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In Vitro Activity of Imipenem-Relebactam against Various Resistance Phenotypes/Genotypes of *Enterobacterales* and *Pseudomonas aeruginosa* Isolated from Patients across Canada: CANWARD 2016-2020

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Introduction

Imipenem/cilastatin (IMI) has been used to treat a variety of infections since the mid-1980's.[1] Relebactam (REL) is a non-β-lactam, β-lactamase inhibitor that is structurally related to avibactam, displaying activity against Ambler class A (including extended-spectrum β-lactamases [ESBLs], *Klebsiella pneumoniae* carbapenemases [KPCs]) and class C β-lactamases (AmpC) enzymes.[2] The addition of relebactam significantly improves the activity of imipenem against most species of Enterobacterales (by lowering the MIC 2- to 128-fold) depending on the presence or absence of β-lactamase enzymes.[3] Against *Pseudomonas aeruginosa*, the addition of relebactam also improves the activity of imipenem (by lowering the MIC by 8-fold).[3]
Imipenem/relebactam (IMI-REL) is FDA approved (2019) for the treatment of adults with complicated urinary tract, complicated intra-abdominal infection, hospital acquired and ventilator-associated bacterial pneumonia. In a recent clinical trial (RESTORE-IMI 1) patients infected with imipenem-non-susceptible (but colistin- and imipenem/relebactam-susceptible) pathogens and treated with IMI-REL or colistin plus imipenem, demonstrated better day 28 favorable clinical response (71% vs 40%) and 28-day mortality (10% vs 30%) with IMI-REL.[4] Drug-related adverse effects occurred in fewer patients in the IMI-REL treatment group (16% vs 31% as did treatment-emergent nephrotoxicity (10% vs 56%).

The current study assessed the *in vitro* activities of imipenem/relebactam, imipenem, and comparator antimicrobial agents against various resistance phenotypes/genotypes of recent (2016-2020) clinical isolates of Enterobacterales and *P. aeruginosa* submitted to the CANWARD study in 2016-2020.

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. [5] Tertiary-care medical centres submitted pathogens from patients attending hospital clinics, emergency rooms, medical and surgical wards, and intensive care units.[5] From Jan. 2016 – Oct. 2020, 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.
Morganellaceae were excluded from the dataset because species in that family of Gram-negative bacilli intrinsically demonstrate elevated imipenem MICs by a mechanism independent of β-lactamase production and relebactam would not be expected to enhance imipenem's activity against *Morganellaceae* isolates. Putative AmpC phenotypes in *E. coli* were defined as an isolate where the ceftriaxone and/or ceftazidime MIC was ≥1 µg/mL**,** the cefoxitin MIC was ≥32 µg/mL, and the isolate tested ESBL-negative by the CLSI phenotypic confirmatory disk test (CLSI M100, 29th Ed., 2019).[5]
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) (M07, 2018) and MICs were interpreted using CLSI M100 (2020) and FDA breakpoints. Imipenem/relebactam FDA breakpoints used were: Enterobacterales ≤1/4 µg/mL susceptible (S), 2/4 µg/mL intermediate (I), and ≥4/4 µg/mL resistant (R); and for *P. aeruginosa* ≤2/4 µg/mL (S), 4/4 µg/mL (I) and ≥8/4 µg/mL (R). The MICs were determined using 96-well custom designed microtitre plates.[5] Colony counts were performed periodically to confirm inocula. Quality control was performed using various ATCC organisms.

