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Contact: Sean T. Nguyen
Email: sean.nguyen@shionogi.com

In vitro Activity of Cefiderocol in Bloodstream Infection Isolates from North American and European Hospitals: SENTRY 2020–2022

Sean T. Nguyen[1], Boudewijn L.M. DeJonge[1], Jason J. Bryowsky[1], Joshua M. Maher[2], Rodrigo E. Mendes[2], Christopher Longshaw[3], Miki Takemura[4], Yoshinori Yamano[4]

1. Shionogi Inc., Florham Park, NJ, USA; 2. JMI Laboratories, North Liberty, IA, USA; 3. Shionogi B.V., London, UK; 4. Shionogi & Co., Ltd., Osaka, Japan

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BACKGROUND

Cefiderocol is approved in the United States[1] for the treatment of patients with complicated urinary tract infections and hospital-acquired/ventilator-associated bacterial pneumonia caused by susceptible Gram-negative pathogens and in Europe[2] for the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options.

Treatment of bloodstream infections (BSIs) in hospitalized patients can be challenging due to antibiotic resistance, which limits the therapeutic options.

OBJECTIVE

We aimed to evaluate the *in vitro* activity of cefiderocol and comparator agents against Gram-negative isolates causing BSI in hospitalized patients from North American and European hospitals from the SENTRY Antimicrobial Surveillance Program in 2020–2022.

METHODS

- A total of 9,655 Gram-negative BSI isolates were collected from 43 North American (N=3,985) and 39 European (N=5,670) medical centers as part of the SENTRY Antimicrobial Surveillance Program (from 2020 to 2022).
- Clinical isolates included 7,863 Enterobacterales, 1,051 *Pseudomonas aeruginosa*, 422 *Acinetobacter baumannii-calcoaceticus* complex (ABC) and 154 *Stenotrophomonas maltophilia*.
- Minimum inhibitory concentrations (MICs) were determined according to 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 2023 CLSI, FDA, and EUCAST breakpoints (Table 1):

Table 1. Susceptibility breakpoints by CLSI, FDA, and EUCAST

Organism	Breakpoint (µg/mL) by organization Susceptible/Intermediate/Resistant		
	CLSI	FDA	EUCAST
Enterobacterales	≤4/8/≥16	≤4/8/≥16	≤2/–/>2
Pseudomonas aeruginosa	≤4/8/≥16	≤1/2/≥4	≤2/–/>2
Acinetobacter spp.	≤4/8/≥16	≤1/2/≥4	≤2/–/>2[†]
Stenotrophomonas maltophilia	≤1/–/–	NA	≤2/–/>2[†]

[†]EUCAST non-species-specific pharmacokinetic/pharmacodynamic breakpoints used

- Carbapenem-nonsusceptible subsets were defined as non-susceptibility to meropenem and imipenem (excluded for *Proteus mirabilis, P. penneri*, and indole-positive Proteeae).

RESULTS

- Among BSI isolates, the most common Gram-negative organism was *Escherichia coli* (n = 3,983) followed by *Klebsiella pneumoniae* (n = 1,577) and *P. aeruginosa* (n = 1,051).
- 2.2% of Enterobacterales, 14.4% of *P. aeruginosa*, 60.4% of *A. baumannii-calcoaceticus* complex, and 100% of *S. maltophilia* tested as carbapenem non-susceptible (Table 2).
- All tested Enterobacterales isolates tested were highly susceptible to cefiderocol (>98%), while 94.3%, 94.3%, and 80.5% of carbapenem-nonsusceptible Enterobacterales isolates were susceptible to cefiderocol using the CLSI, FDA, and EUCAST breakpoints, respectively (Figure 1).
- Cefiderocol was the most active antimicrobial against all *P. aeruginosa* and carbapenem-nonsusceptible *P. aeruginosa* isolates, with $MIC_{50/90}$ values of 0.12/0.25 µg/mL and 0.12/0.5 µg/mL, respectively (Figure 2).
  - *P. aeruginosa* susceptibility to cefiderocol was 99.3%, 98.7%, and 97.4% per CLSI, EUCAST and FDA breakpoints, respectively, while only <76% were susceptible to beta-lactam/beta-lactamase inhibitor combinations for carbapenem-nonsusceptible *P. aeruginosa* isolates.
- Susceptibility of *Acinetobacter baumannii-calcoaceticus* complex isolates to cefiderocol was 97.2%, 95.5%, and 91.7% per CLSI, EUCAST, and FDA breakpoints, respectively (Figure 3).
  - Among carbapenem-nonsusceptible *Acinetobacter baumannii-calcoaceticus* complex BSI isolates, cefiderocol was the most active ($MIC_{50/90}$ 0.25/2 µg/mL) compared with comparator agents including ampicillin/sulbactam ($MIC_{50/90}$ 64/>64 µg/mL) and imipenem/relebactam ($MIC_{50/90}$ >8/>8 µg/mL).
- All *S. maltophilia* isolates were susceptible to cefiderocol per CLSI and EUCAST breakpoints and cefiderocol was the most potent agent with $MIC_{50/90}$ of 0.06/0.25 µg/mL (Figure 4).

