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CORRESPONDENCE

Limited *in vitro* susceptibility of drug-resistant non-fermenting Gram-negative organisms against newer generation antibiotics

To the Editor,

Gram-negative organisms cause a broad range of infections such as urinary tract infection, respiratory infections, and bacteraemia. As a group, they are also among the most common cause of healthcare-associated infections, resulting in increased mortality, morbidity, length-of-stay, and healthcare costs.[1,2] Drug resistance further contributes to increased mortality.[3] Enterobacterales as a group cause are the most commonly isolated pathogens, but non-fermenting Gram-negative bacilli (NFGNB) have more intrinsic resistance mechanisms. They can also acquire new resistance mechanisms, which further limits therapeutic options. *Pseudomonas aeruginosa, Acinetobacter baumannii* complex, *Stenotrophomonas maltophilia,* and *Elizabethkingia anophelis* are NFGNB associated with hospital-acquired infections. While *S. maltophilia* and *Elizabethkingia spp.* commonly have intrinsic β-lactamase production that result in carbapenem resistance, *P. aeruginosa* and *A. baumannii* complex isolates may acquire carbapenem-resistance through various mechanisms including carbapenemase production. The presence of carbapenemases in particular, result in concurrent resistance to various β-lactams.

In 2018, a new term 'difficult-to-treat resistance' (DTR) was proposed, defined as resistance to all β-lactams and quinolones to reflect resistance to first-line agents for treating Gram-negative infections.[3] In a retrospective cohort study, 2.3% (101/4,493) of *P. aeruginosa* and 18.3% (183/999) of *A. baumannii* bloodstream infections were DTR.[3] Infections with DTR isolates in this study were shown to have a higher mortality rate even compared to carbapenem-resistant and quinolone-resistant infections.[3] As drug resistance becomes more problematic, some of the newer β-lactam-β-lactamase-inhibitor (BLBLI) combinations are now recommended as first line therapy for DTR organisms because of their ability to inhibit carbapenemases.[4,5] These include ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-relebactam. The new siderophore antibiotic cefiderocol has also been reported to demonstrate *in vitro* susceptibility against isolates that produce various carbapenemase, including NDM, and is recommended for management.[4,5] These newer generation BLBLI have been suggested as possible treatment options for drug resistant Gram-negative organisms. In addition, other drug classes have also seen new members such as omadacycline and eravacycline (fluorocyclines), plazomicin (aminoglycoside), and delafloxacin (fluoroquinolone).

We have previously demonstrated limited *in vitro* susceptibility of ceftazidime-avibactam and ceftolozane-tazobactam in DTR *P. aeruginosa* isolates in our setting.[6] However, the correlation between these phenotypes and resistance mechanisms (carbapenemases in particular) was not performed. To further assess the feasibility of new antibiotics including BLBLI combinations as treatment options for non-fermenters, susceptibility testing was performed on a collection of NFGNB. Testing for carbapenemase genes was also performed on DTR *P. aeruginosa* and *A. baumannii* complex isolates to identify the presence of common carbapenemase in these isolates. These genotypic results were then compared against phenotypic susceptibility of BLBLI combinations and cefiderocol. Concurrent testing to new non-β-lactam antibiotics was also performed to identify alternative treatment options.

A collection of drug resistant Gram-negative organisms were tested by broth microdilution using Sensititre MDRGN2F plates (ThermoFisher, Singapore). The included isolates were *P. aeruginosa, A. baumannii* complex, *S. maltophilia,* and *E. anophelis.* All isolates were identified by MALDI-TOF (MALDI Biotyper; Bruker, USA). Duplicate isolates of the same bacterial species from the same patient were excluded.

Pseudomonas aeruginosa and *A. baumannii* complex were selected as they are the two most common NFGNB associated with nosocomial infections.[1] DTR *P. aeruginosa* and DTR *A. baumannii* complex isolates from all clinical samples in 2021 were included. DTR in *P. aeruginosa* and *A. baumannii* complex was defined as resistance against ceftazidime, cefepime, piperacillin-tazobactam, imipenem, meropenem, and ciprofloxacin which was routinely tested using Vitek 2 (bioMérieux, France) based on European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints. For *A. baumannii* complex isolates, EUCAST non-species breakpoints were used where species-specific breakpoints were unavailable. Three historical NDM-positive *A. baumannii* complex isolates were also included.

