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Epidemiology and Susceptibility to Imipenem/Relebactam of Gram-Negative Pathogens from Patients with Lower Respiratory Tract Infections – SMART United States 2017-2018

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Introduction

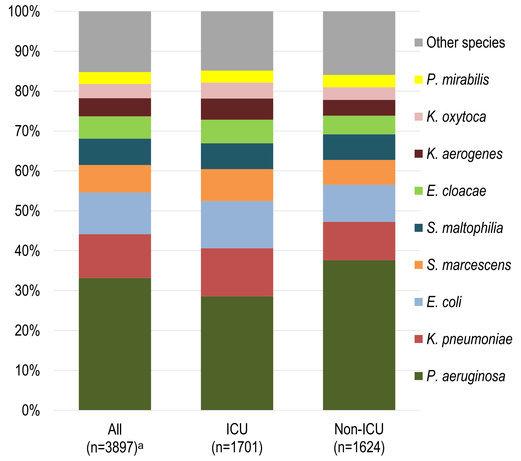
Relebactam (REL) inhibits class A and C β-lactamases and was approved in the United States (US) combined with imipenem/ cilastatin (IMI) for complicated urinary tract and intraabdominal infections in patients with limited treatment options, and for hospital-acquired / ventilator - associated bacterial pneumonia. Using isolates collected as part of the global Study for Monitoring Antimicrobial Resistance Trends (SMART) surveillance program in the US, we evaluated the activity of IMI/REL against gram-negative pathogens from patients with lower respiratory tract infections (LRTI), including a comparison of isolates from ICU and non-ICU wards.

Methods

In 2017-2018, 27 US hospitals each collected up to 100 consecutive aerobic or facultative gram-negative pathogens from LRTI patients per year. MICs were determined using CLSI broth microdilution and 2020 CLSI breakpoints [1-3]. Multidrug-resistance (MDR) was defined as resistance to ≥3 of the following sentinel drugs: amikacin, aztreonam, cefepime, ceftazidime (Enterobacterales only), levofloxacin, colistin, imipenem, and piperacillin/tazobactam.

Fisher's exact test was used to determine statistical significance of the difference in susceptibility rates between isolates from patients in ICU and non-ICU wards.

Figure 1. Species distribution among collected gram-negative isolates from patients with LRTI



[a]Includes isolates from patients in emergency rooms and isolates for which the patient's location was not specified.

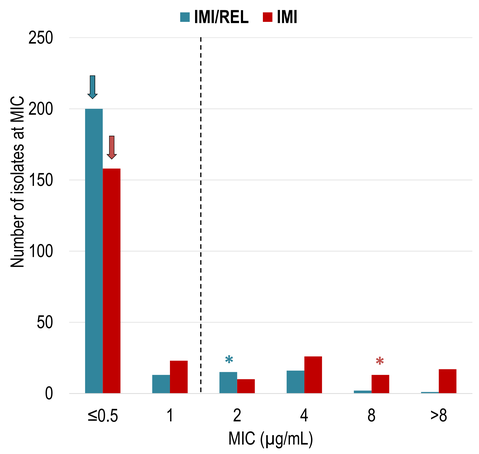
Table 1. Antimicrobial susceptibility of all Enterobacterales combined, the most common Enterobacterales species, *P. aeruginosa*, and Enterobacterales and *P. aeruginosa* combined

