In Vitro Activity of Imipenem-Relebactam (MK-7655) Against *P. aeruginosa* from United States ICU and Non-ICU Wards – SMART 2015-2016

S. Lob[1], M. Hackel[1], R. Badal[1], K. Young[2], M. Motyl[2], D. Sahm[1]

[1]IHMA, Inc., Schaumburg, IL, USA,
[2]MRL Merck & Co., Inc., Kenilworth, NJ, USA

IHMA, Inc.
2122 Palmer Drive
Schaumburg, IL 60173 USA
Phone: +1.847.303.5003
Fax: +1.847.303.5601
www.ihmainc.com

Revised Abstract

Background: Relebactam (MK-7655, REL) is a new β-lactamase inhibitor in development, which restores the in vitro activity of imipenem (IMI) against *Enterobacteriaceae* and *Pseudomonas aeruginosa* that carry class A or C β-lactamases. As antimicrobial resistance is especially high in ICUs, we compared the in vitro activity of IMI/REL against *P. aeruginosa* collected in ICU and non-ICU wards as part of the 2015-2016 SMART surveillance program in the United States.

Methods: 22 US hospitals each collected up to 100 consecutive, aerobic or facultative, gram-negative pathogens from intra-abdominal, 50 from urinary tract, and 100 from lower respiratory infections. MICs were determined for 1,461 *P. aeruginosa* from ICU and non-ICU wards using CLSI broth microdilution. The percent susceptible (S) was assessed using CLSI breakpoints, with IMI S breakpoint of 2 µg/mL applied to IMI/REL.

Results: *P. aeruginosa* represented 21% and 18% of all gram-negative isolates collected in ICU and non-ICU wards, respectively. The cumulative percent of isolates at each MIC is shown below.

	n	Drug	MIC (µg/mL)							
			≤0.5*	1	2	4	8	16	32	>32
P. aeruginosa										
ICU	498	IMI	14.9	56.6	67.7	73.1	80.5	**94.8**	99.4	100
		IMI/REL	69.7	80.1	**93.6**	97.4	99.4	99.8	100	
Non-ICU	963	IMI	20.5	63.7	74.1	79.8	87.0	**95.8**	99.1	100
		IMI/REL	77.2	86.3	**94.9**	97.40	99.1	99.3	99.5	100
***P. aeruginosa*, IMI-NS**										
ICU	161	IMI				16.8	39.8	83.9	**98.1**	100
		IMI/REL	9.9	40.4	80.1	**91.9**	98.1	99.4	100	0
Non-ICU	249	IMI				21.7	49.8	83.9	**96.4**	100
		IMI/REL	16.5	48.2	80.3	89.96	**96.4**	97.2	98	100

*Shaded area indicates susceptible by CLSI imipenem breakpoint; MIC_{90} bolded.
IMI, imipenem; REL, relebactam; NS, non-susceptible.

Among 498 *P. aeruginosa* from ICUs, 67.7% (337 isolates) were S to IMI; of the 161 non-susceptible (NS) isolates, 80.1% (129) were rendered S by the addition of REL, for an overall 93.6% S. Among 963 isolates from non-ICU wards, 74.1% (714) were S to IMI; of the 249 NS isolates, 80.3% (200) were rendered S by the addition of REL, for an overall 94.9% S.

Conclusions: Further development of imipenem-relebactam is warranted given relebactam's ability to restore the in vitro activity of imipenem against many current clinical isolates of *P. aeruginosa* NS to carbapenems and its potential as therapy for treating patients with antimicrobial-resistant gram-negative infections in both ICU and non-ICU wards.

INTRODUCTION

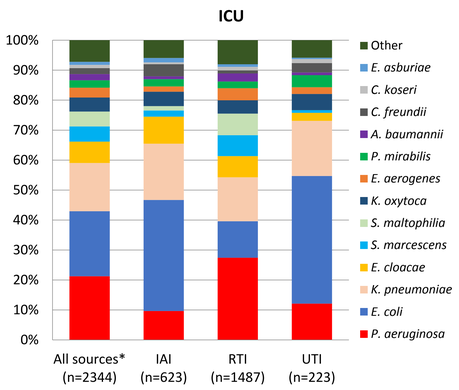
Relebactam (MK-7655, REL) is a new β-lactamase inhibitor in development, which restores the in vitro activity of imipenem (IMI) against *Enterobacteriaceae* and *Pseudomonas aeruginosa* that carry class A or C β-lactamases. REL restores the in vitro activity of imipenem against *P. aeruginosa* that are carbapenem-resistant due to impermeability arising from porin loss combined with AmpC expression. It potentiates the activity of imipenem by inhibiting the AmpC ubiquitous in *P. aeruginosa* that is known to be a weak hydrolyzer of carbapenems As antimicrobial resistance is especially high in ICUs, we compared the in vitro activity of IMI/REL against *P. aeruginosa* collected in ICU and non-ICU wards as part of the 2015-2016 SMART surveillance program in the US.

