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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 2016-2021

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Introduction

Imipenem/cilastatin (IMI) has been used to treat a variety of infections since the mid-1980s.[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 REL significantly improves the activity of IMI 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 REL also improves the activity of IMI, primarily by inhibition of AmpC (PDC).[3]

Imipenem-relebactam (IMI-REL) is FDA approved (2019) for the treatment of adults with complicated urinary tract infection, complicated intra-abdominal infection, hospital acquired and ventilator-associated bacterial pneumonia. In a recent clinical trial (RESTORE-IMI 1) patients infected with IMI-non-susceptible (but colistin- and IMI-REL-susceptible) pathogens and treated with IMI-REL or colistin plus IMI, 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%). Early clinical data suggest that IMI-REL is safe and effective in the treatment of a variety of infections.[5]

The current study assessed the *in vitro* activities of IMI-REL, IMI, and comparator antimicrobial agents against various resistance phenotypes/genotypes of recent (2016-2021) clinical isolates of Enterobacterales and *P. aeruginosa* submitted to the CANWARD study in 2016-2021.

Materials and Methods

Bacterial Isolates: CANWARD is an ongoing, national, Public Health Agency of Canada-partnered study assessing antimicrobial resistance patterns of pathogens causing infections in patients receiving care in hospitals across Canada.[6] Tertiary-care medical centres submitted pathogens from patients attending hospital clinics, emergency rooms, medical and surgical wards, and intensive care units.[6] From January 2016 to October 2021, 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, 31st Ed., 2021).[6]

Antimicrobial Susceptibilities: Following 2 subcultures from frozen stock, the *in vitro* activity of IMI, IMI-REL 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 (31st Ed., 2021) breakpoints. IMI-REL 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_{50}	MIC_{90}	MIC (µg/mL) % S	Range
***Citrobacter freundii* (65)**				
Amikacin	2	2	100	≤ 1 - 8
Cefepime	≤ 0.25	4	89.2	≤ 0.25 - 32
Ceftriaxone	≤ 0.25	> 64	76.9	≤ 0.25 - > 64
Ciprofloxacin	≤ 0.06	1	86.2	≤ 0.06 - > 16
Imipenem	1	2	87.7	0.12 - 4
Imipenem-relebactam	0.25	0.5	98.5	0.12 - 2
Piperacillin-tazobactam	2	256	78.5	≤ 1 - > 512
Trimethoprim-sulfamethoxazole	≤ 0.12	> 8	81.5	≤ 0.12 - > 8
***Enterobacter cloacae* (546)**				
Amikacin	2	2	99.6	≤ 1 - > 64
Cefepime	≤ 0.25	2	90.5	≤ 0.25 - > 64
Ceftriaxone	≤ 0.25	> 64	70.0	≤ 0.25 - > 64
Ciprofloxacin	≤ 0.06	0.12	93.8	≤ 0.06 - > 16
Imipenem	0.5	1	92.3	0.12 - > 32
Imipenem-relebactam	0.25	0.5	98.7	0.06 - > 32
Piperacillin-tazobactam	2	128	75.8	≤ 1 - > 512
Trimethoprim-sulfamethoxazole	≤ 0.12	0.5	92.7	≤ 0.12 - > 8
***Escherichia coli* ALL (3314)**				
Amikacin	2	4	99.6	≤ 1 - > 64
Cefepime	≤ 0.25	4	88.2	≤ 0.25 - > 64
Ceftriaxone	≤ 0.25	> 64	84.3	≤ 0.25 - > 64
Ciprofloxacin	≤ 0.06	> 16	71.9	≤ 0.06 - > 16
Imipenem	0.25	0.25	99.8	≤ 0.03 - > 32
Imipenem-relebactam	0.25	0.25	99.9	≤ 0.03 - > 32
Piperacillin-tazobactam	2	8	93.8	≤ 1 - > 512
Trimethoprim-sulfamethoxazole	≤ 0.12	> 8	71.8	≤ 0.12 - > 8
***Escherichia coli* ESBL (432)**				
Amikacin	2	8	98.6	≤ 1 - 64
Cefepime	16	> 64	14.8	≤ 0.25 - > 64
Ceftriaxone	> 64	> 64	0	2 - > 64
Ciprofloxacin	> 16	> 16	13.9	≤ 0.06 - > 16
Imipenem	0.25	0.25	99.3	0.06 - 16
Imipenem-relebactam	0.25	0.25	99.8	0.06 - 16
Piperacillin-tazobactam	2	16	81.7	≤ 1 - >512
Trimethoprim-sulfamethoxazole	> 8	> 8	33.8	≤ 0.12 - > 8
***Escherichia coli AmpC* (106)**				
Amikacin	2	4	98.9	≤ 1 - > 64
Cefepime	≤ 0.25	2	94.3	≤ 0.25 - > 64
Ceftriaxone	2	64	44.3	≤ 0.25 - > 64
Ciprofloxacin	0.25	> 16	57.5	≤ 0.06 - > 16
Imipenem	0.25	0.5	99.1	0.06 - > 32
Imipenem-relebactam	0.25	0.5	99.0	0.06 - > 32
Piperacillin-tazobactam	8	128	73.6	≤ 1 - >512
Trimethoprim-sulfamethoxazole	≤ 0.12	> 8	66.0	≤ 0.12 - > 8
***Klebsiella pneumoniae* ALL (1241)**				
Amikacin	≤ 1	2	99.9	≤ 1 - 32
Cefepime	≤ 0.25	1	90.7	≤ 0.25 - > 64
Ceftriaxone	≤ 0.25	4	89.5	≤ 0.25 - > 64
Ciprofloxacin	≤ 0.06	1	85.7	≤ 0.06 - > 16
Imipenem	0.25	0.5	98.5	0.06 - > 32
Imipenem-relebactam	0.25	0.5	99.3	0.06 - 2
Piperacillin-tazobactam	4	16	89.9	≤ 1 - > 512
Trimethoprim-sulfamethoxazole	≤ 0.12	> 8	86.2	≤ 0.12 - > 8
***Klebsiella pneumoniae* ESBL (112)**				
Amikacin	2	8	98.9	≤ 1 - 32
Cefepime	> 64	> 64	6.3	≤ 0.25 - > 64
Ceftriaxone	> 64	> 64	1.8	≤ 0.25 - > 64
Ciprofloxacin	4	> 16	13.4	≤ 0.06 - > 16
Imipenem	0.25	1	92.0	0.12 - > 32
Imipenem-relebactam	0.25	0.5	98.2	0.06 - 2
Piperacillin-tazobactam	8	> 512	50.0	2 - >512
Trimethoprim-sulfamethoxazole	> 8	> 8	13.4	≤ 0.12 - > 8
***Klebsiella aerogenes* (142)**				
Amikacin	≤ 1	2	100	≤ 1 - 8
Cefepime	≤ 0.25	0.5	97.9	≤ 0.25 - > 64
Ceftriaxone	≤ 0.25	32	69.0	≤ 0.25 - > 64
Ciprofloxacin	≤ 0.06	0.25	93.7	≤ 0.06 - 8
Imipenem	1	2	71.1	0.12 - > 32
Imipenem-relebactam	0.25	1	97.2	0.06 - 16
Piperacillin-tazobactam	4	64	67.6	≤ 1 - 512
Trimethoprim-sulfamethoxazole	≤ 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 = pip-tazo

