Activity of Imipenem/Relebactam and Comparators Against Gram-Negative MDR and DTR Pathogens from Patients with Respiratory and Bloodstream Infections – SMART United States 2018-2020

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Introduction

Gram-negative pathogens with multidrug resistance (MDR) or difficult-to-treat resistance (DTR) are increasingly common, resulting in limited treatment options. These resistant pathogens are often isolated from the respiratory tract or bloodstream and can result in significant patient morbidity and mortality. Imipenem/ relebactam is a combination of imipenem with relebactam, a β-lactamase inhibitor of class A and C β-lactamases. We evaluated the activity of imipenem/relebactam and comparators against gram-negative MDR and DTR isolates that were collected from patients with lower respiratory tract (RTI) or bloodstream infections (BSI) in the United States (US).

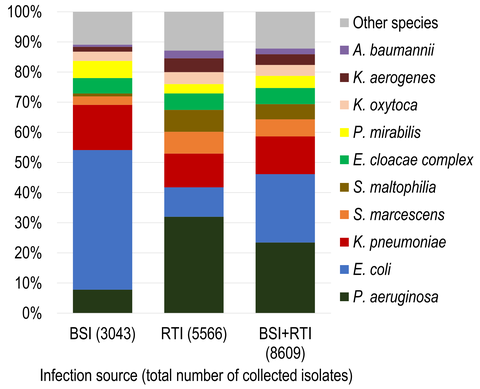
Methods

In 2018-2020, 24 clinical labs participated in the Study for Monitoring Antimicrobial Resistance Trends (SMART) global surveillance program in the US, and each collected up to 100 consecutive aerobic or facultative gram-negative pathogens per year from patients with RTI and 50 from BSI. MICs were determined using CLSI broth microdilution and interpreted with CLSI 2022 breakpoints [1, 2]. *Morganellaceae* (*Proteus*, *Providencia*, and *Morganella* spp.) are intrinsically less susceptible to imipenem by a mechanism independent of β-lactamase production, with relebactam not expected to improve the activity of imipenem. For this reason, no CLSI breakpoint is available for imipenem/relebactam against these isolates and only non-*Morganellaceae* Enterobacterales (NME) species were analyzed for this report.

Multidrug-resistant (MDR) phenotype was defined as resistant (R) to ≥3 sentinel drugs: amikacin, aztreonam, cefepime, ceftazidime (Enterobacterales only), colistin, imipenem, levofloxacin, and piperacillin/tazobactam. Difficult-to-treat resistance (DTR) was defined as nonsusceptibility [I or R] to all tested β-lactams excluding imipenem/relebactam and ceftolozane/tazobactam (aztreonam, cefepime, ceftazidime, cefoxitin, ceftriaxone, ertapenem [latter three for Enterobacterales only], imipenem, meropenem, piperacillin/ tazobactam) and fluoroquinolones (ciprofloxacin [tested in 2018 only], levofloxacin).

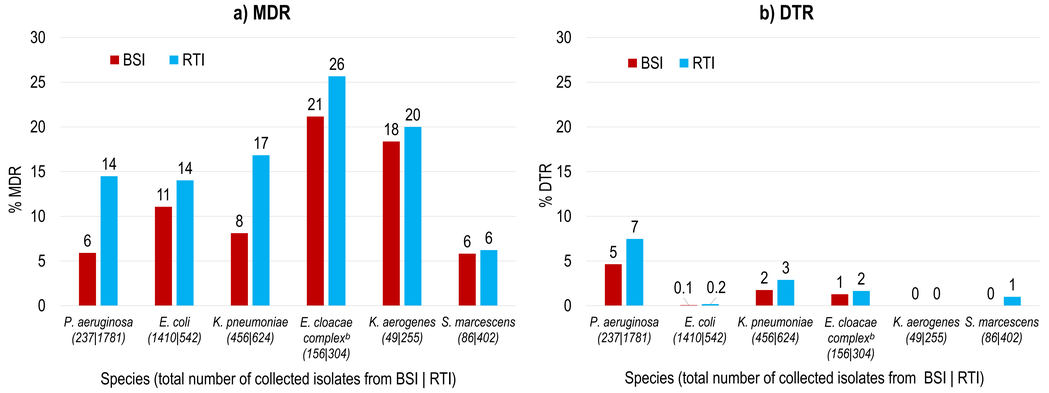
Results

Figure 1. Species distribution among all collected gram-negative pathogens



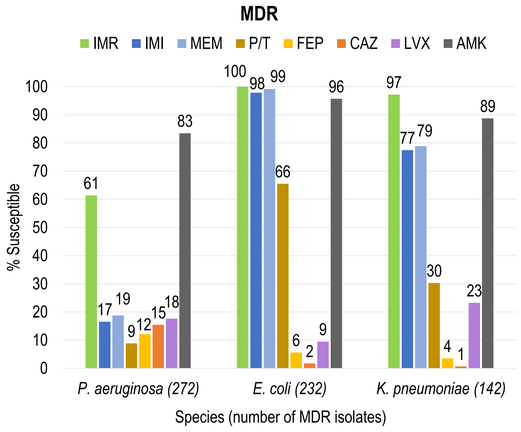
BSI, bloodstream infection; RTI, lower respiratory tract infection.