Results

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

Organism (no. tested) / Antimicrobial Agent	MIC (µg/mL) MIC_{50}	MIC_{90}	% S	Range
***Citrobacter freundii* (56)**				
Amikacin	2	2	100	≤ 1 - 8
Cefepime	≤ 0.25	4	87.5	≤ 0.25 - 32
Ceftriaxone	≤ 0.25	> 64	75.0	≤ 0.25 - > 64
Ciprofloxacin	≤ 0.06	1	87.5	≤ 0.06 - 16
Imipenem	1	2	87.5	0.25 - 4
Imipenem/relebactam	0.25	0.5	98.2	0.12 - 2
Piperacillin/tazobactam	2	256	76.8	≤ 1 - > 512
Trimethoprim Sulfa	≤ 0.12	> 8	82.1	≤ 0.12 - > 8
***Enterobacter cloacae* (464)**				
Amikacin	2	2	99.6	≤ 1 - > 64
Cefepime	≤ 0.25	2	90.5	≤ 0.25 - > 64
Ceftriaxone	≤ 0.25	> 64	71.3	≤ 0.25 - > 64
Ciprofloxacin	≤ 0.06	0.12	94.0	≤ 0.06 - > 16
Imipenem	0.5	1	92.5	0.12 - > 32
Imipenem/relebactam	0.25	0.5	98.5	0.12 - > 32
Piperacillin/tazobactam	2	128	81.0	≤ 1 - > 512
Trimethoprim Sulfa	≤ 0.12	0.5	93.1	≤ 0.12 - > 8
***Escherichia coli* ALL (2831)**				
Amikacin	2	4	99.6	≤ 1 - > 64
Cefepime	≤ 0.25	4	88.7	≤ 0.25 - > 64
Ceftriaxone	≤ 0.25	> 64	84.7	≤ 0.25 - > 64
Ciprofloxacin	≤ 0.06	> 16	72.3	≤ 0.06 - > 16
Imipenem	0.25	0.25	99.8	≤ 0.03 - > 32
Imipenem/relebactam	0.25	0.25	99.8	≤ 0.03 - > 32
Piperacillin/tazobactam	2	8	96.3	≤ 1 - > 512
Trimethoprim Sulfa	≤ 0.12	> 8	71.8	≤ 0.12 - > 8
***Escherichia coli* ESBL (361)**				
Amikacin	2	8	98.6	≤1 - 64
Cefepime	16	> 64	15.8	≤ 0.25 - > 64
Ceftriaxone	> 64	> 64	0	2 - > 64
Ciprofloxacin	> 16	> 16	13.0	≤ 0.06 - > 16
Imipenem	0.25	0.25	99.4	0.06 - 16
Imipenem/relebactam	0.25	0.25	99.7	0.06 - 16
Piperacillin/tazobactam	4	16	91.1	≤ 1 - > 512
Trimethoprim Sulfa	> 8	> 8	33.0	≤ 0.12 - > 8
***Escherichia coli AmpC* (90)**				
Amikacin	2	8	98.9	≤1 - > 64
Cefepime	≤ 0.25	2	94.4	≤ 0.25 - > 64
Ceftriaxone	2	64	45.6	≤ 0.25 - > 64
Ciprofloxacin	0.25	> 16	61.1	≤ 0.06 - > 16
Imipenem	0.25	0.5	98.9	0.06 - > 32
Imipenem/relebactam	0.25	0.5	98.9	0.06 - > 32
Piperacillin/tazobactam	8	64	80.0	≤ 1 - > 512
Trimethoprim Sulfa	≤ 0.12	> 8	68.9	≤ 0.12 - > 8
***Klebsiella pneumoniae* (1036)**				
Amikacin	≤ 1	2	99.9	≤ 1 - 32
Cefepime	≤ 0.25	2	90.7	≤ 0.25 - > 64
Ceftriaxone	≤ 0.25	8	89.5	≤ 0.25 - > 64
Ciprofloxacin	≤ 0.06	1	84.9	≤ 0.06 - > 16
Imipenem	0.25	0.5	98.3	0.12 - > 32
Imipenem/relebactam	0.25	0.5	99.1	0.12 - 2
Piperacillin/tazobactam	4	16	93.9	≤ 1 - > 512
Trimethoprim Sulfa	≤ 0.12	> 8	86.0	≤ 0.12 - > 8
***Klebsiella pneumoniae* ESBL (93)**				
Amikacin	2	8	98.9	≤1 - 32
Cefepime	> 64	> 64	5.4	≤ 0.25 - > 64
Ceftriaxone	> 64	> 64	2.2	≤ 0.25 - > 64
Ciprofloxacin	4	> 16	8.6	≤ 0.06 - > 16
Imipenem	0.25	1	90.3	0.12 - > 32
Imipenem/relebactam	0.25	0.5	97.8	0.06 - 2
Piperacillin/tazobactam	16	> 512	64.5	2 - > 512
Trimethoprim Sulfa	> 8	> 8	12.9	≤ 0.12 - > 8
***Klebsiella aerogenes* (117)**				
Amikacin	≤ 1	2	100	≤ 1 - 8
Cefepime	≤ 0.25	0.5	97.4	≤ 0.25 - > 64
Ceftriaxone	≤ 0.25	32	65.8	≤ 0.25 - > 64
Ciprofloxacin	≤ 0.06	0.25	94.0	≤ 0.06 - 8
Imipenem	1	2	74.4	0.12 - > 32
Imipenem/relebactam	0.25	1	97.4	0.06 - 16
Piperacillin/tazobactam	4	64	75.2	≤ 1 - 512
Trimethoprim Sulfa	≤ 0.12	0.25	100	≤ 0.12 - 1

