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In Vitro Activity of Imipenem-Relebactam Against Various Resistance Phenotypes/Genotypes of Enterobacteriaceae and *Pseudomonas aeruginosa* Isolated from Patients Across Canada: CANWARD 2016-2018

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Introduction

Relebactam is a non-β-lactam, bicyclic diazabicyclooctane, β-lactamase inhibitor that is structurally related to avibactam, differing by the addition of a piperidine ring to the 2-position carbomyl group (1). It displays activity against Ambler class A (including extended-spectrum β-lactamases [ESBLs], *Klebsiella pneumoniae* carbapenemases [KPCs]) and class C β-lactamases (AmpC). The addition of relebactam significantly improves the activity of imipenem against most species of Enterobacteriaceae (by lowering the minimum inhibitory concentration [MIC] by 2- to 128-fold) depending on the presence or absence of β-lactamase enzymes. Against *Pseudomonas aeruginosa*, the addition of relebactam also improves the activity of imipenem (by lowering the MIC by 8-fold). Based on the data available the addition of relebactam does not improve the activity of imipenem against *Acinetobacter baumannii*, *Strenotrophomonas maltophilia* and most anaerobes.

Phase II clinical trials have reported that imipenem/relebactam is as effective as imipenem alone for treatment of complicated intra-abdominal infections and complicated urinary tract infections, including acute pyelonephritis.[1] Imipenem/relebactam is currently in Phase III of development with studies assessing imipenem/relebactam versus imipenem-resistant bacterial infections (preliminary data presented at ECCMID 2018) as well as treatment of hospital-associated bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP). The current study assessed the *in vitro* activities of Imipenem/relebactam, imipenem, and comparator antimicrobial agents against various resistance phenotypes/genotypes of recent (2016-2018) clinical isolates of Enterobacteriaceae and *P. aeruginosa* submitted to the CANWARD study in 2016-2018.

Purpose

1. To assess the *in vitro* activities of imipenem/relebactam, imipenem, and comparator antimicrobial agents against various resistance phenotypes/genotypes of recent clinical isolates of Enterobacteriaceae submitted to the CANWARD study in 2016-2018.

2. To assess the *in vitro* activities of imipenem/relebactam, imipenem, and comparator antimicrobial agents against various resistance phenotypes/genotypes of recent clinical isolates of *P. aeruginosa* submitted to the CANWARD study in 2016-2018.

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 (2). Tertiary-care medical centres submitted pathogens from patients attending hospital clinics, emergency rooms, medical and surgical wards, and intensive care units (2). From January 2016 through October 2018, inclusive, each study site was asked to submit clinical isolates (consecutive, one per patient, per infection site) from inpatients and outpatients with respiratory, urine, wound, and bloodstream infections. The medical centres submitted clinically significant isolates from patients with a presumed infectious disease. Surveillance swabs, eye, ear, nose and throat swabs were excluded. We also excluded anaerobic organisms. Isolate identification was performed by the submitting site and confirmed at the reference site as required, based on morphological characteristics and antimicrobial susceptibility patterns. Isolates were shipped on Amies semi-solid transport media to the coordinating laboratory (Health Sciences Centre, Winnipeg, Canada), subcultured onto appropriate media, and stocked in skim milk at -80˚ C until minimum inhibitory concentration (MIC) testing was carried out.

Antimicrobial Susceptibilities: Following 2 subcultures from frozen stock, the *in vitro* activity of imipenem, imipenem/relebactam and selected antimicrobials was determined by broth microdilution in accordance with the Clinical and Laboratory Standards Institute (CLSI) guidelines (3). Antimicrobial minimum inhibitory concentration (MIC) interpretive standards were defined according to CLSI breakpoints CLSI M100-S28 (4).

Antimicrobial agents were obtained as laboratory grade powders from their respective manufacturers. Stock solutions were prepared and dilutions made as described by CLSI (2018). The MICs of the antimicrobial agents for the isolates were determined using 96-well custom designed microtitre plates (2). These plates contained doubling antimicrobial dilutions in 100µl/well of cation adjusted Mueller-Hinton broth and inoculated to achieve a final concentration of approximately 5 x 10^5 CFU/mL then incubated in ambient air for 24 hours prior to reading. Colony counts were performed periodically to confirm inocula. Quality control was performed using ATCC QC organisms including; *S. pneumoniae* 49619, *S. aureus* 29213, *E. faecalis* 29212, *E. coli* 25922, and *P. aeruginosa* 27853.

