909632

In Vitro Activity of Imipenem/Relebactam against *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* from Patients in ICUs in the Asia/Pacific region – SMART 2015-2018

S. Lob[1], M. Hackel[1], W. Chen[2], Y. Khoo[3], K. Balwani[4], K. Young[5], M. Motyl[5], D. Sahm[1]

[1]IHMA, Schaumburg, IL, USA
[2]MSD, Taipei, Taiwan
[3]MSD, Petaling Jaya, Malaysia
[4]MSD, Singapore
[5]Merck & Co., Inc., Kenilworth, NJ, USA

IHMA
2122 Palmer Drive
Schaumburg, IL 60173 USA
www.ihma.com

Introduction

Elevated antimicrobial resistance rates have been reported in ICUs, requiring new treatment options for patients in this setting. Relebactam (REL) is an inhibitor of class A and C β-lactamases approved in the USA in combination with imipenem/cilastatin (IMI) for complicated urinary tract and intraabdominal infections in patients with limited treatment options, and for hospital-acquired and ventilator-associated bacterial pneumonia. Using isolates collected in Asia/Pacific for the Study for Monitoring Antimicrobial Resistance Trends (SMART) surveillance program, we evaluated the activity of IMI/REL and comparators against *K. pneumoniae* and *P. aeruginosa* from ICU patients.

Methods

In 2015-2018, 52 clinical laboratories in Australia, Hong Kong, Malaysia, New Zealand, Philippines, Singapore, South Korea, Taiwan, Thailand, and Vietnam each collected up to 250 consecutive aerobic or facultatively anaerobic gram-negative pathogens per year. A total of 6925 isolates from patients in ICUs were studied. Susceptibility was determined using CLSI broth microdilution and CLSI breakpoints [1-3]. IMI-nonsusceptible Enterobacterales and *P. aeruginosa* were screened for β-lactamase genes (except isolates from Vietnam 2017 and one Vietnam site in 2018, Enterobacterales from one site in Taiwan in 2018, and a small number of other isolates, which were not available for molecular characterization and were not included in the denominators for the carbapenemase rate calculations) [4].

Figure 1. Species distribution among all gram-negative isolates (n=6925) collected from ICU patients

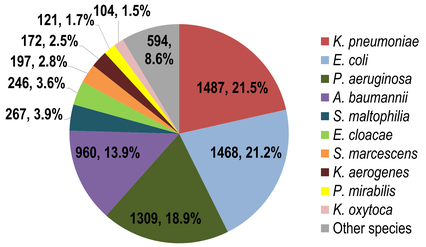


Table 1. Antimicrobial susceptibility of *K. pneumoniae*[a]

		% Susceptible[b]							
Country	n	IMI/REL	IMI	FEP	CAZ	ATM	P/T	CIP	AMK
Australia	173	97.1	96.0	92.5	92.5	91.9	93.6	90.8	98.8
Malaysia	123	95.9	91.9	61.8	60.2	60.2	75.6	68.3	99.2
New Zealand	49	98.0	98.0	85.7	87.8	85.7	93.9	83.7	98.0
Philippines	70	92.9	85.7	75.7	65.7	70.0	75.7	54.3	97.1
Singapore	70	100	97.1	90.0	91.4	88.6	87.1	81.4	98.6
South Korea	130	98.5	97.7	64.6	59.2	63.9	70.8	50.0	94.6
Taiwan	368	97.6	85.6	69.0	60.1	64.7	66.9	52.2	92.4
Thailand	195	79.0	78.0	45.1	42.6	44.1	56.4	39.5	97.4
Vietnam	293	76.5	67.9	43.3	44.4	43.7	51.9	33.5	80.2
Asia/Pacific	1487	90.8	85.0	64.4	61.2	62.6	69.2	55.0	92.9

[a]Showing individually only countries with ≥20 isolates; Hong Kong not shown (n=16).
[b]Susceptibility values ≥90% are shaded green. Results for colistin are not shown because Enterobacterales are no longer considered susceptible to colistin per 2020 CLSI guidelines.
IMI, imipenem; REL, relebactam; FEP, cefepime; CAZ, ceftazidime; ATM, aztreonam; P/T, piperacillin-tazobactam; CIP, ciprofloxacin; AMK, amikacin

