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Antimicrobial Susceptibility Studies

Activity of imipenem-relebactam against multidrug-resistant *Pseudomonas aeruginosa* from the United States — SMART 2015–2017☆

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ABSTRACT

A total of 2732 isolates of *Pseudomonas aeruginosa* collected at 26 United States clinical laboratories in 2015–2017 were tested for susceptibility to imipenem-relebactam. Imipenem-relebactam MICs were interpreted using 2018 CLSI M100 imipenem breakpoints for *P. aeruginosa*. A total of 93.9% of *P. aeruginosa* isolates were susceptible to imipenem-relebactam. Among MDR isolates ($n = 750$), susceptibility to imipenem-relebactam was 79.7%, 46–73 percentage points higher than to other β-lactams tested. Relebactam restored imipenem susceptibility to 78.3% of imipenem-nonsusceptible isolates ($n = 766$) and to 69.6% of imipenem-nonsusceptible isolates with MDR phenotypes ($n = 500$).

One approach to the development of new antimicrobial agents with activity against Gram-negative pathogens involves identifying new β-lactamase inhibitors to be used in combination with established β-lactams. Relebactam is a novel diazabicyclooctane, non–β-lactam, β-lactamase inhibitor of Ambler class A β-lactamases, including extended-spectrum β-lactamases (ESBLs) and *Klebsiella pneumoniae* carbapenemases (KPCs), and chromosomal and plasmid-borne AmpC cephalosporinases, including *Pseudomonas*-derived cehalosporinase (PDC), the major inducible AmpC cephalosporinase in *P. aeruginosa* (Barnes et al., 2018; Haidar et al., 2017; Karlowsky et al., 2018a, 2018b, 2018c; Livermore et al., 2013; Lob et al., 2017a, 2017b, 2018). Relebactam restores imipenem's activity against the majority of clinical isolates of imipenem-resistant *P. aeruginosa* and *Enterobacteriaceae* (Hirsch et al., 2012; Karlowsky et al., 2018a, 2018b, 2018c; Lapuebla et al., 2015; Livermore et al., 2013; Lob et al., 2017a, 2017b, 2018). Relebactam does not inhibit Ambler class B β-lactamases (e.g., metallo-β-lactamases) or class D carbapenemases (e.g., OXA-type β-lactamases) (Hirsch et al., 2012; Livermore et al., 2013; Lob et al., 2017a; Schmidt-Malan et al., 2018). Metallo-β-lactamase–producing *P. aeruginosa* are also not susceptible to ceftazidime-avibactam, meropenem-vaborbactam, or ceftolozane-tazobactam (Castanheira et al., 2017; Livermore et al., 2013; Schmidt-Malan et al., 2018); ceftolozane-tazobactam also lacks activity against isolates of Gram-negative bacilli carrying KPC enzymes (Schmidt-Malan et al., 2018).

The prevalence of multidrug-resistant (MDR) isolates of *Pseudomonas aeruginosa* is significant and is increasing in the United States (Karlowsky et al., 2018a; Sader et al., 2015, 2017a, 2017b) and elsewhere (Castanheira et al., 2014a; Karlowsky et al., 2018c; Lob et al., 2018). MDR *P. aeruginosa* are associated with infection prevention and control challenges; longer hospital stays; and increased patient care costs, morbidity, and mortality (Lister et al., 2009; Lodise Jr et al., 2007; Morata et al., 2012; Tam et al., 2010; Trinh et al., 2017). MDR phenotypes compromise the selection of both empirical and definitive antimicrobial therapies and consequently may delay the administration of appropriate antimicrobial therapy (Micek et al., 2005; Morata et al., 2012). The current study was intended to define the activity of imipenem-relebactam against recent MDR isolates of *P. aeruginosa* in the United States as imipenem-relebactam approaches completion of Phase III clinical testing.

