Activity of Key β-Lactam Agents against Gram-Negative Bacilli from ICU Patients with Lower Respiratory Tract Infections – SMART United States 2015-2017

S. Lob[1], K. Kazmierczak[1], D. Hoban[1], M. Hackel[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
www.ihma.com

INTRODUCTION

Relebactam (REL), formerly MK-7655, is an inhibitor of class A and C β-lactamases that is in clinical development in combination with imipenem (IMI). In this study, we evaluated the activity of IMI/REL against gram-negative bacilli and resistant phenotypes collected in the United States (US) as part of the Study for Monitoring Antimicrobial Resistance Trends (SMART) surveillance program from patients with lower respiratory tract infections (RTI) in ICUs, where antimicrobial resistance is typically higher than in non-ICU wards.

METHODS

In 2015-2017, 26 hospitals in the US each collected up to 100 consecutive aerobic or facultatively anaerobic gram-negative pathogens from RTI per year. Antimicrobial susceptibility was determined for 1,298 non-Proteeae *Enterobacteriaceae* (NPE) and 638 *P. aeruginosa* isolates collected in ICUs, using CLSI broth microdilution and breakpoints; for comparison purposes, the IMI susceptible breakpoint was applied to IMI/REL [1,2]. Proteeae were excluded due to intrinsic non-susceptibility to IMI by a mechanism independent of carbapenemase production [2,3]. Susceptibility was calculated for the four United States census regions and overall [4].

RESULTS

Figure 1. Proportion (%) of NPE and *P. aeruginosa* among all collected gram-negative isolates from ICU patients with RTI

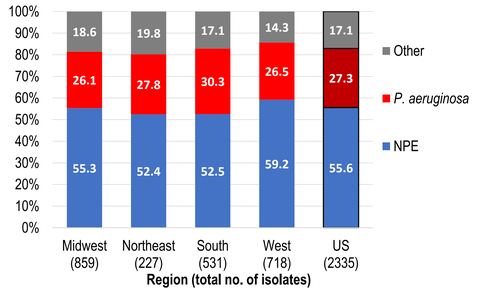


Figure 2. Species distribution (%) among NPE

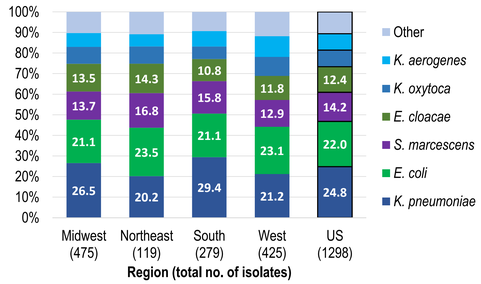
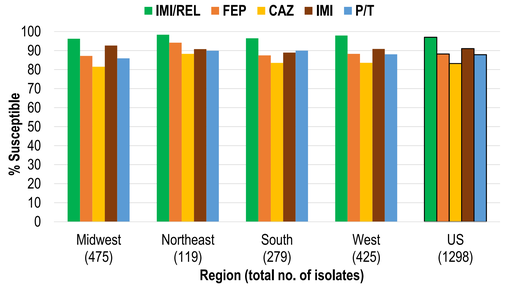
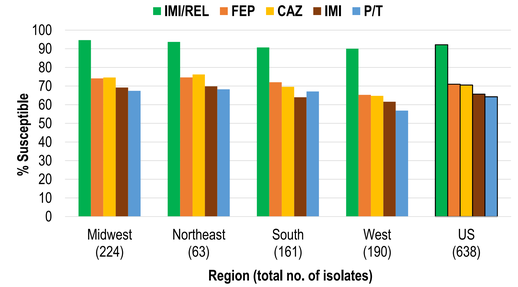


Figure 3. Activity of IMI/REL and comparators against NPE, by census region and overall[a]



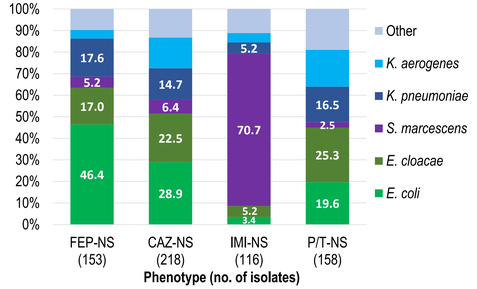
[a] IMI/REL, imipenem-relebactam; FEP, cefepime; CAZ, ceftazidime; IMI, imipenem; P/T, piperacillin-tazobactam

Figure 4. Activity of IMI/REL and comparators against *P. aeruginosa*, by census region and overall[a]



[a] IMI/REL, imipenem-relebactam; FEP, cefepime; CAZ, ceftazidime; IMI, imipenem; P/T, piperacillin-tazobactam

Figure 5. Species distribution (%) among IMI-NS, FEP-NS, CAZ-NS, and P/T-NS NPE, United States[a]



[a] FEP, cefepime; CAZ, ceftazidime; IMI, imipenem; P/T, piperacillin-tazobactam; NS, nonsusceptible

Figure 6. Species distribution (%) among IMI-NS NPE, by census region

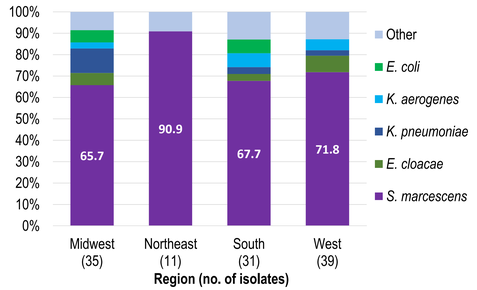


Table 1. Activity of IMI/REL against NPE and nonsusceptible phenotypes, by census region and overall[a]

