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In Vitro Activity of Cefepime/Taniborbactam against Ertapenem-Nonsusceptible *Enterobacterales* Obtained Across Canada: CANWARD 2007-2019

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Introduction

Carbapenems such as ertapenem, imipenem and meropenem are increasingly used both empirically and as directed therapy for infections caused by resistant and MDR pathogens such as MDR *Enterobacterales*. Carbapenems (only available parenterally) and β-lactam/β-lactamase inhibitors are viewed as effective therapies for infections caused by MDR *Enterobacterales*. However, as carbapenem nonsusceptibility increases, clinicians/researchers are looking for carbapenem-sparing regimens such as novel β-lactam/β-lactamase inhibitors (as parenteral and especially oral agents). There is an unmet need for novel parenteral (and oral) carbapenem-sparing β-lactam/β-lactamase inhibitors to treat infections caused by fluoroquinolone-resistant, MDR Gram-negative bacilli. A β-lactam/β-lactamase inhibitor with activity versus carbapenem-nonsusceptible *Enterobacterales* is needed.

Cefepime is a parenteral extended-spectrum cephalosporin that has been used clinically for decades.[1] Taniborbactam (formerly VNRX-5133) is a boronic acid-containing β-lactamase inhibitor that inhibits class A, C and D (serine) β-lactamases, and class B (metallo) β-lactamases, including VIM, NDM, SPM-1, and GIM-1 (but not IMP). Cefepime/taniborbactam is in Phase 3 clinical development for the treatment of complicated urinary tract infection.[1-3]

The current study assessed the *in vitro* activities of cefepime/taniborbactam and comparator antimicrobial agents against ertapenem-nonsusceptible (NS) *Enterobacterales* clinical isolates with various resistance phenotypes obtained from the CANWARD study 2007-2019 inclusive.

Materials and Methods

Bacterial Isolates: CANWARD is an ongoing, national, Health Canada partnered study assessing antimicrobial resistance patterns of pathogens causing infections in patients receiving care in hospitals across Canada.[4] Tertiary-care medical centres submitted pathogens from patients attending hospital clinics, emergency rooms, medical and surgical wards and intensive care units.[4] From January 2007 to October 2019, each study site was asked to submit clinical isolates from inpatients and outpatients with respiratory, urine, wound and bloodstream infections. Isolates were shipped to the coordinating laboratory, subcultured onto appropriate media, and stocked in skim milk at -80°C until minimum inhibitory concentration (MIC) testing was carried out.
From the CANWARD isolate collection, 179 ertapenem-nonsusceptible (MIC ≥1 µg/ml) *Enterobacterales* were tested including *Enterobacter cloacae* (96), *Klebsiella* spp. (47), *E. coli* (26) and other species (n=10). Specimen sources were 43% respiratory, 39% blood, 10% urine, and 8% wound. 51 ertapenem-susceptible (MIC ≤ 0.5 µg/ml) *Enterobacterales* were tested as controls.

Antimicrobial Susceptibilities: Following 2 subcultures from frozen stock, the *in vitro* activities of cefepime/taniborbactam (cefepime 0.03-128 µg/ml with taniborbactam fixed at 4 µg/ml) and comparator agents were determined by reference CLSI broth microdilution (M07, 11th Ed., 2018) using 96-well custom designed microtitre plates.[4] MICs were interpreted using CLSI M100 (30th Ed., 2020) or FDA breakpoints. Colony counts were performed periodically to confirm inocula. Quality control was assured using the ATCC strains specified for *Enterobacterales* in the CLSI M100 document.

Results

Table 1. Activity of cefepime/taniborbactam and comparators versus various resistant phenotypes of *Enterobacterales*