	% Susceptible[a]							
Species (n)	IMI/REL	IMI	FEP	CAZ	ATM	P/T	CIP	AMK
Enterobacterales, All (2055)	92.8	87.1	89.1	83.0	83.4	87.8	76.4	99.2
MDR (247)	86.2	73.3	27.5	8.9	10.1	45.7	27.9	95.1
K. pneumoniae (427)	99.5	95.8	83.6	81.0	82.7	86.4	79.4	99.3
E. coli (407)	100	99.5	81.8	81.6	80.6	90.7	56.3	98.8
S. marcescens (270)	84.4	69.6	94.8	93.0	91.1	94.8	71.5	98.9
E. cloacae (218)	99.5	96.3	84.4	70.2	71.1	78.0	90.8	100
K. aerogenes (177)	98.9	85.9	95.5	70.1	72.3	72.9	93.8	100
K. oxytoca (139)	100	98.6	97.8	97.1	89.2	85.6	93.5	100
P. aeruginosa (1292)	92.9	67.0	75.2	75.2	62.4	68.7	67.6	96.6
MDR (217)	69.1	19.4	8.3	15.7	0.9	4.6	21.2	87.6
Enterobacterales+*P. aeruginosa* (3347)	92.8	79.4	83.7	80.0	75.3	80.4	73.0	98.2
MDR (464)	78.2	48.1	18.5	12.1	5.8	26.5	24.8	91.6

[a]Susceptibility values ≥90% are shaded green. Results for colistin are not shown because Enterobacterales and *P. aeruginosa* are no longer considered susceptible to colistin per CLSI 2020 guidelines, as clinical and PK/PD data demonstrated limited clinical efficacy.
IMI, imipenem; REL, relebactam; FEP, cefepime; CAZ, ceftazidime; ATM, aztreonam; P/T, piperacillin/tazobactam; CIP, ciprofloxacin; AMK, amikacin.

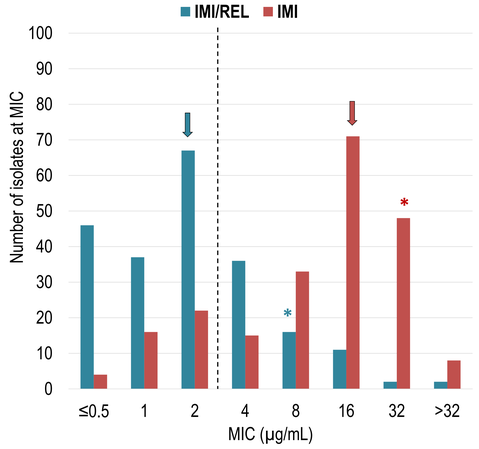
Results

Figure 2. Distribution of IMI/REL and IMI MICs among MDR Enterobacterales (n=247)[a]



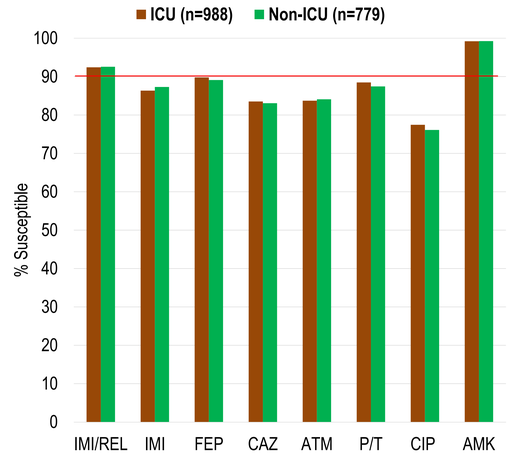
[a]Dashed line represents the Susceptible breakpoint for imipenem and imipenem/relebactam against Enterobacterales; arrows denote the modal MICs for each drug; asterisks denote the MIC_{90} for each drug.

Figure 3. Distribution of IMI/REL and IMI MICs among MDR *P. aeruginosa* (n=217)[a]



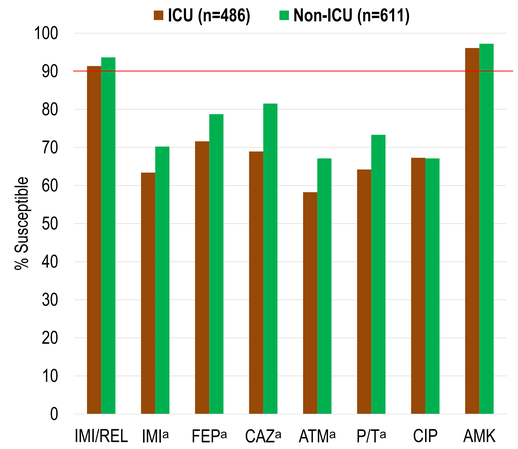
[a]Dashed line represents the Susceptible breakpoint for imipenem and imipenem/relebactam against *P. aeruginosa*; arrows denote the modal MICs for each drug; asterisks denote the MIC_{90} for each drug.

