In Vitro Activity of Imipenem/Relebactam against Class C β-lactamase (*ampC*)-Positive Enterobacterales + ESBL in the Asia/Pacific Region: SMART 2018-2020

S. Lob[1], M. Estabrook[1], W. Chen[2], F. Siddiqui[2], A. DeRyke[2], K. Young[2], M. Motyl[2], D. Sahm[1]

[1]IHMA, Schaumburg, IL, USA
[2]MSD, Taipei, Taiwan
[3]Merck & Co., Inc., Rahway, NJ, USA

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

Introduction

Imipenem/relebactam (IMR) is a combination of imipenem/cilastatin (IMI) with the β-lactamase inhibitor relebactam, an inhibitor of class A and C β-lactamases. We evaluated the activity of IMR and comparators against AmpC- and extended-spectrum β-lactamase (ESBL)-producing *E. coli* and *K. pneumoniae* as well as against isolates of intrinsic AmpC-producing Enterobacterales species that were collected in 9 countries in Asia/Pacific as part of the Study for Monitoring Antimicrobial Resistance Trends (SMART) global surveillance program.

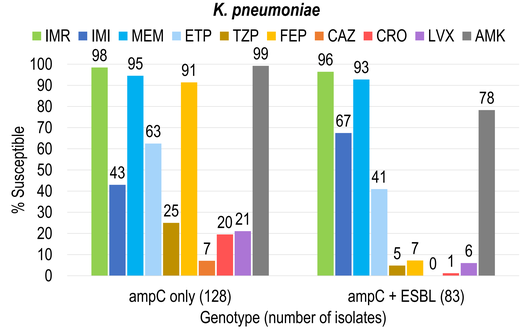
Methods

In 2018-2020, 48 clinical laboratories in Australia, Hong Kong, Malaysia, New Zealand, Philippines, South Korea, Taiwan, Thailand, and Vietnam each collected up to 250 consecutive, aerobic or facultative, gram-negative pathogens per year from patients with bloodstream, intraabdominal, lower respiratory tract, and urinary tract infections. MICs were determined using CLSI broth microdilution and interpreted with 2022 CLSI breakpoints [1, 2]. *Morganellaceae* are intrinsically less susceptible to imipenem by a mechanism independent of β-lactamase production, with relebactam not expected to improve the activity of IMI. For this reason, no CLSI breakpoint is available for IMR against these isolates and only non-*Morganellaceae* species among the Enterobacterales were analyzed for this report. *Enterobacter cloacae* complex was defined as isolates of *E. cloacae*, *E. asburiae*, *E. hormaechei*, *E. kobei*, *E. ludwigii*, and isolates assigned to *E. cloacae* complex based on MALDI-TOF score.

Isolates that were ertapenem- (2018 only), IMI-, IMR-, or ceftolozane/tazobactam-nonsusceptible were screened by PCR and Sanger sequencing for the following β-lactamase genes [3]. MBLs (IMP, VIM, NDM, GIM, SPM), serine carbapenemases (KPC, GES, OXA-48-like), ESBLs (SHV, TEM, CTX-M, VEB, PER, GES), and acquired *ampC* β-lactamases (ACC, ACT, CMY, DHA, FOX, MIR, MOX).

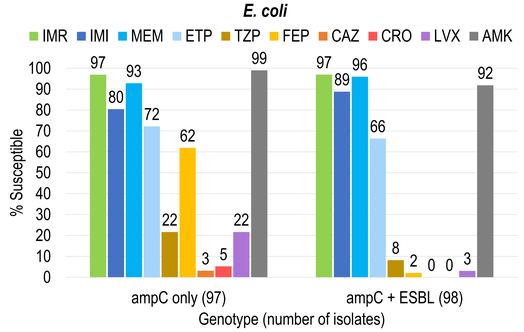
Results

Figure 1. Susceptibility of *K. pneumoniae* isolates carrying *ampC* only and *ampC* + ESBL



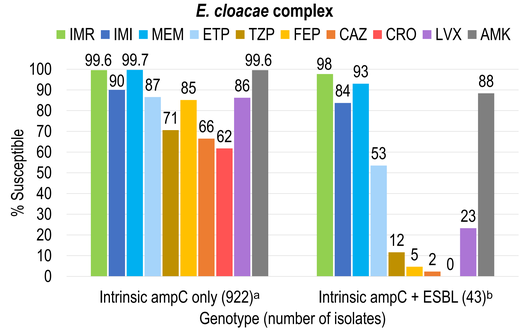
IMR, imipenem/relebactam; IMI, imipenem; MEM, meropenem; ETP, ertapenem; TZP, piperacillin/tazobactam; FEP, cefepime; CAZ, ceftazidime; CRO, ceftriaxone; LVX, levofloxacin; AMK, amikacin.