Figure 2 a and b. Proportion of a) MDR and b) DTR isolates among selected gram-negative species[a], stratified by infection source



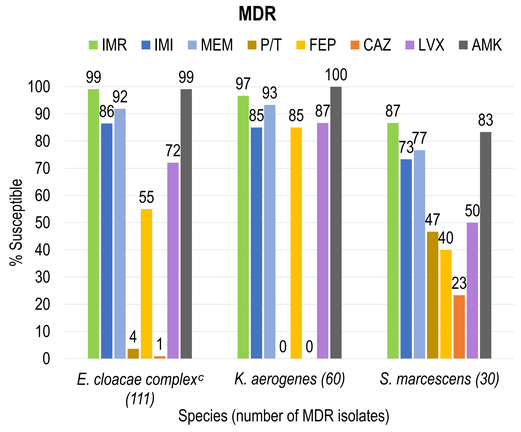
[a] Only showing non-*Morganellaceae* Enterobacterales species with at least 30 MDR isolates.
[b] *E. cloacae* complex is defined as isolates of *Enterobacter cloacae*, *E. asburiae*, *E. hormaechei*, *E. kobei*, *E. ludwigii*, and isolates assigned to *E. cloacae* complex based on MALDI-TOF score.
BSI, bloodstream infection; RTI, lower respiratory tract infection.

Figure 3. Susceptibility of MDR isolates of *P. aeruginosa*, *E. coli*, and *K. pneumoniae*, combining isolates collected from patients with BSI and RTI



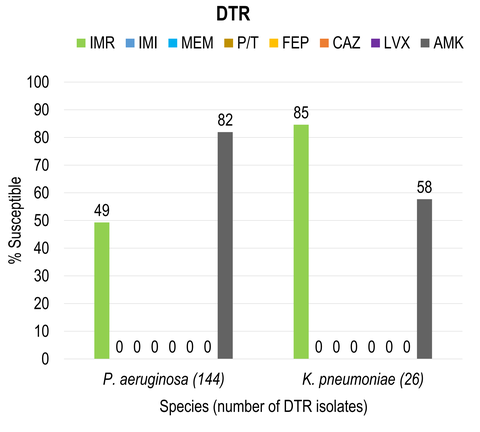
IMR, imipenem/relebactam; IMI, imipenem; MEM, meropenem; TZP, piperacillin/tazobactam; FEP, cefepime; CAZ, ceftazidime; LVX, levofloxacin; AMK, amikacin.

Figure 4. Susceptibility of MDR isolates of *E. cloacae* complex, *K. aerogenes*, and *S. marcescens*, combining isolates collected from patients with BSI and RTI



[a] *E. cloacae* complex is 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.
IMR, imipenem/relebactam; IMI, imipenem; MEM, meropenem; TZP, piperacillin/tazobactam; FEP, cefepime; CAZ, ceftazidime; LVX, levofloxacin; AMK, amikacin.

Figure 5. Susceptibility of DTR isolates of *P. aeruginosa* and *K. pneumoniae*, combining isolates collected from patients with BSI and RTI



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

Results Summary

- The most commonly collected species among RTI isolates and overall was *P. aeruginosa*. Of the collected non-*Morganellaceae* Enterobacterales, *E. coli* (the most common species among BSI isolates), *K. pneumoniae*, *S. marcescens*, and *E. cloacae* complex were most frequently collected (Figure 1).
- MDR prevalence was highest among isolates of *E. cloacae* complex and *K. aerogenes* (≥18%), with higher rates for RTI than BSI isolates (Figure 2a).
- DTR isolates were rare in the US, with only 5-7% among *P. aeruginosa* and 2-3% among *K. pneumoniae* meeting the DTR definition (Figure 2b). Again, rates were higher among RTI isolates.
- Combining isolates from BSI and RTI to increase sample sizes, imipenem/relebactam was active against 61% of MDR *P. aeruginosa*, 43-53 percentage points higher than the studied comparator β-lactams, and against 87-100% of MDR isolates of non-*Morganellaceae* Enterobacterales species, 18-96 percentage points higher than the studied comparator β-lactams (Figures 3 and 4).
- Imipenem/relebactam remained active against 49% of DTR *P. aeruginosa*, which were nonsusceptible to all studied β-lactams and fluoroquinolones, as well as against 85% of DTR *K. pneumoniae* (Figure 5).

Conclusions

Based on these *in vitro* data, imipenem/relebactam represents a promising treatment option in the United States for patients with BSI or RTI caused by MDR and DTR pathogens that pose substantial treatment challenges.

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 – 32nd ed. CLSI Supplement M100. 2022. CLSI, Wayne, PA.

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