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Comparative Activity of Newer β-Lactam/β-Lactamase Inhibitor Combinations against *Pseudomonas aeruginosa* Isolates from United States Medical Centers (2020–2021)

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CONCLUSIONS

Ceftazidime-avibactam, ceftolozane-tazobactam, and imipenem-relebactam were highly active and exhibited similar coverage against a large contemporary collection of *P. aeruginosa* isolates from US hospitals.

Cross-resistance among these 3 new β-lactamase inhibitor combinations varied markedly, indicating that all 3 should be tested in the clinical laboratory.

These 3 agents represent valuable therapeutic options for treating *P. aeruginosa* infections.

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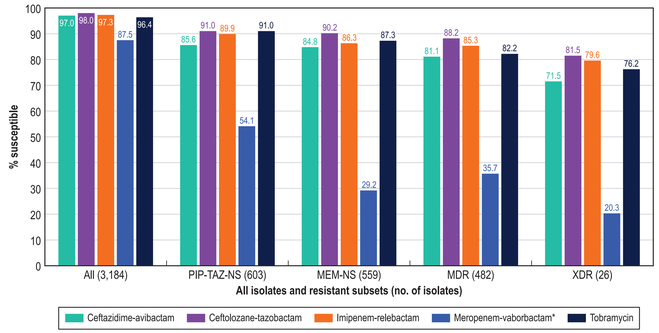
INTRODUCTION

- It is estimated that *Pseudomonas aeruginosa* is responsible for 8% of all healthcare-associated infections in the United States (US).
- For difficult-to-treat *P. aeruginosa*—isolates that exhibit nonsusceptibility to piperacillin-tazobactam, ceftazidime, cefepime, aztreonam, meropenem, imipenem-cilastatin, ciprofloxacin, and levofloxacin—guidelines currently recommend the use of newer β-lactam/β-lactamase inhibitor (BL/BLI) combinations, such as ceftazidime-avibactam, ceftolozane-tazobactam, and imipenem-relebactam.
- We evaluated the *in vitro* activity of ceftazidime-avibactam, ceftolozane-tazobactam, imipenem-relebactam, and comparators, including meropenem-vaborbactam, against a large collection of contemporary *P. aeruginosa* isolates from US hospitals.

METHODS

- The organism collection included 3,184 *P. aeruginosa* isolates from 71 US medical centers across 36 states from all 9 US Census Divisions.
- Participant medical centers were invited to collect a specific number (30 to 100, depending on infection type) of consecutive isolates (1/patient) per infection type per year.
- Only bacterial isolates determined to be significant by local criteria as the reported probable cause of an infection were included in this investigation.
- Antimicrobial susceptibility was evaluated by reference broth microdilution method in a monitoring laboratory (JMI Laboratories) and conducted according to CLSI procedures.
- Ceftazidime-avibactam, ceftolozane-tazobactam, imipenem-relebactam, and piperacillin-tazobactam were tested with the inhibitor at a fixed concentration of 4 mg/L.
- Meropenem-vaborbactam was tested with vaborbactam at a fixed concentration of 8 mg/L.
- MIC results were interpreted according to CLSI and/or US FDA breakpoints when available.
- Meropenem-vaborbactam is not approved for *P. aeruginosa* treatment in the US; thus, meropenem-vaborbactam breakpoints published for Enterobacterales (≤4/8/≥16 mg/L for S/I/R) were applied for comparison.
- Isolates were categorized as multidrug-resistant (MDR) or extensively drug-resistant (XDR) according to criteria defined in 2012 by the joint European and US Centers for Disease Control. These criteria define MDR as nonsusceptible to ≥1 agent in ≥3 antimicrobial classes and XDR as susceptible to ≤2 classes.

Figure 1. Ceftazidime-avibactam, ceftolozane-tazobactam, imipenem-relebactam, meropenem-vaborbactam, and tobramycin activities against a large collection of *P. aeruginosa* and resistant subsets



* % inhibited at Enterobacterales breakpoint of ≤4 mg/L.