METHODS

22 US hospitals each collected up to 100 consecutive, aerobic or facultative, gram-negative pathogens from intra-abdominal infections (IAI), 50 from urinary tract infections (UTI), and 100 from lower respiratory infections (RTI). A total of 7,672 gram-negative bacilli were collected from ICU and non-ICU wards, of which 1,461 (19.0%) were *P. aeruginosa.* MICs were determined using CLSI broth microdilution [1,2]. REL was tested at a fixed concentration of 4 µg/mL in combination with IMI. The percent susceptible was assessed using CLSI breakpoints, with IMI susceptible breakpoint of 2 µg/mL applied to IMI/REL [2].

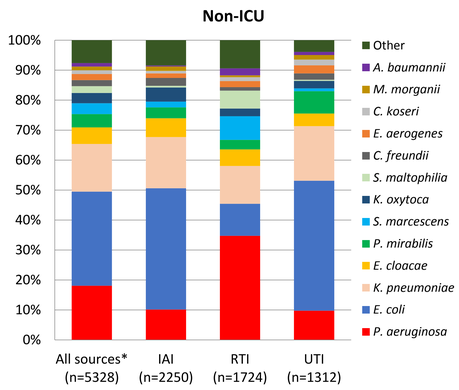
RESULTS

Figure 1. Distribution of gram-negative species collected in ICU wards*



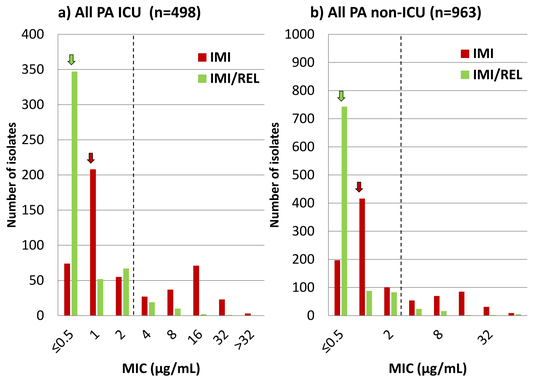
* Includes 11 isolates for which the infection source was not specified.
IAI, intra-abdominal infection; RTI, lower respiratory infection; UTI, urinary tract infection.

Figure 2. Distribution of gram-negative species collected in non-ICU wards*



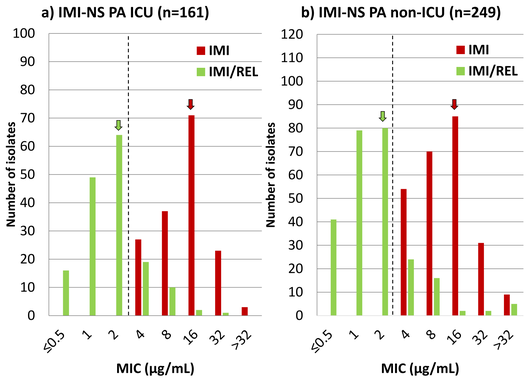
* Includes 42 isolates for which the infection source was not specified.
IAI, intra-abdominal infection; RTI, lower respiratory infection; UTI, urinary tract infection.

Figure 3a and b. IMI and IMI/REL MIC distribution for *P. aeruginosa* (PA) isolates from ICU and non-ICU wards (all sources combined)*



*Arrows indicate the mode of the respective MIC distributions.
Dashed line represents the CLSI susceptibility breakpoint of ≤2 µg/mL for imipenem.
IMI, imipenem; REL, relebactam; NS, non-susceptible.

Figure 4a and b. IMI and IMI/REL MIC distribution for IMI-NS *P. aeruginosa* (PA) isolates from ICU and non-ICU wards (all sources combined)*



*Arrows indicate the mode of the respective MIC distributions.
Dashed line represents the CLSI susceptibility breakpoint of ≤2 µg/mL for imipenem.
IMI, imipenem; REL, relebactam; NS, non-susceptible.

Table 1. Susceptibility of *P. aeruginosa* from ICU and non-ICU wards (all sources combined)