Stenotrophomonas maltophilia and *E. anophelis* were included as they are causes of nosocomial infections in our local setting, and also have intrinsic resistance to carbapenems. These isolates were not pre-selected based on routine antimicrobial susceptibility profiles. *Stenotrophomonas maltophilia* and *E. anophelis* isolates from blood cultures between 2019−2022 were included.

Susceptibility testing by the Sensititre MDRGN2F plates was performed as per manufacturer instructions. The MDRGN2F plates included the following antibiotics [tested minimum inhibitory concentration (MIC) range]: meropenem-vaborbactam (0.008−16 mg/L; vaborbactam fixed concentration 8 mg/L); omadacycline (0.12−8 mg/L); plazomicin (0.12−4 mg/L); imipenem-relebactam (0.03−16 mg/L; relebactam fixed concentration 4 mg/L); ceftazidime-avibactam (0.5−32 mg/L; avibactam fixed concentration 4 mg/L); eravacycline (0.03−8 mg/L); delafloxacin (0.12−1 mg/L); cefiderocol (0.03−32 mg/L); ceftolozane-tazobactam (0.06−8 mg/L; tazobactam fixed concentration 4 mg/L); levofloxacin (0.25−4 mg/L); meropenem (0.25−8 mg/L); imipenem (2−16 mg/L); amikacin (16−32 mg/L). Levofloxacin, meropenem, and imipenem were not analysed as all were resistant because of the selection criteria for *P. aeruginosa* and *A. baumannii* complex isolates. Amikacin was not analysed because of the narrow tested MIC range. Quality control was performed using *Escherichia coli* ATCC 25922 and *P. aeruginosa* ATCC 27853 with all antimicrobial results being within the expected range.

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EUCAST breakpoints are available for *P. aeruginosa* for meropenem-vaborbactam, imipenem-relebactam, ceftazidime-avibactam, ceftolozane-tazobactam, and cefiderocol. PK-PD (non-species-related) breakpoints are also available for these antibiotics. The *P. aeruginosa* and non-species-related breakpoints are currently the same (meropenem-vaborbactam S≤8, R>8; imipenem-relebactam S≤2, R>2; ceftazidime-avibactam S≤8, R>8; ceftolozane-tazobactam S≤4, R>4; cefiderocol S≤2, R>2). Thus, these same breakpoints were applied for all bacterial species in this study. There are currently no interpretive breakpoints available for omadacycline, eravacycline, delafloxacin, or plazomicin.

Pseudomonas aeruginosa and *A. baumannii* complex isolates were also screened for carbapenemase carriage via polymerase chain reaction (PCR). The following carbapenemase genes were targeted: *bla*KPC, *bla*GES, $bla_{\text{OXA-58}}$, $bla_{\text{OXA-48}}$, $bla_{\text{OXA-40}}$, $bla_{\text{OXA-23}}$, bla_{NDM}, bla_{VIM}, and bla_{IMP} as previously described.[7] NDM, KPC, and OXA carbapenemases are the most commonly identified carbapenemases in carbapenemase-producing Enterobacterales locally,[8] while GES, VIM, and IMP are other commonly described carbapenemases in *P. aeruginosa*.[9]

A total of 34 DTR *P. aeruginosa,* 28 DTR *A. baumannii* complex, 15 *S. maltophilia,* and 7 *E. anophelis* isolates were included. The *P. aeruginosa* isolates consisted of three blood, seven respiratory, 13 urine, and 11 miscellaneous (tissue, wound, or fluid) isolates. The *A. baumannii* complex isolates consisted of five blood, four respiratory, 11 urine, and eight miscellaneous isolates. All *S. maltophilia* and *E. anophelis* were blood isolates.

MIC_{50} and MIC_{90} of all antibiotics for all isolates are shown in Table 1. Susceptibility and resistance rates are also shown for meropenem-vaborbactam, imipenem-relebactam, ceftazidime-avibactam, ceftolozane-tazobactam, and cefiderocol for all isolates. Due to the lack of breakpoints including PK-PD (non-species-related) breakpoints, susceptibility/resistance rates could not be reported for omadacycline, eravacycline, delafloxacin, and plazomicin. The MIC distributions of these antibiotics are shown in Table 2.

