Poster 1530

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Evaluation of Phenotypic Cross-Resistance Between Cefiderocol and β-Lactam–β-Lactamase Inhibitor Combinations Against *Pseudomonas aeruginosa* Isolates from US Medical Centers

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BACKGROUND

- As multidrug-resistant strains become more prevalent, the risk of inappropriate empiric antibiotic treatment increases, which can result in a higher risk of poor clinical outcomes.
- Prevalence of multidrug-resistant *Pseudomonas aeruginosa* isolates has been increasing, with cross-resistance reported among β-lactam–β-lactamase inhibitor (BL–BLI) combinations.
- This study evaluated cross-resistance between anti-pseudomonal BL–BLI combinations and cefiderocol against various non-susceptible (NS) subsets of *P. aeruginosa* isolates collected from US hospitals participating in the SENTRY Antimicrobial Surveillance Program.

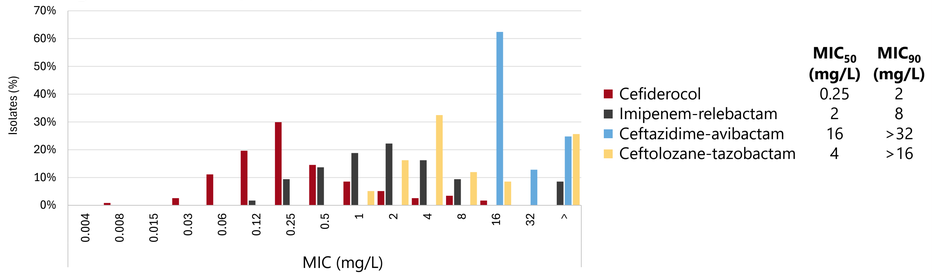
METHODS

- A total of 3384 clinical *P. aeruginosa* isolates were collected during 2020–2022 from hospitalized patients in 34 US hospitals as part of the SENTRY Antimicrobial Surveillance Program.
- Minimum inhibitory concentrations (MICs) were determined according to Clinical and Laboratory Standards Institute (CLSI) guidelines using broth microdilution with cation-adjusted Mueller–Hinton broth (CAMHB) for comparator agents and iron-depleted CAMHB for cefiderocol.
- Susceptibility was assessed according to 2024 CLSI and US Food and Drug Administration (FDA) breakpoints. Carbapenem-non-susceptible (CarbNS) was defined as non-susceptibility to meropenem and imipenem.

RESULTS

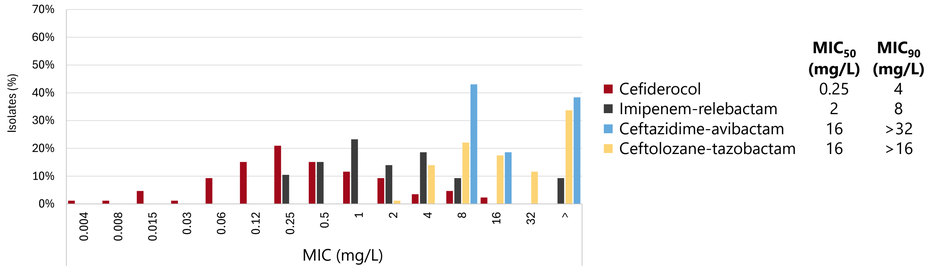
- Among *P. aeruginosa* isolates that were NS to ceftazidime-avibactam (CZA), ceftolozane-tazobactam (C/T), and imipenem-relebactam (I/R), cefiderocol was the most potent agent with the lowest MIC_{50} and MIC_{90} values compared to various BL–BLI combinations (**Figures 1–3**).
- >80% and ≥93% of CZA-NS, C/T-NS, and I/R-NS isolates remained susceptible to cefiderocol according to FDA or CLSI breakpoints, respectively, while susceptibilities for other BL–BLI combinations were below 66% (**Table 1**).
  - In C/T-NS *P. aeruginosa* isolates, only 37.2% and 62.8% of isolates were susceptible to CZA and I/R, respectively.
  - In CZA-NS *P. aeruginosa* isolates, 53.8% and 65.8% were susceptible to C/T and I/R, respectively.
  - In I/R-NS *P. aeruginosa* isolates, 54.5% and 63.6% were susceptible to CZA and C/T, respectively.
- Against various BL–BLI-NS ± Carb-NS phenotypes, susceptibility for cefiderocol remained high (>89% using CLSI breakpoints), while susceptibilities for various BL–BLI combinations ranged from 0 to 64.4% **(Table 1).**
- Cefiderocol-NS in *P. aeruginosa* was rare (<1%), while all were cross resistant to CZA and C/T **(Table 1)**

