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In Vitro Activity of Imipenem/Relebactam against Gram-Negative Pathogens from Patients with Bloodstream Infections in the United States and Canada – SMART 2018

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Introduction

Relebactam (REL) inhibits class A and C β-lactamases, including KPC, and was approved in the United States (US) combined with imipenem/cilastatin (IMI) for complicated urinary tract and intra-abdominal infections in patients with limited treatment options, and for hospital-acquired/ventilator-associated bacterial pneumonia. We evaluated the activity of IMI/REL against non-*Morganellaceae* Enterobacterales (NME) and *Pseudomonas aeruginosa* collected as part of the global Study for Monitoring Anti-microbial Resistance Trends (SMART) surveillance program from patients with bloodstream infections (BSI) in the US and Canada.

Methods

In 2018, 24 US and 8 Canadian hospitals each collected up to 50 consecutive aerobic or facultative gram-negative pathogens from patients with BSI as well as 50 isolates from intraabdominal, 100 from lower respiratory tract, and 50 from urinary tract infections. MICs were determined using CLSI broth microdilution and interpreted with 2020 CLSI breakpoints [1-3]. Multidrug-resistance (MDR) was defined as resistance to ≥3 of the following sentinel drugs: amikacin, aztreonam, cefepime, ceftazidime (NME only), levofloxacin, colistin, imipenem, and piperacillin / tazobactam. Fisher's exact test was used to determine statistical significance of differences in susceptibility rates between isolates from the US and Canada.

Figure 1. Species distribution (n, %) among collected gram-negative isolates from patients with BSI

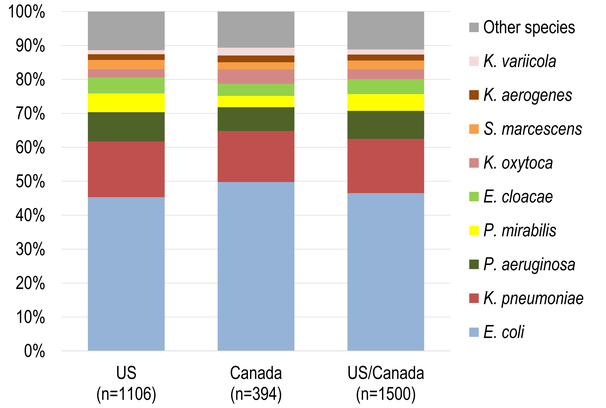


Table 1. Antimicrobial susceptibility of all NME combined, the most common NME species, *P. aeruginosa*, and nonsusceptible phenotypes, US and Canada combined

Species/ Phenotype[a]	n	% Susceptible									
		IMI/REL	IMI	MEM	FEP	CAZ	ATM	P/T	CZA	CIP	AMK
NME	1218	99.8	97.5	99.6	89.2	87.7	87.0	93.5	100	71.0	99.6
FEP-NS	131	100	95.4	97.0	0.0	10.7	4.6	75.6	100	9.9	97.0
CAZ-NS	150	100	95.3	96.7	22.0	0.0	5.3	66.7	100	22.7	97.3
IMI-NS[b]	30	90.0	0.0	86.7	80.0	76.7	73.3	76.7	100	66.7	100
P/T-NS	79	100	91.1	93.7	59.5	36.7	35.4	0.0	100	39.2	97.5
MDR	105	100	94.3	96.2	12.4	0.0	0.0	64.8	100	12.4	96.2
E. coli	697	100	99.9	99.9	86.5	86.5	86.1	96.0	100	62.1	99.4
K. pneumoniae	240	99.2	97.1	98.8	90.8	91.7	90.4	91.7	100	79.6	100
E. cloacae	66	100	95.5	98.5	87.9	74.2	75.8	80.3	100	78.8	100
P. aeruginosa	124	94.4	75.0	84.7	83.9	83.1	75.0	81.5	92.7	81.5	97.6
FEP-NS	20	70.0	55.0	55.0	0.0	10.0	20.0	10.0	55.0	40.0	85.0
CAZ-NS	21	71.4	52.4	57.1	14.3	0.0	28.6	4.8	57.1	52.4	85.7
IMI-NS	31	77.4	0.0	48.4	71.0	67.7	71.0	61.3	74.2	64.5	93.6
MEM-NS	19	63.2	15.8	0.0	52.6	52.6	47.4	47.4	57.9	42.1	89.5
P/T-NS	23	73.9	47.8	56.5	21.7	13.0	26.1	0.0	60.9	47.8	87.0