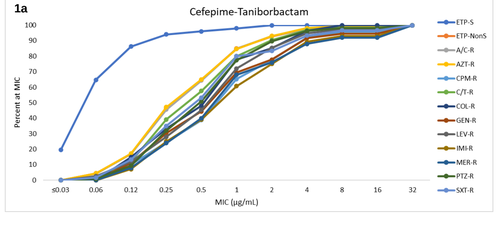
Organism (no. tested) / Antimicrobial Agent	MIC (µg/mL)		
	MIC_{50}	MIC_{90}	% S
Ertapenem-S (51)			
Cefepime/taniborbactam	0.06	0.25	NB
Cefepime	0.12	2	96.1
Ceftolozane/tazobactam	0.5	4	84.3
Gentamicin	0.5	2	94.1
Imipenem	0.5	1	90.2
Imipenem/relebactam	0.25	0.5	96.1
Levofloxacin	≤ 0.25	1	86.3
Meropenem	≤ 0.06	0.12	100
Meropenem/vaborbactam	≤ 0.06	≤ 0.06	100
Piperacillin/tazobactam	4	32	84.3
Ertapenem-NS (179)			
Cefepime/taniborbactam	0.5	2	NB
Cefepime	4	>64	42.5
Ceftolozane/tazobactam	16	>32	20.1
Gentamicin	0.5	>16	77.7
Imipenem	1	8	72.1
Imipenem/relebactam	0.25	1	92.2
Levofloxacin	0.5	>8	50.8
Meropenem	0.25	8	81.6
Meropenem/vaborbactam	≤ 0.06	0.5	96.1
Piperacillin/tazobactam	128	>128	15.1
Aztreonam-R (157)			
Cefepime/taniborbactam	0.5	2	NB
Cefepime	4	>64	36.3
Ceftolozane/tazobactam	16	>32	11.5
Gentamicin	0.5	>16	76.4
Imipenem	0.5	4	73.9
Imipenem/relebactam	0.25	1	94.9
Levofloxacin	0.5	>8	50.3
Meropenem	0.25	8	80.9
Meropenem/vaborbactam	≤ 0.06	0.5	96.2
Piperacillin/tazobactam	128	>128	8.3
Cefepime-R (49)			
Cefepime/taniborbactam	1	4	NB
Cefepime	>64	>64	0
Ceftolozane/tazobactam	>32	>32	16.3
Gentamicin	>16	>16	42.9
Imipenem	1	32	53.1
Imipenem/relebactam	0.25	4	85.7
Levofloxacin	>8	>8	8.2
Meropenem	0.5	32	55.1
Meropenem/vaborbactam	≤ 0.06	8	87.8
Piperacillin/tazobactam	>128	>128	12.2
Ceftolozane/tazobactam-R (125)			
Cefepime/taniborbactam	0.5	4	NB
Cefepime	4	>64	28.0
Ceftolozane/tazobactam	16	>32	0
Gentamicin	0.5	>16	76.0
Imipenem	1	8	71.2
Imipenem/relebactam	0.25	1	92.8
Levofloxacin	0.5	>8	52.0
Meropenem	0.25	16	76.8
Meropenem/vaborbactam	≤ 0.06	1	94.4
Piperacillin/tazobactam	>128	>128	0
Colistin-R (27)			
Cefepime/taniborbactam	1	4	NB
Cefepime	2	>64	66.7
Ceftolozane/tazobactam	8	>32	33.3
Gentamicin	1	>16	77.8
Imipenem	1	8	51.9
Imipenem/relebactam	1	2	70.4
Levofloxacin	1	>8	40.7
Meropenem	0.25	16	81.5
Meropenem/vaborbactam	≤ 0.06	2	96.3
Piperacillin/tazobactam	64	>128	22.2
Levofloxacin-R (75)			
Cefepime/taniborbactam	1	4	NB
Cefepime	16	>64	22.7
Ceftolozane/tazobactam	16	>32	22.7
Gentamicin	2	>16	56.0
Imipenem	1	16	61.3
Imipenem/relebactam	0.25	1	92.0
Levofloxacin	>8	>8	0
Meropenem	0.25	16	68.0
Meropenem/vaborbactam	≤ 0.06	2	94.7
Piperacillin/tazobactam	>128	>128	17.3
Imipenem-R (28)			
Cefepime/taniborbactam	1	8	NB
Cefepime	16	>64	21.4
Ceftolozane/tazobactam	>32	>32	17.9
Gentamicin	2	>16	64.3
Imipenem	8	>32	0
Imipenem/relebactam	1	16	57.1
Levofloxacin	8	>8	21.4
Meropenem	16	>32	10.7
Meropenem/vaborbactam	0.5	16	75.0
Piperacillin/tazobactam	>128	>128	17.9
Meropenem-R (25)			
Cefepime/taniborbactam	1	8	NB
Cefepime	32	>64	8.0
Ceftolozane/tazobactam	>32	>32	8.0
Gentamicin	1	>16	64.0
Imipenem	8	>32	0
Imipenem/relebactam	1	16	60.0
Levofloxacin	>8	>8	16.0
Meropenem	16	>32	0
Meropenem/vaborbactam	1	16	72.0
Piperacillin/tazobactam	>128	>128	8.0
Pip/tazo-R (106)			
Cefepime/taniborbactam	0.5	4	NB
Cefepime	8	>64	20.8
Ceftolozane/tazobactam	32	>32	0.9
Gentamicin	0.5	>16	70.8
Imipenem	1	8	67.0
Imipenem/relebactam	0.25	1	91.5
Levofloxacin	1	>8	48.1
Meropenem	0.25	16	73.6
Meropenem/vaborbactam	≤ 0.06	2	93.4
Piperacillin/tazobactam	>128	>128	0
TMP/SMX-R (60)			
Cefepime/taniborbactam	0.5	4	NB
Cefepime	32	>64	21.7
Ceftolozane/tazobactam	32	32	25.0
Gentamicin	16	>16	41.7
Imipenem	1	16	53.3
Imipenem/relebactam	0.25	2	88.3
Levofloxacin	>8	>8	6.7
Meropenem	0.5	32	61.7
Meropenem/vaborbactam	≤ 0.06	2	95.0
Piperacillin/tazobactam	>128	>128	20.0
Amox/clav-R (171)			
Cefepime/taniborbactam	0.5	2	NB
Cefepime	4	>64	42.7
Ceftolozane/tazobactam	16	>32	16.4
Gentamicin	0.5	>16	77.8
Imipenem	1	8	70.8
Imipenem/relebactam	0.25	1	91.8
Levofloxacin	0.5	>8	52.0
Meropenem	0.25	8	80.7
Meropenem/vaborbactam	≤ 0.06	0.5	95.9
Piperacillin/tazobactam	128	>128	11.7