Figure 1. MIC distributions of cefiderocol, ceftazidime-avibactam, ceftolozane-tazobactam, and imipenem-relebactam against ceftazidime-avibactam non-susceptible *P. aeruginosa* isolates (n=117)



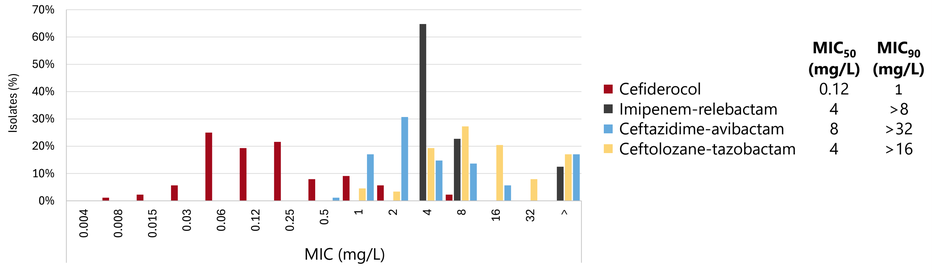
	MIC_{50} (mg/L)	MIC_{90} (mg/L)
Cefiderocol	0.25	2
Imipenem-relebactam	2	8
Ceftazidime-avibactam	16	>32
Ceftolozane-tazobactam	4	>16

Figure 2. MIC distributions of cefiderocol, ceftazidime-avibactam, ceftolozane-tazobactam, and imipenem-relebactam against ceftolozane-tazobactam non-susceptible *P. aeruginosa* isolates (n=86)



	MIC_{50} (mg/L)	MIC_{90} (mg/L)
Cefiderocol	0.25	4
Imipenem-relebactam	2	8
Ceftazidime-avibactam	16	>32
Ceftolozane-tazobactam	16	>16

Figure 3. MIC distributions of cefiderocol, ceftazidime-avibactam, ceftolozane-tazobactam, and imipenem-relebactam against imipenem-relebactam non-susceptible *P. aeruginosa* isolates (n=88)



	MIC_{50} (mg/L)	MIC_{90} (mg/L)
Cefiderocol	0.12	1
Imipenem-relebactam	4	>8
Ceftazidime-avibactam	8	>32
Ceftolozane-tazobactam	4	>16

Table 1. Susceptibility of cefiderocol, ceftazidime-avibactam, ceftolozane-tazobactam, and imipenem-relebactam against various non-susceptible subsets of *P. aeruginosa* isolates from US hospitals participating in the SENTRY Surveillance Program during 2020–2022

		Cefiderocol		CZA	C/T	I/R
Resistance phenotype*	n	FDA % susceptible	CLSI % susceptible	% susceptible	% susceptible	% susceptible
Overall	3384	98.5	99.8	96.5	97.5	97.4
CarbNS	572	96.0	99.3	85.3	89.3	84.8
CZA – NS	117	87.2	94.9	NA	53.8	65.8
C/T – NS	86	80.2	93.0	37.2	NA	62.8
I/R – NS	88	92.0	97.7	54.5	63.6	NA
C/T + I/R – NS	32	84.4	93.8	18.8	NA	NA
CZA + C/T – NS	54	72.2	88.9	NA	NA	51.9
CZA + I/R – NS	40	87.5	95.0	NA	35.0	NA
CZA + C/T + I/R – NS	26	80.8	92.3	NA	NA	NA
Carb + CZA – NS	84	86.9	95.2	NA	54.8	53.6
Carb + C/T – NS	61	78.7	93.4	37.7	NA	49.2
Carb + I/R – NS	87	92.0	97.7	55.2	64.4	NA
Carb + CZA + C/T – NS	38	71.1	89.5	NA	NA	34.2
Carb + CZA + I/R – NS	39	87.2	94.9	NA	35.9	NA
Carb + C/T + I/R – NS	31	83.9	93.5	19.4	NA	NA
Cefiderocol – NS	6	NA	NA	0	0	66.7

CZA, ceftazidime-avibactam; C/T, ceftolozane-tazobactam; I/R, imipenem-relebactam; NS, non-susceptible; Carb, carbapenem; n, number of isolates; NA, non-applicable.
*According to 2024 CLSI or FDA breakpoints.

CONCLUSIONS

- *P. aeruginosa* isolates derived from US hospitalized patients NS to one of the anti-pseudomonal BL–BLI combinations showed a high degree of cross resistance to the other BL–BLI combinations, but not to cefiderocol.
- The data supports the use of cefiderocol as an important early treatment option when *P. aeruginosa* NS is encountered to antipseudomonal BL–BLI combinations.

Conflict of interest. BD, STN, JJB, CL, MT, YY are employees of Shionogi. This study was funded by Shionogi & Co., Ltd., Osaka, Japan.