Table 2. Activity of cefiderocol and selected comparator agents tested against 9,655 isolates of Enterobacterales, *P. aeruginosa, A. baumannii-calcoaceticus* species complex, and *S. maltophilia* isolates collected from 2020–2022 in US and European hospitals

Organism group Agent	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	MIC range (µg/mL)	%S[a] CLSI	%S[a] FDA	%S[a] EUCAST
Enterobacterales (n=7,863)						
Cefiderocol	0.06	0.5	≤0.004 to >64	99.8	99.8	98.8
Meropenem	0.03	0.06	≤0.015 to >32	97.6	97.6	97.8
Imipenem-relebactam	0.12	0.5	≤0.03 to >8	95.0	95.0	98.4
Meropenem-vaborbactam	0.03	0.06	≤0.015 to >8	99.1	99.1	99.2
Ceftazidime-avibactam	0.12	0.25	≤0.015 to >32	99.4	99.4	99.4
Ceftolozane-tazobactam	0.25	1	≤0.12 to >16	93.4	93.4	93.4
Carbapenem nonsusceptible - Enterobacterales (n=174)						
Cefiderocol	1	4	0.015 to >64	94.3	94.3	80.5
Imipenem-relebactam	0.5	>8	0.06 to >8	59.2	59.2	66.1
Meropenem-vaborbactam	2	>8	≤0.015 to >8	62.1	62.1	66.7
Ceftazidime-avibactam	2	>32	≤0.015 to >32	77.6	77.6	77.6
Ceftolozane-tazobactam	>16	>16	2 to >16	0.6	0.6	0.6
***Pseudomonas aeruginosa* (n=1,051)**						
Cefiderocol	0.12	0.25	≤0.004 to 16	99.9	99.1	99.8
Meropenem	0.5	8	≤0.015 to >32	84.0	84.0	84.0
Imipenem-relebactam	0.25	1	≤0.03 to >8	95.7	95.7	95.7
Meropenem-vaborbactam	0.5	8	≤0.015 to >8	N/A	N/A	92.2
Ceftazidime-avibactam	2	4	0.12 to >32	95.7	95.7	95.7
Ceftolozane-tazobactam	0.5	2	≤0.12 to >16	95.1	95.1	95.1
Carbapenem nonsusceptible - *Pseudomonas aeruginosa* (n=151)						
Cefiderocol	0.12	0.5	≤0.004 to 16	99.3	97.4	98.7
Imipenem-relebactam	2	>8	0.5 to >8	72.2	72.2	72.2
Meropenem-vaborbactam	>8	>8	2 to >8	N/A	N/A	47.0
Ceftazidime-avibactam	4	32	1 to >32	76.2	76.2	76.2
Ceftolozane-tazobactam	2	>16	0.5 to >16	71.5	71.5	71.5
***Acinetobacter baumannii-calcoaceticus* complex (n=422)**						
Cefiderocol	0.25	1	0.015 to >64	97.2	91.7	95.5
Meropenem	32	>32	0.03 to >32	39.6	39.6	39.6
Imipenem-relebactam	>8	>8	≤0.03 to >8	N/A	39.6	39.6
Ampicillin-sulbactam	32	>64	≤0.5 to >64	38.2	38.2	N/A
Colistin	0.5	2	≤0.06 to >8	N/A	N/A	91.7
Carbapenem nonsusceptible - *Acinetobacter baumannii-calcoaceticus* complex (n=255)						
Cefiderocol	0.25	2	0.03 to >64	96.1	88.6	93.7
Imipenem-relebactam	>8	>8	4 to >8	NA	0.0	0.0
Ampicillin-sulbactam	64	>64	8 to >64	2.7	2.7	N/A
Colistin	0.5	4	0.12 to >8	N/A	N/A	89.0
***Stenotrophomonas maltophilia* (n=154)**						
Cefiderocol	0.06	0.25	0.008 to 1	100	N/A	100
Levofloxacin	1	4	0.12 to 32	85.1	N/A	N/A
Trimethoprim-sulfamethoxazole	≤0.12	0.5	≤0.12 to >4	96.8	N/A	98.1

MIC, minimum inhibitory concentration; $MIC_{50/90}$, MIC required to inhibit the growth of 50%/90% of organisms; n, number of isolates; N/A, not applicable; S, susceptible. [a]According to 2023 CLSI, FDA and EUCAST breakpoints

Figure 1. Cefiderocol MIC distributions against Enterobacterales in SENTRY 2020–2022*

