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Original article

Comparison of carbapenem minimum inhibitory concentrations of Oxacillin-48-like *Klebsiella pneumoniae* by Sensititre, Vitek 2, MicroScan, and Etest

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ABSTRACT

Objectives: The aim of this laboratory-based study was to compare carbapenem MICs yielded by Sensititre, Vitek 2, MicroScan WalkAway plus and Etest for Oxacillin (OXA)-48-like *Klebsiella pneumoniae* isolates.

Methods: Analysis was performed for categorical agreement for ertapenem, meropenem, and imipenem, and the proportion of isolates with MICs ≤8μg/mL and the MIC50/MIC90 for meropenem and imipenem, from a convenience sample of 82 deduplicated blood culture OXA-48-like *K. pneumoniae* isolates.

Results: The proportion of isolates testing susceptible to ertapenem by Etest (19/82, 23.1%) differed from Sensititre/Vitek (0/82) and MicroScan (2/82, 2.4%) ($p < 0.001$ for all). For meropenem, the proportion of isolates susceptible by Etest (31/82, 37.8%) differed from Sensititre/Vitek (16/82, 19.5%) ($p = 0.015$). There was variation in the proportion of isolates that tested imipenem susceptible when comparing Sensititre (9/82, 11%) and Vitek (8/82, 9.8%) to MicroScan (27/82, 32.9%), $p = 0.001$ and $p < 0.001$, respectively, Sensititre and Vitek to Etest (45/82, 54.9%), $p < 0.001$ for both, and MicroScan to Etest, $p = 0.007$. The proportion of isolates with meropenem MICs ≤8μg/mL with Sensititre and Vitek differed significantly from Etest, 58.5% and 85.4%, respectively, $p < 0.001$. A 2-fold difference between the Sensititre and Vitek meropenem and imipenem MIC at which ≥50% of isolates were inhibited compared to the MicroScan, and a 4-fold difference compared to Etest, was present.

Conclusions: Substantial variability in carbapenem MICs for OXA-48-like carbapenemase-producing Enterobacterales isolates by the four methods was demonstrated. Performance characteristics verification of MIC methods in use for the predominant carbapenemase-producing Enterobacterales type is required by laboratories to optimize the accuracy of carbapenem reporting. **Trusha Nana, Clin Microbiol Infect 2022;28:1650.e1–1650.e5**

Introduction

Antimicrobial resistance is a serious threat to public health [1]. Infections caused by carbapenemase-producing Enterobacterales (CPE) are increasing world-wide, with a varying distribution of the different types of carbapenemases [2–4]. Oxacillinase-48-like (OXA-48-like) carbapenemases are endemic in Turkey and South Africa, and are common in the Middle-East, North Africa and parts of Mediterranean Europe [2–5]. Oxacillin (OXA)-48-like CPE infections are associated with mortality rates between 30% and 50% [6–8].

From a diagnostic perspective, an elevated carbapenem MIC alerts the laboratory to test for the presence of carbapenemases. Ertapenem is the most sensitive indicator carbapenem for the presence of a CPE. Selection of antibiotic treatment regimens are based on these MICs and the type of carbapenemase present.

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Due to the precise nature of broth microdilution (BMD) and the required hands-on time, determination of carbapenem MICs by the reference method of BMD is not feasible in many routine clinical microbiology laboratories. Inconsistency in the accuracy of carbapenem MIC reporting for multidrug-resistant gram-negatives, and CPE specifically, by commercial methods has been highlighted in recent literature [9–13]. However, these publications have focussed largely on *Klebsiella pneumoniae* carbapenemase (KPC)-producing Enterobacterales, and there is a dearth of published data for OXA-48-like CPE.

There are limited treatment options for OXA-48-like CPE infections [14]. Access to the newer antibiotic agents, such as ceftazidime-avibactam and cefiderocol, with activity against OXA-48-like CPEs is limited in low-middle income settings, emphasising the need to optimize treatment using locally available options [15]. Studies have shown that the inclusion of imipenem or meropenem if the MIC is $\leq$ 8μg/mL in CPE treatment regimens is associated with improved outcomes [16–18]. Hence, the provision of accurate carbapenem MIC results for these CPE isolates by clinical microbiology laboratories is crucial to allow for individualized and optimized therapy for these difficult to treat infections.