Results

Table 1. Antimicrobial activity of imipenem/relebactam, imipenem and comparators versus Enterobacteriaceae isolated from Canadian hospitals

Organism (no. tested) / Antimicrobial Agent	MIC (µg/mL)			
	MIC_{50}	MIC_{90}	Range Min	Range Max
***Citrobacter freundii* (n=25)**				
Amikacin	2	4	≤ 1	8
Cefepime	≤ 0.25	4	≤ 0.25	16
Ceftriaxone	≤ 0.25	> 64	≤ 0.25	> 64
Ciprofloxacin	≤ 0.06	2	≤ 0.06	4
Imipenem	0.5	1	0.25	2
Imipenem/relebactam	0.25	0.5	0.12	2
Piperacillin/tazobactam	2	256	≤ 1	> 512
Trimethoprim Sulfa	≤ 0.12	> 8	≤ 0.12	> 8
***Enterobacter cloacae* (n=293)**				
Amikacin	2	2	≤ 1	16
Cefepime	≤ 0.25	2	≤ 0.25	> 64
Ceftriaxone	≤ 0.25	> 64	≤ 0.25	> 64
Ciprofloxacin	≤ 0.06	0.12	≤ 0.06	> 16
Imipenem	0.5	1	0.25	4
Imipenem/relebactam	0.25	0.5	0.12	4
Piperacillin/tazobactam	4	64	≤ 1	> 512
Trimethoprim Sulfa	≤ 0.12	0.25	≤ 0.12	> 8
***Escherichia coli* (n=1386)**				
Amikacin	2	4	≤ 1	> 64
Cefepime	≤ 0.25	4	≤ 0.25	> 64
Ceftriaxone	≤ 0.25	> 64	≤ 0.25	> 64
Ciprofloxacin	≤ 0.06	> 16	≤ 0.06	> 16
Imipenem	0.25	0.5	0.06	> 32
Imipenem/relebactam	0.25	0.25	0.06	> 32
Piperacillin/tazobactam	2	8	≤ 1	> 512
Trimethoprim Sulfa	≤ 0.12	> 8	≤ 0.12	> 8
***Escherichia coli*, ESBL pos (n=155)**				
Amikacin	2	8	≤ 1	32
Cefepime	32	> 64	0.5	> 64
Ceftriaxone	> 64	> 64	2	> 64
Ciprofloxacin	> 16	> 16	≤ 0.06	> 16
Imipenem	0.25	0.5	0.12	1
Imipenem/relebactam	0.25	0.25	0.12	1
Piperacillin/tazobactam	4	32	≤ 1	512
Trimethoprim Sulfa	> 8	> 8	≤ 0.12	> 8
***Escherichia coli*, Ertapenem NonS (n=10)**				
Amikacin	2	8	≤ 1	> 64
Cefepime	4	> 64	≤ 0.25	> 64
Ceftriaxone	> 64	> 64	≤ 0.25	> 64
Ciprofloxacin	> 16	> 16	≤ 0.06	> 16
Imipenem	0.5	1	0.25	> 32
Imipenem/relebactam	0.25	0.25	0.06	> 32
Piperacillin/tazobactam	32	> 512	4	> 512
Trimethoprim Sulfa	> 8	> 8	≤ 0.12	> 8
***Klebsiella aerogenes* (n=62)**				
Amikacin	2	2	≤ 1	8
Cefepime	≤ 0.25	0.5	≤ 0.25	8
Ceftriaxone	≤ 0.25	32	≤ 0.25	> 64
Ciprofloxacin	≤ 0.06	0.12	≤ 0.06	8
Imipenem	1	2	0.25	> 32
Imipenem/relebactam	0.25	1	0.12	16
Piperacillin/tazobactam	4	64	2	256
Trimethoprim Sulfa	≤ 0.12	0.25	≤ 0.12	0.5