Table 1 Susceptibility rates, MIC_{50}, and MIC_{90} of newer generation β-lactam-β-lactamase-inhibitor combinations and cefiderocol

Antibiotic	S	MIC_{50}	MIC_{90}
Pseudomonas aeruginosa			
Meropenem-vaborbactam	8.8% (3/34)	>16	>16
Imipenem-relebactam	5.9% (2/34)	>16	>16
Ceftazidime-avibactam	5.9% (2/34)	>32	>32
Ceftolozane-tazobactam	14.7% (5/34)	>8	>8
Cefiderocol	52.9% (18/34)	2	8
Acinetobacter baumannii complex			
Meropenem-vaborbactam	0.0% (0/28)	>16	>16
Imipenem-relebactam	0.0% (0/28)	>16	>16
Ceftazidime-avibactam	3.6% (1/28)	>32	>32
Ceftolozane-tazobactam	3.6% (1/28)	>8	>8
Cefiderocol	60.7% (17/28)	1	8
Stenotrophomonas maltophilia			
Meropenem-vaborbactam	0.0% (0/15)	>16	>16
Imipenem-relebactam	0.0% (0/15)	>16	>16
Ceftazidime-avibactam	60.0% (9/15)	8	>32
Ceftolozane-tazobactam	40.0% (6/15)	>8	>8
Cefiderocol	93.3% (14/15)	1	8
Elizabethkingia anophelis			
Meropenem-vaborbactam	0.0% (0/7)	>16	>16
Imipenem-relebactam	0.0% (0/7)	>16	>16
Ceftazidime-avibactam	0.0% (0/7)	32	32
Ceftolozane-tazobactam	0.0% (0/7)	>8	>8
Cefiderocol	14.3% (1/7)	32	>32

S, susceptible, standard dosing regimen; MIC_{50}, MIC at which at least 50% of isolates were inhibited; MIC_{90}, MIC at which at least 90% of isolates were inhibited.

Of the 34 DTR *P. aeruginosa*, 18 isolates (52.9%) were positive for carbapenemase genes. Eight were NDM-positive, and ten were IMP-1-positive. Sixteen isolates were negative for carbapenemase genes. All carbapenemase-positive *P. aeruginosa* were resistant to all BLBLI combinations. The susceptibility rates of carbapenemase-negative *P. aeruginosa* are as follows: meropenem-vaborbactam (18.8%, 3/16); imipenem-relebactam (12.5%, 2/16); ceftazidime-avibactam (18.8%, 3/16); ceftolozane-tazobactam (31.3%, 5/16). None of the NDM-positive isolates were susceptible to cefiderocol. Fifty percent (5/10) of IMP-positive isolates and 81.3% (13/16) of carbapenemase-negative isolates were susceptible to cefiderocol.

Of the 28 DTR *A. baumannii* complex, seven isolates (25.0%) were carbapenemase-positive. One was IMP-positive, three were OXA-23-positive, one was OXA-58 and NDM-positive, and two were OXA-23 and NDM-positive. All carbapenemase-positive isolates were resistant to all BLBLI combinations. However, of the carbapenemase-negative isolates, only one isolate was susceptible to both ceftazidime-avibactam and ceftolozane-tazobactam (4.8%, 1/21). All isolates with NDM were resistant to cefiderocol. The single IMP-1-positive isolate was susceptible to cefiderocol, while two of three OXA-23-positive isolates were susceptible to cefiderocol (66.7%). Of the 21 carbapenemase-negative isolates, 66.7% were susceptible to cefiderocol (14/21).

Phenotypic susceptibility to the tested BLBLI and cefiderocol stratified by carbapenemase genotype is presented in Table 3.

Treatment options for drug-resistant Gram-negative bacteria remains limited despite availability of newer generation antimicrobials. We demonstrate that newer-generation BLBLI combinations had limited *in vitro* activity against DTR *P. aeruginosa,* DTR *A. baumannii* complex, *S. maltophilia,* and *E. anophelis.* Cefiderocol also had poor activity against *E. anophelis* but 52.9%, 60.7%, and 93.3% of DTR *P. aeruginosa,* DTR *A. baumannii* complex, and *S. maltophilia* demonstrated *in vitro* susceptibility, respectively. High rates of carbapenemase were identified among our DTR *P. aeruginosa* isolates (>52.9%), while only 25% of DTR *A. baumannii* complex isolates were carbapenemase positive. Isolates which were carbapenemase-positive were more likely to be resistant to BLBLI combinations, and all NDM-positive isolates were resistant to cefiderocol. The association of IMP-positive isolates with cefiderocol resistance was weaker. While susceptibility rates of BLBLI combinations were higher in carbapenemase-negative *P. aeruginosa,* overall activity remains limited, indicating likely presence of other non-carbapenemase mediated resistance mechanisms.