The aim of this laboratory-based study was to compare the carbapenem MICs yielded by four widely used commercially available testing platforms for OXA-48-like *K. pneumoniae* isolates.

Methods

Study design

This was a retrospective, laboratory-based study comparing the ertapenem, meropenem, and imipenem MIC results for 82 clinical OXA-48-like *K. pneumoniae* isolates tested on the Sensititre Gram Negative GN4F plate (Thermo Scientific, Waltham, MA, USA), MicroScan WalkAway *plus* Negative MIC Panel Type 44 (Beckman Coulter, Pasadena, CA, USA), Vitek 2 antimicrobial susceptibility testing (AST)-N255 card (bioMerieux, Marcy-l'Étoile, France) and Etests (bioMerieux).

OXA-48-like *K. pneumoniae* isolates were selected from the list of carbapenem-resistant Enterobacterales (CRE) isolates submitted from a routine clinical microbiology laboratory serving a tertiary hospital in South Africa, the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) microbiology laboratory, to the South African antimicrobial reference laboratory. At the CMJAH microbiology laboratory, Vitek 2 AST-N255 was performed, followed by MIC gradient diffusion tests (Etest) at the CMJAH antimicrobial susceptibility testing laboratory. For the Etests, a 0.5 MacFarland inoculum in normal saline was swabbed on Muller-Hinton agar. Following a 16 to 18 hour incubation period, Etests were read with the naked eye at 100% inhibition by a single person. When the MIC was deemed to be unclear by the first person, a second reader (with readers not blinded to each other's results) was sought and the consensus MIC reported. Control strains were tested once per month and with every new batch of Etests. Etests were stored at -10 to -25°C.

As per Clinical and Laboratory Standards Institute (CLSI) M100 breakpoints (M100Ed30), CRE isolates (based on the Vitek results) were referred to the reference laboratory for CPE gene and carbapenem MIC confirmation by MicroScan WalkAway *plus* Negative MIC Panel Type 44 for surveillance purposes [19]. The OXA-48-like genes were detected using a multiplex RT-PCR assay (LightCycler 480 Probes Master kit, LightMix Carbapenemase Modular kits; Roche Diagnostics, IN, USA) as described previously [5].

A convenience sample of deduplicated (single isolate per patient) blood culture isolates submitted from the CMJAH microbiology laboratory during the period 2017 through 2021 were selected for this study.

The reference laboratory stores all referred isolates at -70°C. The relevant stored isolates were retrieved and tested on-site in 2021 using the Sensititre Gram Negative GN4F plate.

At all centres testing was performed following the relevant manufacturers' recommendations.

The MIC calling range differed for the various test methods (Table 1).

Definitions

MIC50 and MIC90: The lowest antibiotic concentration at which 50% and 90%, respectively, of isolates are inhibited.

Data analysis

Data was analysed in Excel (Microsoft Corp., Redmond, WA). For each test method and carbapenem result, the isolates were categorized as susceptible, intermediate, and resistant as per Clinical and Laboratory Standards Institute M100 (M100Ed30). An analysis of categorical agreement (CA) for each carbapenem-test method combination was performed. The proportion of isolates with MICs $\leq$8μg/mL for meropenem and imipenem was determined. The Fishers exact test with a 2-tailed p value (GraphPad Software Inc., La Jolla, CA) was used for categorical data. The MIC50 and MIC90 were determined for meropenem and imipenem.

Ethics

An ethics waiver was obtained from the Wits Human Research Ethics Committee (W-CBP-200917-01).

Results

The distribution of MICs and susceptibility categorization for the 82 isolates is summarised in Table 2. The full MIC distributions and the comparative (each method compared to the other methods) MIC distributions for all test methods are available in the supplementary material.

The proportion of isolates which tested susceptible to ertapenem by Etest (19, 23.1%) compared to the other methods (Sensititre/Vitek (0) and MicroScan [2, 2.4%]) was statistically significant ($p < 0.001$ for all three).

For meropenem, there was a difference in the proportion of isolates susceptible by Etest (31, 37.8%) compared to that by Sensititre/Vitek (16, 19.5%), ($p = 0.015$). The proportion of isolates with meropenem MICs $\leq$8μg/mL was similar with Sensititre (36, 43.9%) and Vitek (33, 40.3%) (Table 3). However, differences were evident when comparing all four methods—Vitek vs. MicroScan (48, 58.5%) $p = 0.029$, Vitek and Sensititre vs. Etest (70, 85.4%) $p < 0.001$ for both, and MicroScan vs. Etest $p < 0.001$.