Figure 2. Susceptibility of *E. coli* isolates carrying *ampC* only and *ampC* + ESBL



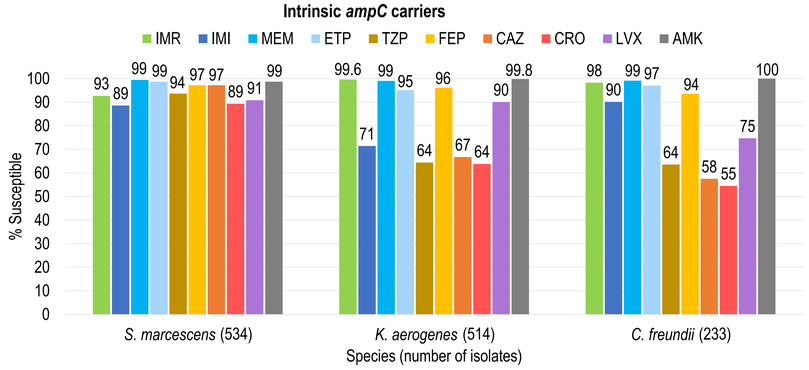
IMR, imipenem/relebactam; IMI, imipenem; MEM, meropenem; ETP, ertapenem; TZP, piperacillin/tazobactam; FEP, cefepime; CAZ, ceftazidime; CRO, ceftriaxone; LVX, levofloxacin; AMK, amikacin.

Figure 3. Susceptibility of *E. cloacae* complex isolates carrying intrinsic *ampC* only and intrinsic *ampC* + ESBL



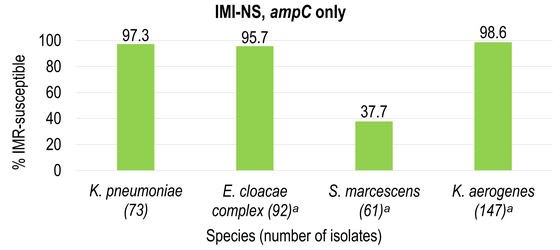
[a] Includes all collected isolates except those that were molecularly characterized and carried any acquired β-lactamases.
[b] Includes molecularly characterized isolates that carried only ESBL.
IMR, imipenem/relebactam; IMI, imipenem; MEM, meropenem; ETP, ertapenem; TZP, piperacillin/tazobactam; FEP, cefepime; CAZ, ceftazidime; CRO, ceftriaxone; LVX, levofloxacin; AMK, amikacin.

Figure 4. Susceptibility of isolates with no detected acquired β-lactamases of species that carry intrinsic *ampC* [a]



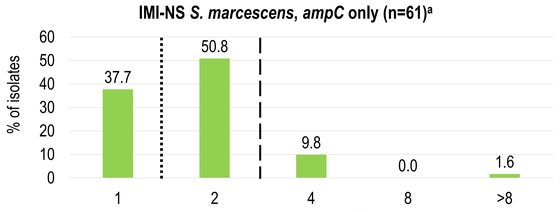
[a] Includes all collected isolates except those that were molecularly characterized and carried any detected acquired β-lactamase.
IMR, imipenem/relebactam; IMI, imipenem; MEM, meropenem; ETP, ertapenem; TZP, piperacillin/tazobactam; FEP, cefepime; CAZ, ceftazidime; CRO, ceftriaxone; LVX, levofloxacin; AMK, amikacin.

Figure 5. IMR-susceptibility of IMI-NS isolates that carried only *ampC*



[a] Includes all IMI-NS isolates except those that were molecularly characterized and carried any acquired β-lactamase.
IMR, imipenem/relebactam; IMI, imipenem; NS, nonsusceptible.

Figure 6. MIC distribution among IMI-NS *S. marcescens* isolates that carried only intrinsic *ampC*



[a] Includes all IMI-NS isolates except those that were molecularly characterized and carried any acquired β-lactamase.
Dotted line represents the 2022 CLSI susceptible breakpoint and dashed line the EUCAST susceptible breakpoint for IMR.

Results Summary

- IMR maintained activity against ≥96% *K. pneumoniae* and *E. coli* that carried *ampC* with or without ESBL, higher than any tested β-lactam comparator, including meropenem (Figures 1 and 2). The addition of relebactam increased the susceptibility to IMI alone by 8-55 percentage points.
- IMR maintained activity against >97% of isolates of intrinsic *ampC* carriers in which no additional β-lactamases or only ESBLs were identified, except against *S. marcescens* (92.7%) (Figures 3 and 4). The addition of relebactam yielded the largest increase in susceptibility to IMI alone among *K. aerogenes* (28 percentage points).
- Among IMI-NS isolates, relebactam restored susceptibility to 97.3% of *ampC*-positive isolates of *K. pneumoniae* and >95% of isolates of *E. cloacae* complex and *K. aerogenes* with no detected acquired β-lactamases, while this proportion was 37.7% among *S. marcescens* using CLSI breakpoints (Figure 5).
- Of the IMI-NS *S. marcescens* isolates, 50.8% tested with an IMR MIC of 2 μg/mL, which would be susceptible according to EUCAST guidelines [4], resulting in overall susceptibility rate of 88.5% using EUCAST breakpoints (Figure 6).

Conclusions

Imipenem/relebactam showed strong activity against clinical Enterobacterales isolates collected in the Asia/Pacific region that carried either acquired or intrinsic *ampC* with or without ESBL.

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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3. 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.
4. European Committee on Antimicrobial Susceptibility Testing. *Breakpoint tables for interpretation of MICs and zone diameters*. Version 12.0, 2022. http://www.eucast.org.

https://bit.ly/3R0hslR

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