhile, molecular methods such as Xpert Carba-R are 'gold standards' to identify carbapenemase-producers but are expensive. Molecular techniques are not currently recommended for preventing outbreaks and identifying carriers, but rather for epidemiological and research purposes, mainly in reference laboratories [25].

An additional 19.7% of the collection of swabs was detected as positive for carbapenemase-encoding genes with Xpert Carba-R (category 2), and this included producers of OXA-48, NDM or both. Molecular methods are used to identify carbapenemase-producers owing to a higher sensitivity and specificity [3]. The Xpert Carba-R assay is well documented in this aspect to be accurate and rapid in studies on rectal swabs [5], isolated pure bacteria [11,26] and, most recently, environmental samples [27]. A recent report has described this method as 100% sensitive to detect Enterobacterales, *Pseudomonas* and *Acinetobacter* with a specificity of 98% [28]. Another advantage of this method is its rapid turnaround time of <2 h, allowing quick results and prompt patient isolation. However, Xpert Carba-R is expensive and does not detect all carbapenemase-producers, as it missed nine of the tested swabs that recovered carbapenem-resistant organisms using CHROMagar KPC (category 3). Xpert Carba-R is capable of detecting NDM, VIM and IMP, as well as OXA-48 and NDM, the latter two being reported in the UAE [15,29]. Nevertheless, it is

unable to detect some less common carbapenemases and some rare alleles of OXA-48, as reported previously [26]. A modified version of the classical Xpert Carba-R is expected to detect such enzymes, like OXA-181 [5].

The culture-based method using CHROMagar KPC detected an additional 14.8% of swabs (category 3) as it extends the spectrum of carbapenem resistance detection not only to carbapenemase-producers but also to isolates with other mechanisms of resistance such as porin mutations and efflux pumps coupled with AmpC β-lactamase enzymes and ESBLs. Although the latter two enzyme categories do not induce carbapenem resistance alone, their co-existence in an isolate with porin mutation or efflux pump overactivity will help in selection of resistant strains and will increase carbapenem MICs [30]. Of nine isolates in category 3, two were ESBL-producers, which is in accordance with another report that found CHROMagar KPC to be among the most sensitive commercial chromogenic media for growth of isolates producing OXA-48 in combination with other β-lactamases [31], making it a useful screening medium for stool samples. In the remaining isolates of category 3, membrane impermeability and overexpressed efflux pumps will theoretically be the main culprit behind carbapenem resistance, although these may have low clinical significance due to limited potential of horizontal spread. Likewise, CHROMagar KPC detected four *Escherichia coli* isolates and eight *K. pneumoniae* isolates in category 1 that harboured only OXA-48. The presence of other non-carbapenemase resistance mechanisms in these isolates may have allowed their growth on this medium, and investigating these mechanisms may be worthwhile.

Compared with molecular assays, CHROMagar KPC is less expensive but is time consuming and labour intensive. Also, some isolates in category 4 were found to be susceptible to meropenem although recovered as resistant by CHROMagar KPC. Hence, while using CHROMagar KPC, the laboratory technologist may need to perform additional work to confirm isolates growing on this medium using their colour indicators. Individual isolates may turn out to be carbapenem-susceptible and, for such isolates, an additional detection method is needed.

Studying the phenotypic properties of the isolates recovered by CHROMagar KPC, the presence of discrepant ertapenem/meropenem susceptibility profiles of Enterobacterales isolates in categories 1 and 3 was noticeable. This may be attributed again to infrequent bla_{OXA-48} variants that cannot be detected by Xpert Carba-R assay or due to porin mutations with a greater effect on ertapenem than meropenem [32].

In conclusion, this tested collection of rectal swabs from patients in Cleveland Clinic Abu Dhabi showed a heterogeneous profile towards detection of carbapenem resistance by culture-based and molecular assays. Both the CHROMagar KPC and Xpert Carba-R assay could be utilised for rectal surveillance swabs for the purpose of infection control and mitigating the spread of carbapenem-resistant pathogens, although the molecular method appeared slightly more sensitive. The performance of both methods was comparable with previously published data of performance evaluation with regard to specificity, but sensitivity was lower, although it was more promising for Xpert Carba-R [5,22]. The results of this comparative analysis should be interpreted in light of local epidemiology of carbapenem resistance, and the choice for a preferable method will rely on cost, time, workflow and gene coverage. More investigations are needed before either method can be routinely endorsed to screen for carriage of carbapenem-resistant organisms.

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Competing interests

None declared.

Ethical approval

Not required.

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