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

Organism (no. tested) / Antimicrobial Agent	MIC_{50}	MIC_{90}	MIC (µg/mL) % S	Range
***Klebsiella oxytoca / Raoultella* spp. (359)**				
Amikacin	≤ 1	4	100	≤ 1 - 8
Cefepime	≤ 0.25	0.5	95.5	≤ 0.25 - > 64
Ceftriaxone	≤ 0.25	16	86.4	≤ 0.25 - > 64
Ciprofloxacin	≤ 0.06	≤ 0.06	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	87.7	≤ 1 - > 512
Trimethoprim-sulfamethoxazole	≤ 0.12	0.25	93.6	≤ 0.12 - > 8
***Serratia marcescens* (321)**				
Amikacin	2	4	100.0	≤ 1 - 16
Cefepime	≤ 0.25	0.5	99.1	≤ 0.25 - 16
Ceftriaxone	≤ 0.25	2	89.7	≤ 0.25 - > 64
Ciprofloxacin	≤ 0.06	1	84.4	≤ 0.06 - > 16
Imipenem	1	2	81.3	0.25 - 8
Imipenem-relebactam	1	2	73.5	0.25 - > 32
Piperacillin-tazobactam	2	8	94.1	≤ 1 - 128
Trimethoprim-sulfamethoxazole	0.25	1	97.5	≤ 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													**65**
Imipenem			1	9	16	31	7	1					
Imipenem-Relebactam			2	51	8	3	1						
Enterobacter cloacae													**546**
Imipenem			10	132	220	142	34	6	1			1	
Imipenem-Relebactam		2	47	352	126	12	5	1				1	
Escherichia coli													**3314**
Imipenem	2	13	813	2236	216	28	3	1		1		1	
Imipenem-Relebactam	2	50	1342	1774	130	11	2			1		1	
***Escherichia coli* ESBL**													**432**
Imipenem		3	96	298	23	9	1	1		1			
Imipenem-Relebactam		5	154	254	14	4				1			
***Escherichia coli* AmpC**													**106**
Imipenem		1	11	49	35	9						1	
Imipenem-Relebactam		2	30	61	11							1	
Klebsiella pneumoniae													**1241**
Imipenem		1	106	747	279	90	9	3	1	3	1	1	
Imipenem-Relebactam		3	144	712	280	93	9						
***Klebsiella pneumoniae* ESBL**													**112**
Imipenem			14	65	21	3	3	2		2	1	1	
Imipenem-Relebactam		1	21	66	20	2	2						
Klebsiella aerogenes													**142**
Imipenem			1	11	30	59	37	2				2	
Imipenem-Relebactam		1	16	66	41	14	2	1		1			
Klebsiella oxytoca /Raoultella spp.													**359**
Imipenem		1	14	254	77	12	1						
Imipenem-Relebactam	1		30	265	55	8							
Serratia marcescens													**321**
Imipenem				13	82	166	48	11	1				
Imipenem-Relebactam				8	70	158	78	5		1		1	

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

Organism (no. tested) / Antimicrobial Agent	MIC_{50}	MIC_{90}	MIC (µg/mL) % S	Range
***Pseudomonas aeruginosa* (1912)**				
Amikacin	4	16	92.4	≤ 1 - > 64
Cefepime	4	32	76.4	≤ 0.25 - > 64
Ciprofloxacin	0.25	4	72.0	≤ 0.06 - > 16
Colistin	1	2	98.3[a]	≤ 0.06 - > 16
Imipenem	2	32	60.1	≤ 0.03 - > 32
Imipenem-relebactam	0.5	2	91.4	≤ 0.03 - > 32
Piperacillin-tazobactam	8	256	72.4	≤ 1 - > 512
Tobramycin	≤ 0.5	2	93.9	≤ 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													**1912**
Imipenem	1		8	36	67	391	646	217	150	186	173	36	
Imipenem/relebactam	1	5	31	367	884	259	201	100	39	11	5	9	

Conclusions

1. Imipenem-relebactam was highly active (MIC_{90}, 0.25-2 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 imipenem-resistant *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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