***Klebsiella oxytoca* / *Raoultella spp.* (n=188)**				
Amikacin	≤ 1	4	≤ 1	8
Cefepime	≤ 0.25	0.5	≤ 0.25	> 64
Ceftriaxone	≤ 0.25	8	≤ 0.25	> 64
Ciprofloxacin	≤ 0.06	≤ 0.06	≤ 0.06	> 16
Imipenem	0.25	0.5	0.25	1
Imipenem/relebactam	0.25	0.5	0.12	1
Piperacillin/tazobactam	2	32	≤ 1	> 512
Trimethoprim Sulfa	≤ 0.12	≤ 0.12	≤ 0.12	> 8
***Klebsiella pneumoniae* (n=578)**				
Amikacin	≤ 1	2	≤ 1	16
Cefepime	≤ 0.25	1	≤ 0.25	> 64
Ceftriaxone	≤ 0.25	1	≤ 0.25	> 64
Ciprofloxacin	≤ 0.06	1	≤ 0.06	> 16
Imipenem	0.25	1	0.12	> 32
Imipenem/relebactam	0.25	1	0.12	2
Piperacillin/tazobactam	4	16	≤ 1	> 512
Trimethoprim Sulfa	≤ 0.12	> 8	≤ 0.12	> 8
***Klebsiella pneumoniae* ESBL pos (n=49)**				
Amikacin	2	8	≤ 1	16
Cefepime	64	> 64	≤ 0.25	> 64
Ceftriaxone	> 64	> 64	≤ 0.25	> 64
Ciprofloxacin	4	> 16	≤ 0.06	> 16
Imipenem	0.25	4	0.12	> 32
Imipenem/relebactam	0.25	0.5	0.12	2
Piperacillin/tazobactam	16	> 512	2	> 512
Trimethoprim Sulfa	> 8	> 8	≤ 0.12	> 8
***Klebsiella pneumoniae*, Ertapenem NonS (n=13)**				
Amikacin	2	8	≤ 1	16
Cefepime	> 64	> 64	≤ 0.25	> 64
Ceftriaxone	> 64	> 64	≤ 0.25	> 64
Ciprofloxacin	> 16	> 16	0.25	> 16
Imipenem	2	32	0.25	> 32
Imipenem/relebactam	0.5	2	0.12	2
Piperacillin/tazobactam	> 512	> 512	2	> 512
Trimethoprim Sulfa	> 8	> 8	2	> 8
***Morganella morganii* (n=38)**				
Amikacin	2	8	≤ 1	8
Cefepime	≤ 0.25	≤ 0.25	≤ 0.25	> 64
Ceftriaxone	≤ 0.25	1	≤ 0.25	> 64
Ciprofloxacin	≤ 0.06	4	≤ 0.06	> 16
Imipenem	4	8	1	8
Imipenem/relebactam	2	4	1	4
Piperacillin/tazobactam	≤ 1	4	≤ 1	256
Trimethoprim Sulfa	≤ 0.12	1	≤ 0.12	> 8
***Proteus mirabilis* (n=118)**				
Amikacin	4	8	≤ 1	32
Cefepime	≤ 0.25	≤ 0.25	≤ 0.25	4
Ceftriaxone	≤ 0.25	≤ 0.25	≤ 0.25	2
Ciprofloxacin	≤ 0.06	4	≤ 0.06	> 16
Imipenem	2	4	0.25	16
Imipenem/relebactam	4	8	0.25	16
Piperacillin/tazobactam	≤ 1	≤ 1	≤ 1	64
Trimethoprim Sulfa	≤ 0.12	> 8	≤ 0.12	> 8
***Serratia marcescens* (n=177)**				
Amikacin	2	4	≤ 1	16
Cefepime	≤ 0.25	0.5	≤ 0.25	16
Ceftriaxone	≤ 0.25	1	≤ 0.25	> 64
Ciprofloxacin	0.12	1	≤ 0.06	16
Imipenem	1	2	0.25	8
Imipenem/relebactam	1	2	0.5	> 32
Piperacillin/tazobactam	2	4	≤ 1	128
Trimethoprim Sulfa	0.5	1	≤ 0.12	> 8