Figure 4. Antimicrobial susceptibility of all Enterobacterales combined from patients in ICU and non-ICU wards[a]



[a]None of the differences between ICU and non-ICU wards were statistically significant (p>0.05).
IMI, imipenem; REL, relebactam; FEP, cefepime; CAZ, ceftazidime; ATM, aztreonam; P/T, piperacillin/tazobactam; CIP, ciprofloxacin; AMK, amikacin.

Figure 5. Antimicrobial susceptibility of *P. aeruginosa* isolates from patients in ICU and non-ICU wards



[a]Statistically significant difference between ICU and non-ICU wards (p<0.05).
IMI, imipenem; REL, relebactam; FEP, cefepime; CAZ, ceftazidime; ATM, aztreonam; P/T, piperacillin/tazobactam; CIP, ciprofloxacin; AMK, amikacin.

Results Summary

- Among all collected gram-negative isolates from patients with LRTI, the most common species were *P. aeruginosa* (34%), *K. pneumoniae* (11%), and *E. coli* (10%) (Figure 1). There was a smaller proportion of *P. aeruginosa* and a larger proportion of Enterobacterales among ICU isolates than was seen in non-ICU isolates.
- IMI/REL inhibited 93% of *P. aeruginosa* and Enterobacterales, which included 176 isolates of *Morganellaceae* that are not expected to be susceptible to IMI or IMI/REL. *S. marcescens* also showed low susceptibility to IMI (69.6%), which improved upon addition of REL (84.4%) but was still reduced compared to the other common Enterobacterales species (>98%) (Table 1).
- The activity of IMI/REL against all collected Enterobacterales and *P. aeruginosa* combined was 9-18 percentage points higher than the comparator β-lactams. Of the tested comparators, only amikacin exceeded the activity of IMI/REL (Table 1).
- IMI/REL maintained activity against 86% of MDR Enterobacterales and 69% MDR *P. aeruginosa*, 13-77 percentage points higher than the tested comparator β-lactams (Table 1).
- MIC_{90} values for IMI/REL were two doubling dilutions lower than IMI among MDR Enterobacterales and *P. aeruginosa* (Figures 2 and 3).
- Only *P. aeruginosa* showed substantial differences in susceptibility between isolates from ICU and non-ICU wards, with significantly lower activity of most β-lactams against ICU isolates (p<0.05).Susceptibility to IMI/REL was >91% in both ward types (Figures 4 and 5).

Conclusions

Among LRTI isolates collected in the US, IMI/REL was active against 93% of all Enterobacterales and *P. aeruginosa* isolates and against 78% of isolates in the MDR subset. Although resistance rates have frequently been reported to be higher in ICU than non-ICU wards, this pattern was only seen in the current study among *P. aeruginosa* isolates. IMI/REL maintained activity against >90% of Enterobacterales and *P. aeruginosa* isolates from ICU patients. These *in vitro* data suggest that IMI/REL could provide an important treatment option for patients with LRTI in the US, including those in ICUs.

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.
2. Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial Susceptibility Testing – 30th ed*. CLSI Supplement M100. 2020. CLSI, Wayne, PA.
3. Clinical and Laboratory Standards Institute Subcommittee on AST Testing. January 2020 meeting minutes. https://clsi.org/meetings/ast-file-resources/

Funding for this research was provided by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ USA. The authors thank all the participants in the SMART program for their continuing contributions to its success.

https://bit.ly/322FDZ1

Presented at IDWeek 2020, Philadelphia, PA, October 21-25, 2020