From 2015 to 2017, 26 clinical laboratories in the United States participated in the Study for Monitoring Antimicrobial Resistance Trends (SMART) global surveillance program and were requested to collect up to 250 clinically significant, consecutive, aerobic or facultatively anaerobic Gram-negative bacilli per year. In 2015–2016, the 250 requested isolates per year comprised 100, 100, and 50 isolates,

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respectively, from patients with lower respiratory tract, intraabdominal, and urinary tract infections; in 2017, they comprised 100, 75, and 75 isolates, respectively. Only 1 isolate per patient per Gram-negative species was permitted per year. From 2015 to 2017, the SMART program collected a total of 14,331 isolates of Gram-negative bacilli in the United States, of which 2732 (19.1%) were *P. aeruginosa*. The prevalence of *P. aeruginosa* was approximately 3 times higher among lower respiratory tract isolates (32.1%, 1868/5823) than among intraabdominal (10.7%, 486/4530) and urinary tract isolates (9.3%, 360/3884); specimen source was not specified for 18 isolates of *P. aeruginosa*. All isolates were transported to International Health Management Associates, Inc. (IHMA; Schaumburg, IL) where they were reidentified using matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry (Bruker Daltonics, Billerica, MA, USA). MICs were determined using the Clinical and Laboratory Standards Institute (CLSI) reference broth microdilution method with custom-made dehydrated panels from TREK Diagnostic Systems (Thermo Fisher Scientific, Oakwood Village, OH) (CLSI, 2018a, 2018b). Relebactam was tested at a fixed concentration of 4 μg/mL. MICs were interpreted using 2018 CLSI breakpoints (CLSI, 2018b) for all agents except imipenem-relebactam for which MICs were interpreted using CLSI imipenem MIC breakpoints for *P. aeruginosa*. MDR isolates were defined phenotypically as those testing nonsusceptible (intermediate or resistant) to 3 or more of the following 7 sentinel antimicrobial agents: amikacin, aztreonam, cefepime, ciprofloxacin, colistin, imipenem, and piperacillin-tazobactam.

Against all 2732 isolates of *P. aeruginosa*, the concentrations of imipenem-relebactam inhibiting 50% (MIC_{50}) and 90% (MIC_{90}) of isolates were 0.5 and 2 μg/mL, respectively; 93.9% of isolates were imipenem-relebactam susceptible compared to 72.0% susceptibility to imipenem alone. The 22–percentage point difference in susceptibilities to imipenem-relebactam and imipenem alone was associated with an 8-fold lower MIC_{90} for imipenem-relebactam (2 μg/mL) compared to imipenem alone (16 μg/mL). The *in vitro* activities of the other antimicrobial agents tested are presented in Supplementary Table 1 describing all *P. aeruginosa* isolates. Among the imipenem-nonsusceptible subset, the addition of relebactam to imipenem conferred susceptibility to 78.3% (600/766) of isolates.

Over one-quarter of all isolates of *P. aeruginosa* tested were MDR (27.5%, 750/2732). Table 1 depicts the *in vitro* activities of imipenem-relebactam and comparator antimicrobial agents against all MDR *P. aeruginosa* isolates and against subsets resistant to increasing numbers of antimicrobial agents. Imipenem-relebactam inhibited 79.7% of all MDR isolates of *P. aeruginosa* at the imipenem-susceptible MIC breakpoint (2 μg/mL), while susceptibility to imipenem was 46 percentage points lower. MDR isolates resistant to 3 and 4 agents constituted almost two-thirds of all MDR isolates identified in our study; >84% of MDR isolates resistant to 3 and 4 agents were susceptible to imipenem-relebactam. The susceptibility of MDR isolates to imipenem-relebactam was 25–80 percentage points higher than to β-lactam comparator antimicrobial agents and ciprofloxacin. Only amikacin and colistin showed higher susceptibility rates than imipenem-relebactam against almost all subsets of MDR isolates of *P. aeruginosa*.

