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Activity of Cefiderocol and Comparator Agents Against Difficult-to-Treat Resistant (DTR) Gram-negative Isolates, Collected During 2020–2022 as Part of the SENTRY Antimicrobial Surveillance Program

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Background

- Difficult-to-treat resistant (DTR) Gram-negative isolates show treatment-limiting resistance to all first-line agents (i.e., β-lactams and fluoroquinolones).
- Cefiderocol is a siderophore-conjugated cephalosporin with a unique mode of entry and broad activity against Gram-negative bacteria.

Objective

- To determine the activity of cefiderocol and comparator agents against DTR isolates of Enterobacterales, *Pseudomonas aeruginosa,* and *Acinetobacter baumannii-calcoaceticus* species complex.

Methods

- Minimum inhibitory concentrations (MICs) were determined according to CLSI guidelines against 24,084 Enterobacterales, 7,310 *P. aeruginosa*, and 2,479 *A. baumannii-calcoaceticus* complex isolates, collected in 2020–2022 in Europe and the USA as part of the SENTRY program. Broth microdilution with cation-adjusted Mueller–Hinton broth (CAMHB) was used for comparator agents and iron-depleted CAMHB was used for cefiderocol.
- Susceptibility was assessed according to CLSI, EUCAST, and FDA breakpoints.
- DTR phenotype was defined as being non-susceptible to fluoroquinolones and β-lactams according to CLSI breakpoints.

Results

Cefiderocol was the most active agent against DTR phenotypes of Enterobacterales (Table 1), *P. aeruginosa* (Table 2), and *A. baumannii-calcoaceticus* species complex (Table 3).

Figure 1. Prevalence of DTR Enterobacterales, *P. aeruginosa*, and *A. baumannii-calcoaceticus* complex among isolates collected in 2020–2022 in Europe and the USA as part of the SENTRY program (left) and DTR Enterobacterales by species (right)

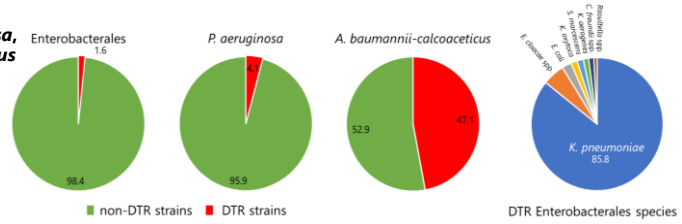


Table 1. Activity of cefiderocol and comparator agents against DTR[a] Enterobacterales (N=387)

	CLSI[b]			FDA[b]			EUCAST[b]		
	%S	%I	%R	%S	%I	%R	%S	%I	%R
Antimicrobial agent									
Cefiderocol	95.3	4.4	0.3	95.3	4.4	0.3	81.1	-	18.9
Imipenem-relebactam[c]	61.5	4.9	33.6	61.5	4.9	33.6	66.4	-	33.6
Meropenem-vaborbactam	61.8	4.7	33.6	61.8	4.7	33.6	66.4	-	33.6
Ceftazidime-avibactam	78.6	-	21.4	78.6	-	21.4	78.6	-	21.4
Ceftolozane-tazobactam	0.0	0.8	99.2	0.0	0.8	99.2	0.0	-	100
Piperacillin-tazobactam	0.0	0.0	100	0.0	0.5	99.5	0.0	-	100
Ampicillin-sulbactam	0.0	0.0	100	0.0	0.0	100	-	-	-
Amikacin	36.7	9.8	53.5	36.7	9.8	53.5	46.5[d]	-	53.5
Gentamicin	43.4	3.1	53.5	43.4	3.1	56.6	43.4[d]	-	53.5
Trimethoprim-sulfamethoxazole	17.6	-	82.4	17.6	-	80.4	17.6	2.1	82.4
Tigecycline	-	-	-	94.1	3.9	2.1	-	-	-
Minocycline	56.8	17.8	25.3	56.8	17.8	25.3	-	-	-
Colistin	-	71.8	28.2	-	-	-	71.8	-	28.2

S, susceptible; I, intermediate; R, resistant; [a]DTR Enterobacterales was defined as being non-susceptible, according to CLSI breakpoints, to aztreonam, ceftriaxone, ceftazidime, cefepime, meropenem, imipenem, ciprofloxacin, and levofloxacin; [b]Criteria as published by CLSI (2023), EUCAST (2023), and US FDA (2023); [c]All Enterobacterales species were included in the analysis, but CLSI excludes *Morganella*, *Proteus*, and *Providencia* species, and EUCAST excludes *Morganellaceae*; [d]For infections originating from the urinary tract. For systemic infections, aminoglycosides must be used in combination with other active therapy.