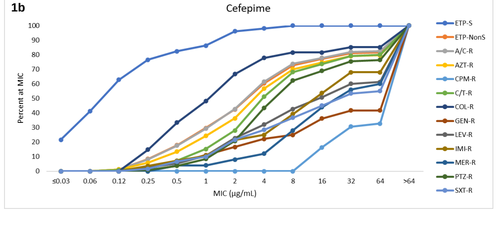
[a] NB: no breakpoint defined

Table 2. Cefepime/taniborbactam and cefepime MIC distributions (µg/mL) vs. various resistant phenotypes of *Enterobacterales*

Phenotype (n)	0.25	0.5	1	2	4	8	16	32	64	> 64
Imipenem/relebactam-R (8)										
Cefepime		1				1	2			4
Cefepime/taniborbactam		1	1	2	2			2		
Ceftazidime/avibactam-R (4)										
Cefepime									1	3
Cefepime/taniborbactam			2					2		
Meropenem/vaborbactam-R (4)										
Cefepime							1			3
Cefepime/taniborbactam			1	1				2		
Amikacin-R (3)										
Cefepime							1			2
Cefepime/taniborbactam			1		1			1		

Figure 1a and 1b. MIC distributions (µg/mL) for cefepime/taniborbactam and cefepime versus various resistant phenotypes of *Enterobacterales*





Conclusions

1. Cefepime/taniborbactam was highly active (MIC_{50}, 0.25 µg/ml and MIC_{90} 2 µg/ml) against ertapenem-nonsusceptible *Enterobacterales*.
2. Cefepime/taniborbactam was highly active against ertapenem-nonsusceptible *Enterobacterales* with various phenotypes including amoxicillin/clavulanate-resistant; amikacin-resistant; aztreonam-resistant; cefepime-resistant; ceftolozane/tazobactam-resistant; colistin-resistant; imipenem-resistant; levofloxacin-resistant; meropenem-resistant; and piperacillin/tazobactam-resistant-resistant.
3. Although the number of such isolates was limited, cefepime/taniborbactam also demonstrated activity versus some isolates resistant to ceftazidime-avibactam, imipenem-relebactam and meropenem-vaborbactam.
4. Our data support the ongoing development of cefepime-taniborbactam for the treatment of complicated urinary tract infections.

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