Table 2. Antimicrobial susceptibility of *P. aeruginosa*[a]

		% Susceptible[b]							
Country	n	IMI/REL	IMI	FEP	CAZ	ATM	P/T	CIP	AMK
Australia	214	95.3	78.5	88.8	83.2	72.9	79.4	86.0	99.1
Malaysia	80	95.0	77.5	83.8	78.8	70.0	75.0	87.5	97.5
New Zealand	58	100	81.0	82.8	82.8	69.0	84.5	91.4	100
Philippines	50	82.0	64.0	74.0	72.0	60.0	76.0	54.0	92.0
Singapore	37	94.6	64.9	81.1	75.7	62.2	67.6	78.4	100
South Korea	102	83.3	56.9	61.8	60.8	42.2	46.1	52.9	95.1
Taiwan	398	96.2	75.4	77.6	76.6	62.1	67.3	76.9	98.5
Thailand	138	77.5	59.4	70.3	67.4	56.5	62.3	71.7	85.5
Vietnam	217	63.1	44.7	53.0	56.2	42.9	59.9	40.1	64.1
Asia/Pacific	1309	86.8	66.9	73.6	72.0	58.9	67.2	69.9	91.1

[a]Showing individually only countries with ≥20 isolates; Hong Kong not shown (n=15).
[b]Results for colistin are not shown because *P. aeruginosa* are no longer considered susceptible to colistin per 2020 CLSI guidelines.
IMI, imipenem; REL, relebactam; FEP, cefepime; CAZ, ceftazidime; ATM, aztreonam; P/T, piperacillin-tazobactam; CIP, ciprofloxacin; AMK, amikacin

Results

Figure 2. Distribution of infection sources among *K. pneumoniae* isolates collected from ICU patients (n=1487)

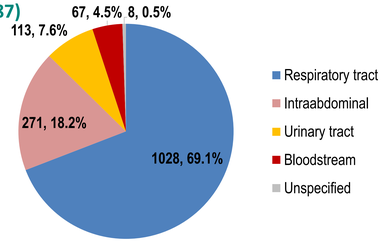


Figure 3. Distribution of infection sources among *P. aeruginosa* isolates from ICU patients (n=1309)

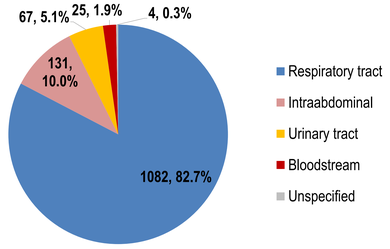
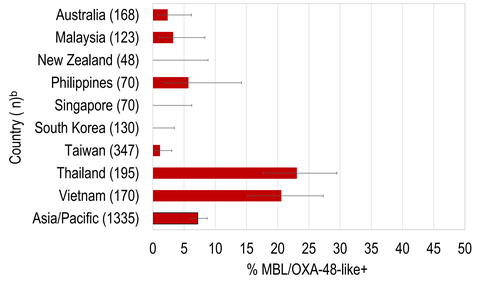
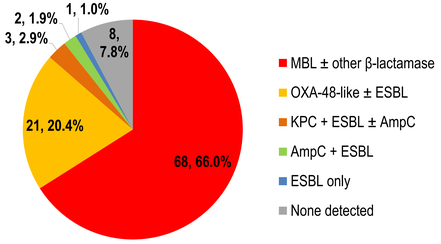


Figure 4. Proportion of *K. pneumoniae* isolates carrying metallo-β-lactamases (MBLs) and/or OXA-48-like carbapenemases[a]