Table 2. Activity of cefiderocol and comparator agents against DTR[a] *P. aeruginosa* (N=299)

	CLSI[b]			FDA[b]			EUCAST[b]		
	%S	%I	%R	%S	%I	%R	%S	%I	%R
Antimicrobial agent									
Cefiderocol	98.3	1.0	0.7	89.6	8.0	2.3	97.7	-	2.3
Imipenem-relebactam	54.8	16.4	28.8	54.8	16.4	28.8	54.8	-	45.2
Meropenem-vaborbactam	-	-	-	-	-	-	25.8	-	74.2
Ceftazidime-avibactam	54.5	-	45.5	54.5	-	45.5	54.5	-	45.5
Ceftolozane-tazobactam	53.5	13.4	33.1	53.5	13.4	33.1	53.5	-	46.5
Piperacillin-tazobactam	3.7	11.7	84.6	3.7	11.7	84.6	-	3.7	96.3
Amikacin	[c]	72.6	27.4	62.9[c]	9.7	27.4	62.9[d]	-	37.1
Colistin	-	99.7	0.3	-	-	-	99.7	-	0.3

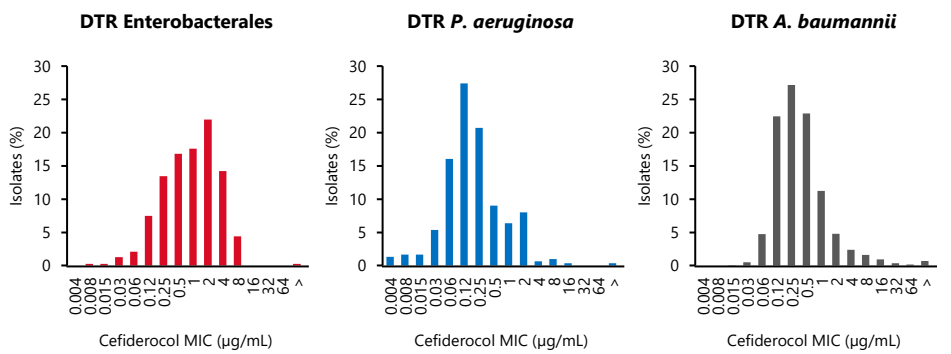
S, susceptible; I, intermediate; R, resistant; [a]DTR *P. aeruginosa* was defined as being non-susceptible, according to CLSI breakpoints, to aztreonam, ceftazidime, cefepime, meropenem, imipenem, ciprofloxacin, and levofloxacin; [b]Criteria as published by CLSI (2023), EUCAST (2023), and US FDA (2023); [c]Using urinary tract infection only breakpoints; [d]For infections originating from the urinary tract. For systemic infections, aminoglycosides must be used in combination with other active therapy.

Table 3. Activity of cefiderocol and comparator agents against DTR[a] *A. baumannii-calcoaceticus* complex (N=1,167)

	CLSI[b]			FDA[b]			EUCAST[b]		
	%S	%I	%R	%S	%I	%R	%S	%I	%R
Antimicrobial agent									
Cefiderocol	96.2	1.6	2.1	89.0	4.8	6.2	93.8	-	6.2
Imipenem-relebactam	-	-	-	0.1	0.4	99.5	0.1	-	99.9
Piperacillin-tazobactam	0.1	0.7	99.2	0.1	0.7	99.2	-	-	-
Ampicillin-sulbactam	2.5	6.0	91.5	2.5	6.0	91.5	-	-	-
Amikacin	17.9	6.9	75.1	17.9	6.9	75.1	14.3[c]	-	85.7
Gentamicin	13.9	6.3	79.8	-	-	-	13.9[c]	-	86.1
Trimethoprim-sulfamethoxazole	14.5	-	85.5	-	-	-	14.5	1.1	84.4
Minocycline	36.3	20.2	43.4	36.3	20.2	43.4	-	-	-
Colistin	-	81.2	18.8	-	-	-	81.2	-	18.8

S, susceptible; I, intermediate; R, resistant; [a]DTR *A. baumannii-calcoaceticus* species complex was defined as being non-susceptible, according to CLSI breakpoints, to ceftazidime, cefepime, meropenem, imipenem, ciprofloxacin, and levofloxacin; [b]Criteria as published by CLSI (2023) and US FDA (2023); for EUCAST, non-species-specific PK-PD breakpoints were used (2023); [c]For infections originating from the urinary tract. For systemic infections, aminoglycosides must be used in combination with other active therapy.

Figure 2. Cefiderocol MIC distributions against DTR strains of Enterobacterales (N=387), *P. aeruginosa* (N=299), and *A. baumannii-calcoaceticus* species complex (N=1,167)



Conclusion

DTR Gram-negative isolates remain highly susceptible to cefiderocol in contrast to other comparator agents, including novel β-lactam/β-lactamase inhibitor combinations, such as meropenem-vaborbactam, imipenem-relebactam, ceftolozane-tazobactam, and ceftazidime-avibactam.