ESBL = extended spectrum ß-lactamase

Table 3. Antimicrobial activity of imipenem/relebactam, imipenem and comparators versus *Pseudomonas aeruginosa* isolated from Canadian hospitals

Organism (no. tested) / Antimicrobial Agent	MIC (µg/mL)			
	MIC_{50}	MIC_{90}	Range Min	Range Max
***Pseudomonas aeruginosa* (975)**				
Amikacin	4	16	≤ 1	> 64
Cefepime	4	16	≤ 0.25	> 64
Ciprofloxacin	0.25	4	≤ 0.06	> 16
Colistin	1	2	≤ 0.06	> 16
Imipenem	2	16	0.12	> 32
Imipenem/relebactam	0.5	2	0.06	> 32
Piperacillin/tazobactam	8	128	≤ 1	> 512
Tobramycin	≤ 0.5	2	≤ 0.5	> 64

Table 4. MIC (µg/m) distributions of imipenem/relebactam, imipenem and comparators versus *Pseudomonas aeruginosa* isolated from Canadian hospitals

Organism	Antimicrobial Agent	0.06	0.12	0.25	0.5	1	2	4	8	16	32	> 32	Total
Pseudomonas aeruginosa													**975**
	Imipenem		1	16	36	180	370	135	77	72	63	25	
	Imipenem/relebactam	2	11	137	533	127	88	50	13	7	0	7	

Table 2. MIC (µg/mL) distributions of imipenem/relebactam, imipenem and comparators versus Enterobacteriaceae isolated from Canadian hospitals

Organism	Antimicrobial Agent	0.06	0.12	0.25	0.5	1	2	4	8	16	32	> 32	Total
Citrobacter freundii													**25**
	Imipenem			7	7	9	2						
	Imipenem/relebactam		1	17	5	1	1						
Enterobacter cloacae													**293**
	Imipenem			75	112	85	16	5					
	Imipenem/relebactam		12	198	69	10	3	1					
Escherichia coli													**1386**
	Imipenem	1	30	1204	133	15	2					1	
	Imipenem/relebactam	5	428	867	77	6	2					1	
***Escherichia coli* - ESBL pos**													**155**
	Imipenem		2	132	13	8							
	Imipenem/relebactam		38	107	7	3							
***Escherichia coli* - Ertapenem NonS**													**10**
	Imipenem			2	6	1						1	
	Imipenem/relebactam	1	1	7								1	
Klebsiella aerogenes													**62**
	Imipenem			9	14	25	12	1				1	
	Imipenem/relebactam		9	26	17	8	1			1			
Klebsiella oxytoca* / *Raoultella spp.													**188**
	Imipenem			132	47	9							
	Imipenem/relebactam		13	140	29	6							
Klebsiella pneumoniae													**578**
	Imipenem		2	375	142	46	6	3	1	1	1	1	
	Imipenem/relebactam		31	313	160	68	6						
***Klebsiella pneumoniae* - ESBL pos**													**49**
	Imipenem		1	29	9	2	3	2		1	1	1	
	Imipenem/relebactam		7	29	9	2	2						
***Klebsiella pneumoniae* - Ertapenem NonS**													**13**
	Imipenem			2	1	1	3	2	1	1	1	1	
	Imipenem/relebactam		2	4	3	2	2						
Morganella morganii													**38**
	Imipenem					3	6	24	5				
	Imipenem/relebactam						2	21	15				
Proteus mirabilis													**118**
	Imipenem			16	8	14	35	35	5	5			
	Imipenem/relebactam			5	5	2	27	61	16	2			
Serratia marcescens													**177**
	Imipenem			9	56	81	23	7	1				
	Imipenem/relebactam				32	84	55	4		1		1	

ESBL = extended spectrum ß-lactamase

Conclusions

1. Imipenem/relebactam was ~2 fold more active than imipenem versus Enterobacteriaceae.
2. Imipenem/relebactam was 2-8 fold more active than imipenem against ESBL-producing Enterobacteriaceae and retained its activity against ertapenem-nonsusceptible Enterobacteriaceae.
3. Imipenem/relebactam was highly active against *P. aeruginosa*.
4. Imipenem/relebactam was 4-8 fold more active than imipenem against *P. aeruginosa*.

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