	% IMI/REL-susceptible (total n)				
Organism/phenotype	Midwest	Northeast	South	West	US
NPE, All	**96.2 (475)**	**98.3 (119)**	**96.4 (279)**	**97.9 (425)**	**97.0 (1298)**
Cefepime-NS	98.4 (61)	7 of 7[b]	97.1 (35)	98.0 (50)	98.0 (153)
Ceftazidime-NS	98.9 (88)	100 (14)	97.8 (46)	98.6 (70)	98.6 (218)
Imipenem-NS	48.6[c] (35)	81.8 (11)	71.0 (31)	76.9 (39)	67.2 (116)
Piperacillin-tazobactam-NS	98.5 (67)	100 (12)	96.4 (28)	98.0 (51)	98.1 (158)

[a] IMI/REL, imipenem-relebactam; NS, nonsusceptible
[b] % susceptible not shown if n<10
[c] 18 of the 35 IMI-NS isolates were IMI/REL-NS; 16 of these were *S. marcescens*, of which 6 came from just one of 12 sites in the region. The IMI/REL-NS *S. marcescens* isolates showed IMI/REL MICs of 2 µg/mL (n=10), 4 µg/mL (n=5), and 8 µg/mL (n=1)

Table 2. Activity of IMI/REL against *P. aeruginosa* and nonsusceptible phenotypes, by census region and overall[a]

	% IMI/REL-susceptible (total n)				
Organism/phenotype	Midwest	Northeast	South	West	US
***P. aeruginosa*, All**	**94.6 (224)**	**93.7 (63)**	**90.7 (161)**	**90.0 (190)**	**92.2 (638)**
Cefepime-NS	82.8 (58)	81.3 (16)	73.3 (45)	75.8 (66)	77.8 (185)
Ceftazidime-NS	87.7 (57)	86.7 (15)	79.6 (49)	79.1 (67)	82.4 (188)
Imipenem-NS	82.6 (69)	79.0 (19)	74.1 (58)	74.0 (73)	77.2 (219)
Piperacillin-tazobactam-NS	83.6 (73)	85.0 (20)	77.4 (53)	78.1 (82)	80.3 (228)

[a] IMI/REL, imipenem-relebactam; NS, nonsusceptible

RESULTS SUMMARY

- The proportion of NPE and *P. aeruginosa* among all collected gram-negative isolates as well as the species distribution among the NPE were similar across census regions (Figures 1 and 2)
- Susceptibility of NPE to ceftazidime and cefepime was lowest in the Midwest and highest in the Northeast. Activity of IMI/REL was >96% in all regions, 4 to 15 percentage points higher than the other tested β-lactams (Figure 3)
- Susceptibility of *P. aeruginosa* to the 4 β-lactam comparators was lowest in the West region and highest in the Midwest and Northeast. Activity of IMI/REL was ≥90% in all regions, 19 to 33 percentage points higher than the comparators (Figure 4)
- IMI/REL remained active against ≥98% of NPE isolates with resistant phenotypes, except the IMI-NS subset (67% susceptible) (Table 1) that was composed mainly of *S. marcescens* (Figure 5). The upper end of the IMI MIC distribution observed for the population of wild-type *S. marcescens* is one dilution above the CLSI susceptible breakpoint of 1 µg/mL [5]. Against IMI-NS *S. marcescens* (most of which have an IMI MIC of 2 or 4 µg/mL), IMI MICs typically decrease only 1-2 dilutions or remain unchanged upon addition of REL (data not shown).
- IMI/REL activity was lowest against IMI-NS NPE isolates collected in the Midwest (Table 1), although the proportion of *S. marcescens* among IMI-NS isolates was not higher than in other regions (65.7%, Figure 6). However, sample sizes were small across regions, and over one-third of the IMI/REL-NS isolates were collected from just one of 12 sites in the Midwest.
- IMI/REL remained active against 77-82% of *P. aeruginosa* isolates with resistant phenotypes, including 77.2% of imipenem-NS isolates (Table 2).

CONCLUSIONS

IMI/REL maintained activity >96% in all regions against NPE and ≥90% against *P. aeruginosa*, including potent activity against all subsets of β-lactam-NS isolates, except the imipenem-NS subset of NPE. IMI/REL may provide a valuable therapeutic option for the treatment of ICU patients with RTI caused by organisms resistant to commonly used β-lactams.

References and Acknowledgments:

1. Clinical and Laboratory Standards Institute. 2018. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically*; Approved Standards – Eleventh Edition. CLSI document M07-Ed11. CLSI, 940 West Valley Road, Wayne, PA.
2. Clinical and Laboratory Standards Institute. 2018. *Performance Standards for Antimicrobial Susceptibility Testing* – 28th ed. CLSI Supplement M100. CLSI, 940 West Valley Road, Wayne, PA.
3. Neuwirth C, Siébor E, Duez JM, Péchinot A, Kazmierczak A. 1995. Imipenem resistance in clinical isolates of *Proteus mirabilis* associated with alterations in penicillin-binding proteins. J Antimicrob Chemother 36:335-342.
4. U.S. Census Bureau. *Census Regions and Divisions of the United States*. https://www2.census.gov/geo/pdfs/maps-data/maps/reference/us_regdiv.pdf
5. EUCAST. *EUCAST MIC and zone diameter distributions and ECOFFs*. https://mic.eucast.org/Eucast2/SearchController/search.jsp?action=performSearch&BeginIndex=0&Micdif=mic&NumberIndex=50&Antib=-1&Specium=265

Funding for this research was provided by 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/2LKDA8i