Currently, screening of drug-resistant *P. aeruginosa* and *A. baumannii* complex isolates for the presence of carbapenemase (genes) is not routinely performed in our local setting. Our data indicate that the presence of carbapenemase genes is predictive of resistance to BLBLI combinations (particularly for *P. aeruginosa*), and in the case of NDM, resistance to cefiderocol too. High rates of resistance to

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Table 2 MIC distribution, MIC_{50}, and MIC_{90} to omadacycline, eravacycline, delafloxacin, and plazomicin

Antibiotic	Minimum inhibitory concentration (MIC), mg/L										MIC_{50}	MIC_{90}
	0.03	0.06	0.12	0.25	0.5	1	2	4	8	>8		
Pseudomonas aeruginosa												
Omadacycline			0	0	0	0	0	0	0	34[a]	>8	>8
Eravacycline	0	0	0	0	0	0	0	0	14	20[a]	>8	>8
Delafloxacin			0	0	0	4	30[a]				>1	>1
Plazomicin			0	0	0	1	2	12	19[a]		>4	>4
Acinetobacter baumannii complex												
Omadacycline			1	2	1	3	11	7	0	3[a]	2	>8
Eravacycline	1	2	0	5	14	3	1	1	0	1[a]	0.5	2
Delafloxacin			1	0	1	3	23[a]				>1	>1
Plazomicin			0	0	1	2	3	1	21[a]		>4	>4
Stenotrophomonas maltophilia												
Omadacycline			0	0	0	1	5	5	1	3[a]	4	>8
Eravacycline	0	0	1	0	7	4	1	0	2		0.5	8
Delafloxacin			2	0	4	3	6[a]				1	>1
Plazomicin			0	0	0	0	0	1	14[a]		>4	>4
Elizabethkingia anophelis												
Omadacycline			0	0	0	0	1	3	2	1[a]	4	>8
Eravacycline	0	0	0	0	0	3	4	0	0		2	2
Delafloxacin			3	3	1	0					0.25	0.5
Plazomicin			0	0	0	0	0	0	7[a]		>4	>4

[a] Indicates isolates with MIC outside of tested range.

Table 3 Susceptibility rates of DTR *P. aeruginosa* and *A. baumannii* complex isolates to newer generation β-lactam-β-lactamase-inhibitor combinations and cefiderocol, stratified by carbapenemase

	Antibiotic				
	Meropenem-vaborbactam	Imipenem-relebactam	Ceftazidime-avibactam	Ceftolozane-tazobactam	Cefiderocol
Pseudomonas aeruginosa (*n*=34)					
Carbapenemase-negative (*n*=16)	18.8% (3/16)	12.5% (2/16)	18.8% (3/16)	31.3% (5/16)	81.3% (13/16)
IMP (*n*=10)	0.0% (0/10)	0.0% (0/10)	0.0% (0/10)	0.0% (0/10)	50% (5/10)
NDM (*n*=8)	0.0% (0/8)	0.0% (0/8)	0.0% (0/8)	0.0% (0/8)	0.0% (0/8)
Acinetobacter baumannii complex (*n*=28)					
Carbapenemase-negative (*n*=21)	0.0% (0/21)	0.0% (0/21)	4.8% (1/21)	4.8% (1/21)	66.7% (14/21)
IMP (*n*=1)	0.0% (0/1)	0.0% (0/1)	0.0% (0/1)	0.0% (0/1)	100.0% (1/1)
OXA-23 (*n*=3)	0.0% (0/3)	0.0% (0/3)	0.0% (0/3)	0.0% (0/3)	66.7% (2/3)
OXA-58 and NDM (*n*=1)	0.0% (0/1)	0.0% (0/1)	0.0% (0/1)	0.0% (0/1)	0.0% (0/1)
OXA-23 and NDM (*n*=2)	0.0% (0/2)	0.0% (0/2)	0.0% (0/2)	0.0% (0/2)	0.0% (0/2)