The proportion of isolates that tested susceptible to imipenem with the Sensititre (9, 11%) and Vitek (8, 9.8%) assays were similar (Table 2). There was variation in the proportion of isolates that tested imipenem susceptible when comparing Sensititre and Vitek to the MicroScan (27, 32.9%), $p = 0.001$ and $p < 0.001$, respectively, Sensititre and Vitek to the Etests (45, 54.9%), $p < 0.001$ for both, and MicroScan to Etests, p 0.007. There was a larger proportion of isolates with intermediate susceptibility results across the four testing methods (testing intermediate by any of the methods) for imipenem (48, 58.5%) compared to meropenem (18, 22%), $p < 0.001$. For the proportion of isolates with an imipenem MIC $\leq$8μg/mL, there was a difference when Sensititre (56, 68.3%) and Vitek (61, 74.4%)

Table 1
MIC calling range for the various test methods

Test method	Carbapenem	MIC range (μg/mL)
Vitek 2 AST-N255	Ertapenem	≤0.5–(≥8)
	Meropenem/imipenem	≤0.25–(≥16)
MicroScan Negative MIC Panel Type 44	Ertapenem	≤0.5–(≥2)
	Meropenem/imipenem	≤1–(≥16)
Sensititre GN4F	Ertapenem/meropenem/imipenem	≤0.25–(≥16)
Etest	Ertapenem/meropenem/imipenem	≤0.002–(≥32)

were compared to Etest (72, 87.8%) results, $p = 0.004$ and $p = 0.045$, respectively (Table 3).

Across the four testing methods, there were 59/82 (72%) isolates that demonstrated CA for ertapenem and 60 (73.2%) for meropenem. Fewer isolates showed CA across the four methods for imipenem 28 (34.1%), compared to ertapenem and meropenem ($p < 0.001$).

The MIC50 and MIC90 data is presented in Table 4

Discussion

To our knowledge, this was the largest published comparative study on commonly used OXA-48-like carbapenem MIC methods. A similar number of isolates yielded susceptible results with the Sensititre and Vitek for the three carbapenems (and similar proportions of intermediate and resistant results for ertapenem and meropenem). However, significant differences in the proportion of ertapenem and meropenem susceptible isolates were demonstrated between Sensititre/Vitek and Etest. For imipenem, only Sensititre and Vitek yielded similar MICs, with variation in the number of susceptible isolates present when comparisons with the other methods were made.

A significant difference ($p < 0.001$) in the proportion of isolates susceptible to ertapenem by Etest (23%) compared to the other methods (MicroScan 2% and Sensititre/Vitek 0%) was observed. Etest results may be consistent with low-level carbapenem hydrolysis characteristic of the OXA-48-like carbapenemases [20]. Alternatively, these may be falsely low MICs, which may result in missed OXA-48like detection.

The variability in meropenem MICs between Sensititre/Vitek and Etest was also marked, with isolates having susceptible Etest results compared to Sensititre MICs at 8 μg/mL and Vitek MICs ≥16 μg/mL. Similar disparities were observed for imipenem. Of note is the similarity between Sensititre and Vitek despite their different methodology and incubation requirements. Unexpectedly, there were more differences between the Sensititre and MicroScan, systems with similar methodologies and incubation times.

A high rate of carbapenem MIC reporting variability for CPEs has been documented in other studies. Large disparities in the proportion of susceptible results for KPC-producing *Escherichia coli* were reported for Sensititre, MicroScan, Vitek 2, and Etest [13]. Twenty-five percent of the meropenem MICs for the OXA-48-like isolates reported by the Vitek 2 were ≥4-fold higher than those from BMD in a study assessing the performance of various AST methods on a panel of Enterobacterales with elevated meropenem MICs. A pattern of over calling of MICs for the CPE isolates was noted for the Vitek 2 and Phoenix. Gradient strip methods (including Etest) showed overall essential agreement of 70% with BMD. As with the current study, the overall results from the Vitek 2 and gradients strips differed significantly ($p < 0.0001$) [12].