[a]Because of small sample sizes, results are not shown for MEM-NS Enterobacterales (n=5) and MDR *P. aeruginosa* (n=10).
[b]Among the 30 IMI-NS NME, 23 tested with an IMI MIC of 2 µg/mL (intermediate) and 21 were intrinsic AmpC producers against which meropenem typically shows higher activity than imipenem.
IMI, imipenem; REL, relebactam; MEM, meropenem; FEP, cefepime; CAZ, ceftazidime; ATM, aztreonam; P/T, piperacillin/tazobactam; CZA, ceftazidime/avibactam; CIP, ciprofloxacin; AMK, amikacin; NS, nonsusceptible; MDR, multidrug-resistant

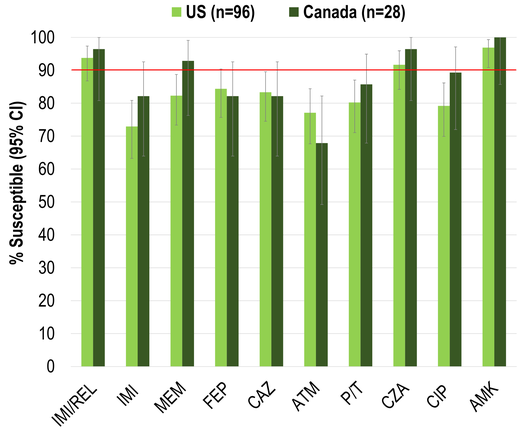
Results

Table 2. Comparing antimicrobial susceptibility of NME and *P. aeruginosa* from BSI to other infection sources, US and Canada combined

Species/ Source	n	% Susceptible									
		IMI/REL	IMI	MEM	FEP	CAZ	ATM	P/T	CZA	CIP	AMK
NME											
BSI	1218	99.8	97.5	99.6	89.2	87.7	87.0	93.5	100	71.0	99.6
IAI	840	99.2	97.4	98.6	90.0	85.4	84.8	87.9	99.6	75.1	99.4
LRTI	1107	97.1	92.5	98.3	89.3	83.0	82.5	86.5	99.9	77.1	99.3
UTI	1261	99.1	97.5	99.1	90.4	88.0	87.8	93.8	99.8	70.8	99.4
P. aeruginosa											
BSI	124	94.4	75.0	84.7	83.9	83.1	75.0	81.5	92.7	81.5	97.6
IAI	122	93.4	73.8	78.7	82.0	79.5	68.0	77.1	94.3	77.1	99.2
LRTI	802	91.8	63.7	70.1	73.8	74.6	62.0	68.2	94.0	67.1	94.4
UTI	109	93.6	70.6	84.4	83.5	83.5	70.6	78.0	94.5	71.6	99.1

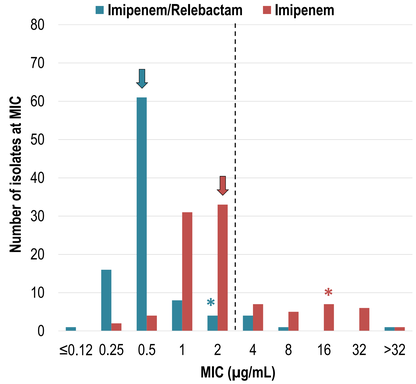
[a]The specimen source was not specified for an 19 NME and 2 isolates that are not included in this table
IMI, imipenem; REL, relebactam; MEM, meropenem; FEP, cefepime; CAZ, ceftazidime; ATM, aztreonam; P/T, piperacillin/tazobactam; CZA, ceftazidime/avibactam; CIP, ciprofloxacin; AMK, amikacin; BSI, bloodstream infection; IAI, intraabdominal infection; LRTI, lower respiratory tract infection; UTI, urinary tract infection.