BLBLI were seen in *A. baumannii* complex isolates, regardless of the presence of carbapenemase. In our context, IMP and NDM [both metallo-β-lactamases (MBL)] predominated in carbapenemase-positive *P. aeruginosa,* but none of the *P. aeruginosa* isolates in our collection was positive for group A (such as KPC or GES) or group D (OXA-group) carbapenemases. This is consistent with global trends, where group D carbapenemases are rarely described, with higher rates of group A carbapenemases, followed by MBLs.[9] None of these MBL-positive *P. aeruginosa* isolates were susceptible to the new BLBLI combinations which is expected as the β-lactamase-inhibitors (vaborbactam, avibactam, relebactam, and tazobactam) do not inhibit MBL. Carbapenemase testing in *P. aeruginosa* can predict resistance to BLBLI when positive for a MBL. However, phenotypic testing is still required confirming susceptibility in carbapenemase-negative isolates. In regions where group A carbapenemases are more commonly seen in *P. aeruginosa*, phenotypic susceptibility to other newer BLBLI may still be retained. A few *A. baumannii* complex isolates with MBLs were identified although globally, group D Carbapenemases (OXA) are the most common carbapenemases identified in *A. baumannii,* including intrinsic OXA-51 genes.

Further typing of carbapenemase-positive isolates was not performed in this study. However, it is important to note that >50% of DTR *P. aeruginosa* and 25% of DTR *A. baumannii* complex isolates were positive for carbapenemase. Clonal transmission of NDM-positive *P. aeruginosa* was demonstrated previously.[10] Of note, IMP and VIM were identified in both *P. aeruginosa* and *A. baumannii* complex isolates. Clonal transmission of bacterial isolates or horizontal transmission of mobile genetic elements is another aspect with potential infection control implications with regards to carbapenemase testing in NFGNB. This may be important to consider in future studies as part of international efforts to combat drug resistance in healthcare settings.

The MICs of *P. aeruginosa* for omadacycline, eravacycline, delafloxacin, and plazomicin were generally on the higher end of the tested range indicating limited *in vitro* activity. MICs to omadacycline and eravacycline may be due to

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intrinsic class resistance of *P. aeruginosa* to tetracyclines. In addition, high rates of acquired resistance (to aminoglycosides and fluoroquinolones) is expected as these isolates were selected on basis of having DTR phenotype. Similarly, MICs of delafloxacin and plazomicin for *A. baumannii* complex isolates were also high. The MICs to omadacycline and eravacycline were more variable, suggesting possible *in vitro* activity amongst DTR isolates. The MIC_{50} and MIC_{90} for eravacycline were similar to those reported in other *A. baumannii* isolates,[11] but higher for omadacycline.[12]

Stenotrophomonas maltophilia and *E. anophelis* are known to have intrinsic resistance mechanisms against aminoglycosides which reflects limited inhibition by plazomicin. Variable MICs were seen for omadacycline, eravacycline, and delafloxacin. Further data are required to establish breakpoints with which to interpret whether these antibiotics are suitable treatment options for these organisms. Cefiderocol may be a possible treatment option of *S. maltophilia.* Ceftazidime-avibactam and ceftolozane-tazobactam also has better activity for *S. maltophilia* compared to other BLBLI, although clinical data are required given the presence of intrinsic β-lactamases. All BLBLI and cefiderocol appear to have limited activity against *E. anophelis.*

With the exception of >90% susceptibility to cefiderocol seen in *S. maltophilia,* our data indicate that newer generation antibiotics do not appear to offer significant advantage for the tested isolates. In DTR *P. aeruginosa* and *A. baumannii* complex isolates, the activity of BLBLI is limited. While some of this is correlated with the presence of carbapenemase genes, particularly *P. aeruginosa*, high rates of resistance are seen even in carbapenemase-negative isolates. Similarly, almost all *A. baumannii* complex isolates were resistant to BLBLI combinations. The fluorocyclines may have activity for *A. baumannii* complex, *S. maltophilia,* and *E. anophelis* infections, although additional clinical data are required.

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