Organisms (n)/Drugs	% S	% I	% R	MIC_{50}	MIC_{90}
All *P. aeruginosa* from ICUs (n=498)					
Imipenem	**67.7**	**5.4**	**26.9**	**1**	**16**
Imipenem-Relebactam[a]	**93.6**	**3.8**	**2.6**	**0.5**	**2**
Amikacin	96.6	2.0	1.4	≤ 4	8
Aztreonam	60.6	14.1	25.3	8	> 16
Cefepime	72.1	14.9	13.1	4	32
Ceftazidime	74.9	6.2	18.9	4	> 32
Colistin	99.4	0.0	0.6	≤ 1	≤ 1
Levofloxacin	67.5	7.2	25.3	≤ 1	> 4
Piperacillin Tazobactam	67.7	15.3	17.1	8	> 64
All *P. aeruginosa* from non-ICU wards (n=963)					
Imipenem	**74.1**	**5.6**	**20.3**	**1**	**16**
Imipenem/Relebactam[a]	**94.9**	**2.5**	**2.6**	**0.5**	**2**
Amikacin	95.9	2.2	2.0	≤ 4	8
Aztreonam	65.1	12.6	22.3	8	> 16
Cefepime	76.4	11.3	12.3	4	32
Ceftazidime	79.1	4.2	16.7	4	> 32
Colistin	99.5	0.0	0.5	≤ 1	≤ 1
Levofloxacin	68.0	8.4	23.6	≤ 1	> 4
Piperacillin Tazobactam	72.9	9.6	17.6	8	> 64

[a] In the absence of breakpoints for imipenem-relebactam, CLSI breakpoints for imipenem were applied.
S, susceptible; I, intermediate; R, resistant.

Table 2. Susceptibility of IMI-NS *P. aeruginosa* from ICU and non-ICU wards (all sources combined)

Organisms (n)/Drugs	% S	% I	% R	MIC_{50}	MIC_{90}
IPM-NS *P. aeruginosa* from ICUs (n=161)					
Imipenem	**0.0**	**16.8**	**83.2**	**16**	**32**
Imipenem-Relebactam[a]	**80.1**	**11.8**	**8.1**	**2**	**4**
Amikacin	92.6	4.4	3.1	≤ 4	16
Aztreonam	32.3	17.4	50.3	> 16	> 16
Cefepime	46.6	23.6	29.8	16	> 32
Ceftazidime	54.0	12.4	33.5	8	> 32
Colistin	98.8	0.0	1.2	≤ 1	≤ 1
Levofloxacin	36.7	9.9	53.4	> 4	> 4
Piperacillin Tazobactam	41.6	25.5	32.9	32	> 64
IPM-NS *P. aeruginosa* from non-ICU wards (n=249)					
Imipenem	**0.0**	**21.7**	**78.3**	**16**	**32**
Imipenem/Relebactam[a]	**80.3**	**9.6**	**10.0**	**2**	**8**
Amikacin	89.6	4.4	6.0	≤ 4	32
Aztreonam	32.9	19.3	47.8	16	> 16
Cefepime	43.0	24.9	32.1	16	> 32
Ceftazidime	51.8	7.2	41.0	8	> 32
Colistin	98.4	0.0	1.6	≤ 1	≤ 1
Levofloxacin	34.5	13.7	51.8	> 4	> 4
Piperacillin Tazobactam	41.8	17.3	41.0	32	> 64

[a] In the absence of breakpoints for imipenem-relebactam, CLSI breakpoints for imipenem were applied.
S, susceptible; I, intermediate; R, resistant; IMI-NS, imipenem non-susceptible.

RESULTS SUMMARY

- Although *E. coli* was the most common gram-negative species overall, *P. aeruginosa* was a very close second in ICUs. Among RTI isolates, *P. aeruginosa* was the most common species in both ICU and non-ICU settings (Figures 1 and 2).
- Among the *P. aeruginosa* isolates from ICUs, the modal IMI MIC dropped from 1 to ≤0.5 µg/ml in the presence of REL (Figure 3a), MIC_{90} dropped from 16 to 2 µg/ml, and susceptibility increased from 67.7 to 93.6% (Table 1).
- Very similar results were seen in isolates from non-ICU wards (Figure 3b and Table 1).
- Among the IMI-NS *P. aeruginosa* isolates from both ICU and non-ICU wards, the modal IMI MIC dropped from 16 to 2 µg/ml in the presence of REL (Figures 4a and b), and ~80% of isolates were rendered susceptible in both patient locations (Table 2).
- All studied comparator agents except amikacin and colistin were active against <55% of IMI-NS isolates in either patient settings (Table 2).

CONCLUSIONS

Further development of imipenem-relebactam is warranted given relebactam's ability to restore the in vitro activity of imipenem against many current clinical isolates of *P. aeruginosa* non-susceptible to carbapenems and given its potential as therapy for treating patients with antimicrobial-resistant gram-negative infections in both ICU and non-ICU wards.

References and Acknowledgments:

1. Clinical and Laboratory Standards Institute. 2015. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standards – Tenth Edition. CLSI document M07-A10 (ISBN 1-56238-987-4). CLSI, Wayne, PA.
2. Clinical and Laboratory Standards Institute (CLSI), 2017. Performance Standards for Antimicrobial Susceptibility Testing – Twenty-Seventh Informational Supplement. CLSI Document M100S (ISBN 1-56238-923-8). CLSI, Wayne, PA.

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