RESULTS

- Overall, ceftazidime-avibactam ($MIC_{50/90}$, 2/4 mg/L; 97.0% S), ceftolozane-tazobactam ($MIC_{50/90}$, 0.5/2 mg/L; 98.0% S), and imipenem-relebactam ($MIC_{50/90}$, 0.25/1 mg/L; 97.3% S) were the most active compounds against *P. aeruginosa* isolates (Table 1 and Figure 1).
- Meropenem-vaborbactam inhibited 87.5% of isolates at ≤4 mg/L (CLSI/US FDA susceptible breakpoint for Enterobacterales) and 92.3% at ≤8 mg/L (EUCAST susceptible breakpoint for *P. aeruginosa*).
- Tobramycin was the most active comparator agent ($MIC_{50/90}$, 0.5/1 mg/L; 96.4% S; Table 1).
- Ceftazidime-avibactam, ceftolozane-tazobactam, imipenem-relebactam, and tobramycin showed more consistent activity across infection types compared to other agents (Table 1).
- Ceftazidime-avibactam, ceftolozane-tazobactam, and imipenem-relebactam retained potent activity against isolates nonsusceptible to piperacillin-tazobactam or meropenem (Figure 1).
- Ceftazidime-avibactam, ceftolozane-tazobactam, imipenem-relebactam, and tobramycin were the only compounds with good activity against MDR and XDR *P. aeruginosa* isolates (Figure 1).
- Cross-resistance is shown in Table 2 for these 3 recently approved BL/BLI for *P. aeruginosa* treatment in the US.
- Most importantly, 72.1% to 82.1% of isolates resistant to 1 of 3 newer BL/BLIs approved for *P. aeruginosa* treatment remained susceptible to at least 1 of the other 2 BL/BLIs (Table 2).

Table 1. Antimicrobial susceptibility of *P. aeruginosa* stratified by infection type

Antimicrobial	% Susceptible (no. of isolates)[a]					
	Pneumonia (1,462)	SSSI (606)	UTI (542)	BSI (372)	Others (202)	All (3,184)
Ceftazidime-avibactam	95.7	97.4	99.4	97.6	98.0	97.0
Ceftolozane-tazobactam	97.0	98.8	99.6	97.6	99.5	98.0
Imipenem-relebactam	96.8	96.4	99.1	98.7	99.0	97.3
Meropenem-vaborbactam[b]	[83.5][b]	[90.2][b]	[92.4][b]	[89.5][b]	[92.0][b]	[87.5]
Piperacillin-tazobactam	76.4	82.2	88.4	84.1	86.1	81.1
Ceftazidime	80.8	86.6	91.5	87.4	87.6	84.9
Meropenem	77.2	85.5	87.6	87.4	88.6	82.4
Ciprofloxacin	79.1	81.4	77.1	83.6	83.7	80.0
Tobramycin	95.4	97.9	96.5	97.8	97.0	96.4

[a] Criteria as published by CLSI (2022).
[b] Not approved to treat *P. aeruginosa* infections in the United States; Enterobacterales breakpoints of ≤4/8/≥16 mg/L (S/I/R) were applied for comparison.
Abbreviations: SSSI, skin and skin structure infection; UTI, urinary tract infection; BSI, bloodstream infection.

Table 2. Cross-resistance among newer β-lactamase inhibitor combinations

Resistance phenotype (no.)	% Susceptible[a]			
	CAZ-AVI	C-T	IMI-REL	CAZ-AVI or C-T or IMI-REL[b]
CAZ-AVI-NS (95)	—	54.7	64.2	82.1
C-T-NS (63)	31.7	—	64.8	73.0
IMI-REL-NS (61)	52.5	68.9	—	72.1

[a] Criteria as published by CLSI (2022).
[b] Percentages of isolates susceptible to at least one of the other two BL/BLIs.
Abbreviations: CAZ-AVI, ceftazidime-avibactam; NS, nonsusceptible; C-T, ceftolozane-tazobactam; IMI-REL, imipenem-relebactam.