Figure 2. Antimicrobial susceptibility of *P. aeruginosa* from BSI, stratified by country[a]



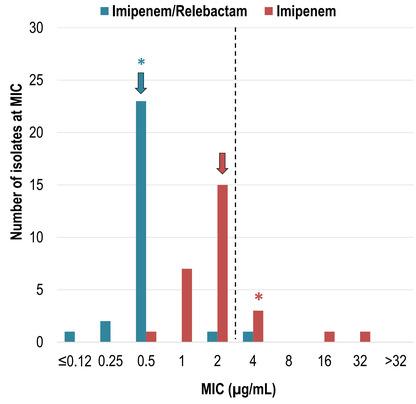
[a]None of the differences between isolates from US and Canada were statistically significant (p>0.05).
IMI, imipenem; REL, relebactam; MEM, meropenem; FEP, cefepime; CAZ, ceftazidime; ATM, aztreonam; P/T, piperacillin/tazobactam; CZA, ceftazidime/avibactam; CIP, ciprofloxacin; AMK, amikacin.

Figure 3. Distribution of IMI/REL and IMI MICs among *P. aeruginosa* collected from BSI in the US (n=96)[a]



[a]Dashed line represents the Susceptible breakpoint for imipenem and imipenem/relebactam; arrows denote the modal MICs for each drug; asterisks denote the MIC_{90} for each drug.

Figure 4. Distribution of IMI/REL and IMI MICs among *P. aeruginosa* collected from BSI in Canada (n=28)[a]



[a]Dashed line represents the Susceptible breakpoint for imipenem and imipenem/relebactam; arrows denote the modal MICs for each drug; asterisks denote the MIC_{90} for each drug.

Results Summary

- The species distribution among all collected BSI isolates was similar in the US and Canada, with the same 5 most prevalent species: *E. coli* (46% of isolates in both countries combined), *K. pneumoniae* (16%), *P. aeruginosa* (8%), *P. mirabilis* (5%), and *E. cloacae* (4%) (Figure 1).
- IMI/REL was active against 99.8% of NME isolates; only meropenem, ceftazidime/avibactam, and amikacin showed comparable activity (Table 1). Per 2020 CLSI guidelines, Enterobacterales and *P. aeruginosa* are no longer considered susceptible to colistin [2].
- IMI/REL maintained activity against 90-100% of NME isolates that were nonsusceptible (NS) to β-lactams or MDR (Table 1).
- Among *P. aeruginosa*, IMI/REL was active against 94.4% of isolates, 2-19 percentage points higher than all studied comparator β-lactams. IMI/REL maintained activity against 63-77% of *P. aeruginosa* isolates NS to β-lactams; susceptibility rates only exceeded by amikacin (Table 1).
- BSI isolates generally showed susceptibility rates similar to UTI isolates, similar or slightly higher than IAI isolates, and higher than LRTI isolates (Table 2). Only small differences between sources were seen for IMI/REL, ceftazidime/avibactam, and amikacin.
- When comparing BSI isolates collected in the US and Canada, susceptibility rates of NME to all tested agents were within 3 percentage points (data not shown). The differences were slightly larger for *P. aeruginosa*, but none were statistically significant (p>0.05) (Figure 2).
- The addition of relebactam lowered the IMI MIC_{90} for *P. aeruginosa* by 3 doubling dilutions among BSI isolates from US (IMI/REL MIC_{90} of 2 mg/L) and Canada (IMI/REL MIC_{90} of 0.5 mg/L) (Figure 3 and 4).

Conclusions

In the US and Canada, IMI/REL could provide an important treatment option for patients with BSI caused by resistant gram-negative organisms, including MDR NME and carbapenem-NS *P. aeruginosa*.

References:

1. Clinical and Laboratory Standards Institute. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standards – Eleventh Edition*. CLSI document M07-Ed11. 2018. CLSI, Wayne, PA.
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