The poor categorical agreement across the four methods in this study was of concern, particularly for imipenem (34%). Variable performance of automated systems for the different carbapenems has been previously reported. A comparison of the Vitek 2 Compact system to BMD for KPC AST reported high (14.3%) very major error rates for imipenem, major errors (false resistance) of 2.4% and 1.2% for ertapenem and meropenem, respectively, and minor errors (one result intermediate and the other susceptible or resistant) of 2.4% and 3.6% for meropenem and imipenem, respectively [21].

The proportion of isolates with meropenem and imipenem MICs ≤8 μg/mL, was markedly higher with Etest compared to Sensititre and Vitek. The proportion of isolates determined to have meropenem MICs ≤8 μg/mL ranged from 40% for Vitek to 85% for Etest. It is difficult to reconcile the differences in the MICs yielded by these two methods when making individual patient therapy decisions. In many South African public sector laboratories, all CPE isolates are tested by gradient diffusion methods following the initial Vitek 2 AST.

There was a 2-fold difference between the Sensititre and Vitek MIC50 compared to the MicroScan, and a 4-fold difference compared to Etest, for both meropenem and imipenem. The meropenem MIC50 for the MicroScan and Etest data was ≤8 μg/mL. Based on published data showing improved survival in CPE infections with combination therapy, particularly carbapenem-containing regimens where the meropenem MICs are ≤8 μg/mL, the use of high dose, prolonged meropenem infusions, in settings where alternate antibiotic options are limited, is appropriate [16,18,22,23]. Montecarlo simulations have shown that for CPE isolates with meropenem MICs ≤8 μg/mL, 100% time above four times MIC was possible for creatinine clearances ranging from 10 to 200 mL/min using continuous infusions of 6 to 11 g/day [24]. Based on the MicroScan meropenem MIC50 of 8 μg/mL, for 50% of the OXA-48-like isolates included in this study 100% time above four times MIC would be achievable using appropriate creatinine clearance-based dosing strategies.

Despite newer antibiotics targeting OXA-48-like isolates reaching the market, global access is not consistent. In a cross-sectional global survey addressing antimicrobial combinations for multidrug resistant gram-negative infections respondents from 57/95 countries reported no access to ceftazidime-avibactam [15]. Hence, although the limited available data has suggested superior clinical outcomes with ceftazidime-avibactam compared to carbapenem therapy for OXA-48-like infections, carbapenem-based combination therapy is still standard therapy in many settings [25–27].

The OXA-48-like carbapenemases generally hydrolyse carbapenems at a low level and may result in carbapenem MICs close to the susceptible breakpoint [20]. However, the presence of other resistance mechanisms, such as porin loss can further increase the MIC [12]. The number of gene copies present on the plasmid may also result in higher MICs [28]. Fifty-six percent of OXA-48-like CPE isolates submitted to Public Health England for the period 2015 through 2016 displayed meropenem MICs of ≤1 μg/mL [25]. In the present study, 19.5 to 37.8% (depending on the test method) of isolates tested susceptible to meropenem. The hydrolytic capacity of the different OXA-48-like enzymes vary, and this may partly explain the relatively high carbapenem MICs in this study [26]. Due to the lack of testing for additional β-lactam resistance

Table 2
MIC distribution and susceptibility categorization

Carbapenem susceptibility number (%)			
Ertapenem	Susceptible ≤0.5 μg/mL	Intermediate 1 μg/mL	Resistant ≥2 μg/mL
Sensititre	0	1 (1.2)	81 (98.8)
Vitek	0	0	82 (100)
MicroScan	2 (2.4)	10 (12.2)	70 (85.4)
Etest	19 (23.1)	4 (4.9)	59 (72)
Meropenem	Susceptible ≤1 μg/mL	Intermediate 2 μg/mL	Resistant ≥4 μg/mL
Sensititre	16 (19.5)	8 (9.8)	58 (70.7)
Vitek	16 (19.5)	8 (9.8)	58 (70.7)
MicroScan	24 (29.3)	0	58 (70.7)
Etest	31 (37.8)	2 (2.4)	49 (59.8)
Imipenem	Susceptible ≤1 μg/mL	Intermediate 2 μg/mL	Resistant ≥4 μg/mL
Sensititre	9 (11)	16 (19.5)	57 (69.5)
Vitek	8 (9.8)	28 (34.1)	46 (56.1)
MicroScan	27 (32.9)	18 (22)	37 (45.1)
Etest	45 (54.9)	9 (11)	28 (34.1)