ESBL = extended spectrum ß-lactamase

Table 5. Antimicrobial activity (µg/ml) of imipenem/relebactam, imipenem and comparators versus KPC-producing *Klebsiella pneumoniae* isolated from Canadian hospitals

Isolate #	Organism	ESBL	KPC	Region	AMK	CPM	CTR	CIP	IMI	IMI-REL	PTZ
129439	*K. pneumoniae*	POS	KPC-2	Quebec	≤ 1	64	>64	8	**32**	**0.25**	>512
129502	*K. pneumoniae*	POS	KPC-3	Quebec	16	>64	>64	>16	**>32**	**0.5**	>512
129832	*K. pneumoniae*	POS	KPC-2	Quebec	≤ 1	4	>64	1	**4**	**2**	64

AMK= amikacin; CPM= cefepime; CTR= ceftriaxone; CIP= ciprofloxacin; IMI= imipenem; IMI-REL= imipenem-relebactam; PTZ=piperacillin-tazobactam

Table 1. Antimicrobial activity of imipenem/relebactam, imipenem and comparators versus Enterobacterales isolated from Canadian hospitals (Continued)

Organism (no. tested) / Antimicrobial Agent	MIC (µg/mL) MIC_{50}	MIC_{90}	% S	Range
***Klebsiella oxytoca / Raoultella* spp. (309)**				
Amikacin	≤ 1	4	100	≤ 1 - 8
Cefepime	≤ 0.25	0.5	95.5	≤ 0.25 - > 64
Ceftriaxone	≤ 0.25	16	86.7	≤ 0.25 - > 64
Ciprofloxacin	≤ 0.06	0.12	95.8	≤ 0.06 - > 16
Imipenem	0.25	0.5	99.7	0.06 - 2
Imipenem/relebactam	0.25	0.5	100	≤ 0.03 - 1
Piperacillin/tazobactam	2	64	88.7	≤ 1 - > 512
Trimethoprim Sulfa	≤ 0.12	0.25	93.5	≤ 0.12 - > 8
***Serratia marcescens* (279)**				
Amikacin	2	4	100	≤ 1 - 16
Cefepime	≤ 0.25	0.5	98.9	≤ 0.25 - 16
Ceftriaxone	≤ 0.25	1	90.3	≤ 0.25 - > 64
Ciprofloxacin	≤ 0.06	1	85.3	≤ 0.06 - > 16
Imipenem	1	2	80.6	0.25 - 8
Imipenem/relebactam	1	2	71.3	0.25 - 4
Piperacillin/tazobactam	2	8	98.2	≤ 1 - 128
Trimethoprim Sulfa	0.25	1	98.2	≤ 0.12 - > 8

Table 2. MIC (µg/ml) distributions of imipenem/relebactam and imipenem versus Enterobacterales isolated from Canadian hospitals

Organism	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	> 32	Total
Citrobacter freundii													**56**
Imipenem				8	15	26	6	1					
Imipenem/Relebactam				1	44	7	3	1					
Enterobacter cloacae													**464**
Imipenem				9	108	181	131	28	5	1		1	
Imipenem/Relebactam				29	289	120	12	5	1			1	
Escherichia coli													**2831**
Imipenem	1	12	638	1948	200	27	2	1		1		1	
Imipenem/Relebactam	1	17	715	1532	121	11	2			1		1	
***Escherichia coli* ESBL**													**361**
Imipenem		3	72	255	20	9		1		1			
Imipenem/Relebactam		5	121	217	13	4				1			
Escherichia coli AmpC													**90**
Imipenem		1	7	40	33	8						1	
Imipenem/Relebactam		2	22	55	10							1	
Klebsiella pneumoniae													**1036**
Imipenem			69	622	246	81	9	3	1	3	1	1	
Imipenem/Relebactam			66	576	256	86	9						
Klebsiella pneumoniae ESBL													**93**
Imipenem			11	51	19	3	3	2		2	1	1	
Imipenem/Relebactam		1	17	52	19	2	2						
Klebsiella aerogenes													**117**
Imipenem			1	11	26	49	26	2				2	
Imipenem/Relebactam		1	12	54	34	13	1	1		1			
Klebsiella oxytoca /Raoultella spp.													**309**
Imipenem		1	11	213	72	11	1						
Imipenem/Relebactam	1		21	223	51	7							
Serratia marcescens													**279**
Imipenem				11	70	144	44	9	1				
Imipenem/Relebactam				4	60	135	75	5					