Thirty-six different MDR phenotypes (isolates testing as intermediate or resistant to different combinations of ≥3 of the 7 sentinel antimicrobial agents chosen to define MDR) were identified among the isolates tested in this study. The 10 most common MDR phenotypes are listed in Table 2. Imipenem-relebactam was active against 67% of isolates with the most common MDR phenotype (nonsusceptible to aztreonam, cefepime, piperacillin-tazobactam, imipenem, and ciprofloxacin), which represented over a quarter of all MDR isolates. Susceptibility rates to imipenem-relebactam ranged from 75% to 100% for 7 of the other 9 most common MDR phenotypes, which together comprised 54% of all MDR isolates identified. Among all MDR phenotypes that included nonsusceptibility to imipenem, relebactam restored imipenem susceptibility to 69.6% (348/500) of isolates.

Supplementary Table 2 shows the *in vitro* activities of imipenem-relebactam and comparator antimicrobial agents against MDR isolates from different specimen sources. A higher proportion of MDR isolates was observed among lower respiratory tract isolates (31.6%, 590/1868) than among intraabdominal (24.3%, 118/486) or urinary tract isolates (23.9%, 86/360). Imipenem-relebactam maintained activity against 78% of MDR *P. aeruginosa* from lower respiratory tract, 87% of isolates from intraabdominal, and 85% of isolates from urinary tract infections.

Published studies describing infections with MDR pathogens (Karlowsky et al., 2018a; Sader et al., 2015, 2017a, 2017b), including intensive care unit (ICU) patients with pneumonia (Sader et al., 2018; Trinh et al., 2017) and patients with bacteremia (Lodise Jr et al., 2007; Tam et al., 2010) in U.S. hospitals from 2001 to 2017 have reported that ~15–30% of unique patient isolates of *P. aeruginosa* demonstrated an MDR phenotype. In the current study, 27.5% of all isolates of *P. aeruginosa* tested were MDR, comparable to the aforementioned studies, and 79.7% of MDR isolates were susceptible to imipenem-relebactam (Table 1), comparable to results reported in previous surveillance studies of patients in the United States or United States/Canada combined that included stratification by ICU and non-ICU wards (80–82% susceptible) (Karlowsky et al., 2018a, 2018c; Lob et al., 2018).

Relebactam restored imipenem susceptibility to 78.3% of imipenem-nonsusceptible isolates, comparable to rates reported in previous studies of imipenem-relebactam tested against clinical isolates of *P. aeruginosa* from U.S. patients and from patients from other countries, where relebactam restored imipenem susceptibility to 77–92% of

Table 1
In vitro activity of imipenem-relebactam and comparator antimicrobial agents against isolates of *P. aeruginosa* with increasingly resistant MDR phenotypes.

MDR phenotype[a]	*n* (% of all MDR phenotypes)	% Susceptible								
		Imipenem-relebactam[b]	Imipenem	Cefepime	Ceftazidime	Aztreonam	Piperacillin-tazobactam	Ciprofloxacin	Amikacin	Colistin
Resistant to 3 antimicrobial agents	277 (36.9)	92.8	66.1	38.3	41.9	11.2	22.7	66.1	96.0	99.6
Resistant to 4 antimicrobial agents	198 (26.4)	84.3	29.3	17.2	27.8	5.6	6.1	47.5	94.9	99.5
Resistant to 5 antimicrobial agents	238 (31.7)	66.8	3.8	1.3	13.0	2.9	0.4	3.8	88.2	99.6
Resistant to ≥6 antimicrobial agents	37 (4.9)	40.5	0.0	0.0	8.1	0.0	5.4	0.0	2.7	83.8
All MDR isolates	750 (100)	79.7	33.3	19.1	27.3	6.5	10.4	38.1	88.7	98.8

[a] Sentinel antimicrobial agents used to define MDR were aztreonam, cefepime, piperacillin-tazobactam, imipenem, ciprofloxacin, amikacin, and colistin.
[b] In the absence of breakpoints for imipenem-relebactam, CLSI breakpoints for imipenem (susceptible, ≤2 μg/mL; intermediate 4 μg/mL; resistant, ≥8 μg/mL) were applied.

Table 2
In vitro activity of imipenem-relebactam against the 10 most common MDR phenotypes of *P. aeruginosa*.

