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Cefiderocol Activity Across Highly Resistant *Pseudomonas aeruginosa* Ventilator-Associated Pneumonia Isolates: A Global Surveillance Study of SENTRY 2020–2024

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INTRODUCTION

- *Pseudomonas aeruginosa* is a leading cause of ventilator-associated pneumonia (VAP) and remains a significant driver of mortality in critically ill patients.
- Increasing resistance to contemporary β-lactam–β-lactamase inhibitor (BL–BLI) therapies has reduced the effectiveness of these combinations as treatment options for infections caused by highly resistant *P. aeruginosa*.
- Therapeutic challenges are further complicated by multidrug-resistant and metallo-β-lactamase (MBL)-producing isolates, highlighting the need for treatment options active against highly resistant phenotypes.

METHODS

- A total of 1400 *P. aeruginosa* VAP isolates were collected from the United States and Europe through the SENTRY Antimicrobial Surveillance Program between 2020 and 2024.
- Antimicrobial susceptibility testing was performed using Clinical and Laboratory Standards Institute (CLSI) reference broth microdilution methodology, and iron-depleted cation-adjusted Mueller–Hinton broth was used for cefiderocol.
- Susceptibility results were interpreted according to the 2026 breakpoint criteria from the CLSI, European Committee on Antimicrobial Susceptibility Testing (EUCAST), and US Food and Drug Administration (FDA).
- Cefiderocol activity was evaluated alongside key BL–BLI comparators, including:
  - Imipenem-relebactam (I-R)
  - Meropenem-vaborbactam (M-V)
  - Ceftazidime-avibactam (CZA)
  - Ceftolozane-tazobactam (C-T).
- Activity was evaluated against clinically significant resistance phenotypes, including:
  - Isolates nonsusceptible to BL–BLI agents
  - MBL-producing isolates (Verona integron-encoded [VIM], New Delhi [NDM], and imipenemase [IMP] MBL producers).

RESULTS

- Among 1400 global *P. aeruginosa* VAP isolates collected through the SENTRY Program (2020–2024), cefiderocol demonstrated low minimum inhibitory concentration (MIC) values ($MIC_{50}/_{90}$: 0.12/0.5 mg/L) and high susceptibility using CLSI (99.5%), EUCAST (98.9%), and FDA (97.9%) interpretive criteria (**Table 1**).
  - Activity was sustained among isolates nonsusceptible to CZA, C-T, and I-R, with cefiderocol susceptibility ranging from 91.4% to 96.0% (CLSI).
  - Cefiderocol demonstrated activity against MBL-producing isolates (n=30; VIM [n=23], NDM [n=5], and IMP [n=2]), while susceptibility to comparator BL–BLI agents was limited among MBL-producing strains.
- Across BL–BLI nonsusceptible phenotypes, susceptibility to BL–BLI agents was ≤42%, showing a high degree of cross-resistance (**Tables 2–5**).
  - Cefiderocol susceptibility was >91% across all evaluated BL–BLI nonsusceptible phenotypes, suggesting sustained activity despite resistance to contemporary BL–BLI antibiotics.

CONCLUSION

- Cefiderocol maintained high susceptibility against a contemporary global collection of *P. aeruginosa* VAP isolates, including highly resistant phenotypes where cross-resistance among comparator BL–BLI agents was observed.

Table 1. Cefiderocol *in vitro* activity against *P. aeruginosa* VAP isolates (2020–2024)

Isolate set	n	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC range (mg/L)	CLSI %S	FDA %S	EUCAST %S
All *P. aeruginosa* VAP isolates	**1400**	**0.12**	**0.5**	**≤0.004 to >64**	**99.5**	**97.9**	**98.9**
CZA NS	79	0.5	4	0.015 to >64	92.4	79.7	88.6
C-T NS	81	0.25	4	≤0.004 to >64	91.4	79.0	87.7
I-R NS	75	0.25	2	≤0.004 to >64	96.0	82.7	92.0
MBL-producing	30	0.25	4	0.03 to 32	93.3	73.3	73.3

Table 2. Ceftazidime-avibactam *in vitro* activity against *P. aeruginosa* VAP isolates (2020–2024)

Isolate set	n	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC range (mg/L)	CLSI %S	FDA %S	EUCAST %S
All *P. aeruginosa* VAP isolates	**1399**	**2**	**8**	**0.12 to >32**	**94.4**	**94.4**	**94.4**
CZA NS	79	32	>32	16 to >32	NA	NA	NA
C-T NS	81	32	>32	1 to >32	32.1	32.1	32.1
I-R NS	74	32	>32	0.5 to >32	37.8	37.8	37.8
MBL-producing	30	32	>32	4 to >32	6.7	6.7	6.7

Table 3. Ceftolozane-tazobactam *in vitro* activity against *P. aeruginosa* VAP isolates (2020–2024)

Isolate set	n	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC range (mg/L)	CLSI %S	FDA %S	EUCAST %S
All *P. aeruginosa* VAP isolates	**1400**	**0.5**	**4**	**≤0.12 to >16**	**94.2**	**94.2**	**94.2**
CZA NS	79	>16	>16	1 to >16	30.4	30.4	30.4
C-T NS	81	>16	>16	8 to >16	NA	NA	NA
I-R NS	75	>16	>16	0.5 to >16	32.0	32.0	32.0
MBL-producing	30	>16	>16	16 to >16	0.0	0.0	0.0

Table 4. Imipenem-relebactam *in vitro* activity against *P. aeruginosa* VAP isolates (2020–2024)

Isolate set	n	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC range (mg/L)	CLSI %S	FDA %S	EUCAST %S
All *P. aeruginosa* VAP isolates	**1400**	**0.25**	**2**	**≤0.03 to >8**	**94.6**	**94.6**	**94.6**
CZA NS	79	4	>8	0.25 to >8	41.8	41.8	41.8
C-T NS	81	4	>8	0.25 to >8	37.0	37.0	37.0
I-R NS	75	8	>8	4 to >8	NA	NA	NA
MBL-producing	30	>8	>8	4 to >8	0.0	0.0	0.0

Table 5. Meropenem-vaborbactam *in vitro* activity against *P. aeruginosa* VAP isolates (2020–2024)

Isolate set	n	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC range (mg/L)	CLSI %S[a]	FDA %S[a]	EUCAST %S
All *P. aeruginosa* VAP isolates	**1396**	**0.5**	**>8**	**≤0.015 to >8**	**–**	**–**	**86.4**
CZA NS	79	>8	>8	0.5 to >8	–	–	20.3
C-T NS	81	>8	>8	0.25 to >8	–	–	35.8
I-R NS	75	>8	>8	2 to >8	–	–	12.0
MBL-producing	30	>8	>8	2 to >8	–	–	13.3

[a]No CLSI- or FDA-defined susceptibility breakpoints are currently available for meropenem-vaborbactam.

CLSI, Clinical and Laboratory Standards Institute; C-T, ceftolozane-tazobactam; CZA, ceftazidime-avibactam; EUCAST, European Committee on Antimicrobial Susceptibility Testing; FDA, US Food and Drug Administration; I-R, imipenem-relebactam; MBL, metallo-β-lactamase; MIC, minimum inhibitory concentration; NA, not applicable; NS, nonsusceptible; VAP, ventilator-associated pneumonia.

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