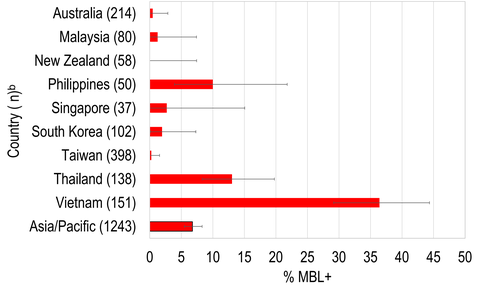
[a]Showing individually only countries with ≥20 isolates; Hong Kong not shown (n=14).
bOnly isolates available for molecular characterization were included in the denominators

Figure 5. Acquired β-lactamases detected in 103 molecularly characterized IMI/REL-nonsusceptible *K. pneumoniae* isolates (n, %)[a]



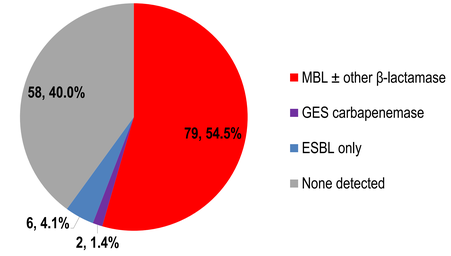
[a]Original spectrum β-lactamases (e.g., TEM-1, SHV-1) are not included in this analysis

Figure 6. Proportion of *P. aeruginosa* isolates carrying MBLs[a]



[a]Showing individually only countries with ≥20 isolates; Hong Kong not shown (n=15).
bOnly isolates available for molecular characterization were included in the denominators

Figure 7. Acquired β-lactamases detected in 145 molecularly characterized IMI/REL-nonsusceptible *P. aeruginosa* isolates (n, %)[a]



[a]Intrinsic AmpC β-lactamases common to *P. aeruginosa* are not included in this analysis

Results Summary

- Among all isolates collected from ICU patients, the 3 most common species collected were *K. pneumoniae*, *E. coli*, and *P. aeruginosa* (Figure 1).
- The most common source of the collected *K. pneumoniae* and *P. aeruginosa* isolates was lower respiratory tract infections (Figures 2 and 3).
- The proportion of IMI/REL-susceptible *K. pneumoniae* ranged from <80% in Thailand and Vietnam to >92% in 7 countries (Table 1). Of the tested comparators, only amikacin exceeded the activity of IMI/REL in some countries. For the region overall, the activity of the tested comparator β-lactams was 6-30 percentage points lower than IMI/REL (91% susceptible).
- Lower susceptibility to IMI/REL correlated with higher proportions of isolates carrying MBL and/or OXA-48-like carbapenemases (23% and 21% in Thailand and Vietnam, respectively), which REL does not inhibit (Figure 4).
- Overall in the region, 66% of molecularly characterized IMI/REL-nonsusceptible *K. pneumoniae* isolates carried MBL and 20% carried OXA-48-like carbapenemases (Figure 5).
- The proportion of IMI/REL-susceptible *P. aeruginosa* ranged from 63% in Vietnam and 78% in Thailand to >94% in 5 countries (Table 2), again with correspondingly higher MBL rates in Thailand (13%) and Vietnam (36%) than elsewhere (Figure 6). The regional susceptibility rates for the comparator β-lactams were 13-28 percentage points lower than for IMI/REL (87% susceptible).
- Among molecularly characterized IMI/REL-nonsusceptible *P. aeruginosa*, over half carried MBL (Figure 7).

Conclusions

IMI/REL was active against 91% of *K. pneumoniae* and 87% of *P. aeruginosa* from ICU patients in Asia/Pacific overall, with higher activity in countries with lower prevalence of MBL or OXA-48-like carbapenemases. IMI/REL provides a potential treatment option for ICU patients in Asia/Pacific with infections caused by *K. pneumoniae* and *P. aeruginosa*, which is especially important in light of the reduced activity of commonly used β-lactams against the studied ICU isolates.

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
4. Lob SH, Biedenbach DJ, Badal RE, Kazmierczak KM, Sahm DF. *Antimicrobial resistance and resistance mechanisms of Enterobacteriaceae in ICU and non-ICU wards in Europe and North America: SMART 2011–2013*. J Glob Antimicrob Resist 2015; 3: 190-7

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/34cT5x4

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