MDR phenotype[a]	*n* (% of all MDR phenotypes)	% of isolates with each specific MDR phenotype that were susceptible to imipenem-relebactam[b]
Aztreonam, cefepime, piperacillin-tazobactam, imipenem, ciprofloxacin	209 (27.9)	67.0
Aztreonam, cefepime, piperacillin-tazobactam	136 (18.1)	100
Aztreonam, cefepime, piperacillin-tazobactam, imipenem	87 (11.6)	75.9
Aztreonam, cefepime, piperacillin-tazobactam, ciprofloxacin	53 (7.1)	100
Aztreonam, piperacillin-tazobactam, imipenem, ciprofloxacin	32 (4.3)	87.5
Aztreonam, piperacillin-tazobactam, imipenem	32 (4.3)	75.0
Aztreonam, cefepime, piperacillin-tazobactam, imipenem, ciprofloxacin, amikacin	31 (4.1)	41.9
Aztreonam, imipenem, ciprofloxacin	31 (4.1)	80.6
Aztreonam, piperacillin-tazobactam, ciprofloxacin	30 (4.0)	100
Aztreonam, cefepime, piperacillin-tazobactam, imipenem, amikacin	9 (1.2)	55.6
Total for 10 most common MDR phenotypes	650 (86.7)[c]	80.0

[a] Sentinel antimicrobial agents used to define MDR were aztreonam, cefepime, piperacillin-tazobactam, imipenem, ciprofloxacin, amikacin, and colistin. Sentinel agents listed as part of an MDR phenotype tested as nonsusceptible; sentinel agents not shown as part of an MDR phenotype tested as susceptible.
[b] In the absence of breakpoints for imipenem-relebactam, CLSI breakpoints for imipenem (susceptible, ≤2 μg/mL; intermediate 4 μg/mL; resistant, ≥8 μg/mL) were applied.
[c] In total, there were 750 isolates with an MDR phenotype. The top 10 MDR phenotypes accounted for 86.7% (650/750) of all MDR isolates.

imipenem-nonsusceptible isolates (Karlowsky et al., 2018a, 2018b, 2018c; Lapuebla et al., 2015; Lob et al., 2017a, 2017b, 2018). Among imipenem-nonsusceptible isolates of *P. aeruginosa* with MDR phenotypes, relebactam restored imipenem susceptibility to 69.6% of isolates. In the United States, isolates of *P. aeruginosa* with carbapenem-resistant phenotypes generally do not carry carbapenemases but rather demonstrate AmpC derepression or hyperexpression of efflux pumps in combination with decreased expression of OprD (Castanheira et al., 2014b; Kazmierczak et al., 2016). Notably, imipenem alone among the group 2 carbapenems (imipenem, meropenem, doripenem) is not a substrate of the MDR efflux pump MexA-MexB-OprM in *P. aeruginosa* (Livermore et al., 2013).

New agents are needed to address the rise in carbapenem-resistant and MDR *P. aeruginosa,* as many isolates demonstrate *in vitro* resistance to most or all currently marketed antipseudomonal agents (CDC, 2013). Colistin and amikacin, although active *in vitro* against MDR *P. aeruginosa*, have important spectral limitations and toxicities that prohibit their use as both empirical and definitive antimicrobial treatment for serious Gram-negative infections (CLSI, 2018b). β-Lactams, including carbapenems, remain the most important and safest class of antimicrobial agents currently available for treating patients with serious Gram-negative infections.

We conclude that imipenem-relebactam is highly active against isolates of *P. aeruginosa* infecting patients in the United States, including isolates with carbapenem-resistant and MDR phenotypes. Following regulatory agency approval, imipenem-relebactam is positioned to be an important treatment option for patients infected with carbapenem-resistant and/or MDR phenotypes of *P. aeruginosa* that are not susceptible to available antipseudomonal agents, and for patients where the well-established toxicities associated with colistin and aminoglycoside use exclude these agents from therapeutic consideration.

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Data availability

The data generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diagmicrobio.2019.05.001.

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