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}	% S	Range
***Pseudomonas aeruginosa* (1608)**				
Amikacin	4	16	92.4	≤ 1 - > 64
Cefepime	4	32	79	≤ 0.25 - > 64
Ciprofloxacin	0.25	4	71.3	≤ 0.06 - > 16
Colistin	1	2	98.1[a]	≤ 0.06 - > 16
Imipenem	2	32	59.1	0.12 - > 32
Imipenem/relebactam	0.5	2	91.3	0.06 - > 32
Piperacillin/tazobactam	8	256	74.9	≤ 1 - > 512
Tobramycin	≤ 0.5	2	94.1	≤ 0.5 - > 64

[a] MIC ≤2 µg/ml

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

Organism	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	> 32	Total
Pseudomonas aeruginosa													**1608**
Imipenem			7	30	54	291	588	196	132	139	137	34	
Imipenem/Relebactam	3	21	261	799	220	166	77	32	11	5	9		

Conclusions

1. Imipenem/relebactam was highly active (MIC_{90}, 0.25-1 µg/ml) against commonly encountered species of *Enterobacterales* (excluding *Morganellaceae*).
2. Imipenem/relebactam was highly active against ESBL-producing, AmpC-producing and KPC-producing *Enterobacterales*.
3. Imipenem/relebactam was 4-fold more active than imipenem against IMI-R *Enterobacterales*.
4. Imipenem/relebactam was highly active against *P. aeruginosa*.
5. Imipenem/relebactam was 4 to 16-fold more active than imipenem against *P. aeruginosa*.

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References

1. Zhanel GG, Simor A, Vercaigne L, Mandell L and the Canadian Imipenem/Meropenem Advisory Group. Imipenem/meropenem: review of in-vitro activity, pharmacokinetics, clinical trials and adverse effects. Can J Infect Dis 1998;44:391-396.
2. Zhanel GG, Lawrence CK, Adam H, Schweizer F, Zelenitsky S, Zhanel MA, Lagace-Wiens PR, Walkty A, Golden A, Gin AS, Hoban DJ, Lynch JP, and Karlowsky JA. Imipenem-relebactam and meropenem-vaborbactam: Two novel carbapenem-β-Lactamase inhibitor combinations. Drugs 2018;Jan;78(1):65-98.
3. Karlowsky JA, Lob SH, Raddatz J, DePestel DD, Young K, Motyl MR, Sahm DF. In vitro activity of imipenem/relebactam and ceftolozane/tazobactam against clinical isolates of gram-negative bacilli with difficult to treat resistance and multi-resistant phenotypes – SMART United Sates 2015-2017. Clin Infect Dis 2020 Apr 3.
4. Motsch J, Murta de Oliveira C, Stus V, Köksal I, Lyulko O, Boucher HW, Kaye KS, File TM, Brown ML, Khan I, Du J, Joeng HK, Tipping RW, Aggrey A, Young K, Kartsonis NA, Butterton JR, Paschke A. RESTORE-IMI 1: A multicenter randomized double-blind trial comparing efficacy and safety of imipenem/relebactam vs colistin plus imipenem in patients with imipenem nonsusceptible bacterial infections. Clin Infect Dis 2020; 70(9):1799-1808.
5. Zhanel GG, Adam H, Baxter M, Fuller J, Nichol K, Denisuik AJ, Golden A, Hink R, Lagacé-Wiens P, Walkty A, Mulvey M, Schweizer F, Bay D, Hoban DJ, Karlowsky JA, the Canadian Antimicrobial Resistance Alliance (CARA). 42,936 pathogens from Canadian hospitals: 10 years of results (2007-2016) from the CANWARD surveillance study. Journal of Antimicrobial Chemotherapy 2019;74(Suppl 4):5-21.