Table 3
Isolates with meropenem and imipenem MICs ≤8 μg/mL

Meropenem MIC ≤8 μg/mL, number (%)	
Sensititre	36 (43.9)
Vitek	33 (40.3)
MicroScan	48 (58.5)
Etest	70 (85.4)
Imipenem MIC ≤8 μg/mL, number (%)	
Sensititre	56 (68.3)
Vitek	61 (74.4)
MicroScan	65 (79.3)
Etest	72 (87.8)

Table 4
MIC50 and MIC90 data

Carbapenem	Method	MIC50	MIC90
Meropenem	Sensititre	≥16	≥16
	Vitek	≥16	≥16
	MicroScan	8	≥16
	Etest	4	≥16
Imipenem	Sensititre	4	≥16
	Vitek	4	≥16
	MicroScan	2	≥16
	Etest	1	8

mechanisms, it is not possible to comment on the possible contribution of these to the elevation of the carbapenem MICs.

The MIC testing can be challenging with regards to both accuracy and precision [29]. Known reasons for variability in MIC results include the impact of inoculum, incubation time, incubation conditions, types of media used, and strain-to-strain differences. Hence, for comparative evaluations ideally the use of a single inoculum to simultaneously inoculate the various MIC test methods is required in a single laboratory. Altered expression of resistance genes may result from multiple passages of a single strain, resulting in variability of MIC results. Even with the use of a single inoculum, variability in MICs when assessed in replicates in a single laboratory occurs due to the other factors mentioned above. Interobserver variability when reading carbapenem gradient diffusion method and Sensititre MICs needs to be accounted for by having multiple blinded readers and selection of the MIC reading for which there is consensus. However, additional reasons for the observed variability in MICs in this and other studies requires investigation.

Factors related to the test medium may affect MIC values. This has been recently demonstrated for metallo-β-lactamase-producing Enterobacterales, where supraphysiologic concentrations of zinc in Mueller-Hinton broth results in over-reporting carbapenem resistance [30]. Similarly, additives to Mueller-Hinton broth, microtitre plate type and degradation of antimicrobial powders within the test medium have been shown to affect the MIC reported [31]. Considering the vast dissemination of OXA-48-like CPE globally these aspects of microbiological testing specific to OXA-48-like isolates may require further investigation.

This study had several limitations: (a) lack of reference BMD testing to allow for definitive categorisation of discrepant results, (b) the isolates were from a single centre and typing for relatedness was not performed, (c) the overall number of isolates included was small, (d) testing by the various methods was not performed from a single inoculum, (e) each isolate was only tested once with each test method, (f) assessment of essential agreement was not possible due the limited MIC calling range of some of the test methods, and (g) Etest and Sensititre reading was performed by a single reader.

This study demonstrated that there is a substantial variability in the carbapenem MICs for OXA-48-like CPE isolates determined by the Sensititre, Vitek 2, MicroScan, and Etest methods. Based on the burden of OXA-48-like–related disease and the associated poor clinical outcomes, optimization of therapeutic approaches and the laboratory results on which these are based is required. The use of different AST panels, software versions, and reference standards (commercial vs. reference BMD) must be considered when interpreting the currently available data. Well-standardized evaluations that include reference broth microdilution as the reference standard and many diverse OXA-48-like CPE isolates must be undertaken to better delineate the performance of the various commercially available MIC test methods. Clinical laboratories must establish the performance characteristics of the AST method in use for the predominant CPE types prevalent in their setting. Verification of these commercial MIC methods using well-characterized CPE strains from national reference laboratories is recommended. Microbiologists and clinicians must consider the limitations of a single MIC measurement when making antibiotic therapy decisions.

Transparency declaration

All authors have no conflicts of interests to declare.

Author's contributions

TN was involved in the study conception and design, acquisition, analysis and interpretation of the data, drafting of the article and approval of the submitted version. VC was involved in the analysis and interpretation of the data, revising the article and approval of the submitted version. OP was involved in the acquisition of the data, revising the article and approval of the submitted version.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2022.06.023.

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