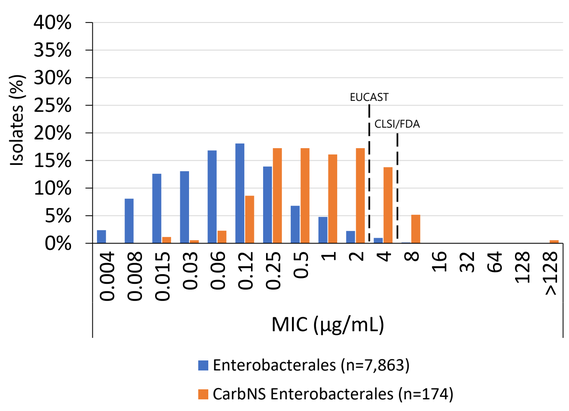


Figure 2. Cefiderocol MIC distributions against *P. aeruginosa* in SENTRY 2020–2022

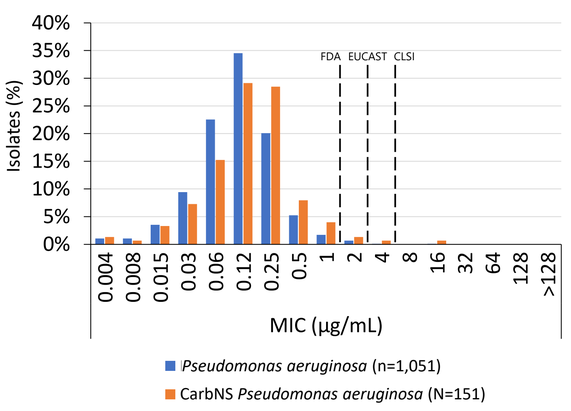


Figure 3. Cefiderocol MIC distributions against *A. baumannii-calcoaceticus* complex in SENTRY 2020–2022

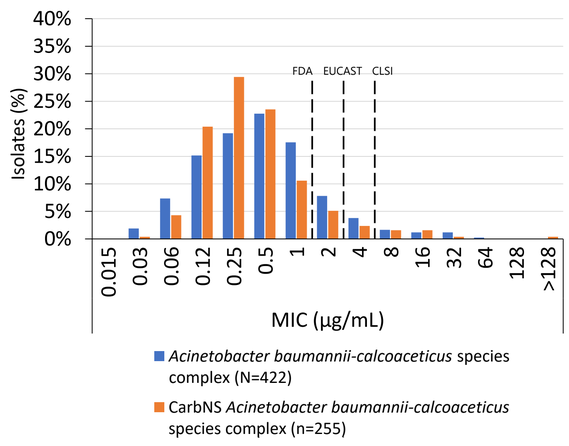
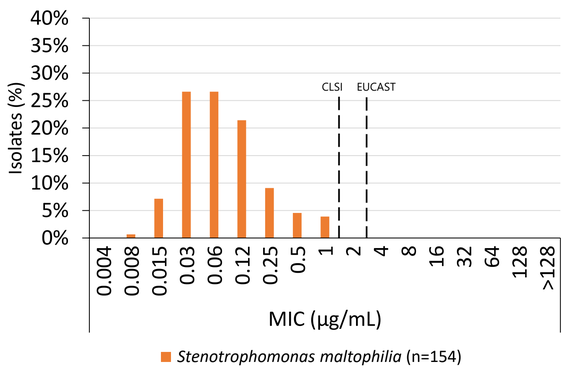


Figure 4. Cefiderocol MIC distributions against *S. maltophilia* in SENTRY 2020–2022



Criteria as published by CLSI (2023), EUCAST (2023), and US FDA (2023). MIC, minimum inhibitory concentration.

*Enterobacterales included: *Citrobacter amalonaticus / farmeri* (6), *C. braakii* (1), *C. freundii* (2), *C. freundii* species complex (134), *C. koseri* (96), *C. sedlakii* (1), *Enterobacter asburiae* (2), *E. cloacae* (234), *E. cloacae species* complex (310), *E. hormaechei* (5), *E. kobei* (1), *Escherichia coli* (3,983), *E. fergusonii* (1), *E. hermannii* (1), *E. marmotae* (1), *E. vulneris* (2), Gram-negative rods in the family Enterobacteriaceae (1), *Hafnia alvei* (10), *Klebsiella aerogenes* (172), *K. oxytoca* (274), *K. pneumoniae* (1,577), *K. variicola* (82), *Kluyvera ascorbata* (2), *K. georgiana* (1), *Leclercia adecarboxylata* (2), *Morganella morganii* (84), *Pantoea agglomerans* (15), *P. ananatis* (2), *P. anthophila* (1), *P. dispersa* (1), *Phytobacter diazotrophicus* (1), *Pluralibacter gergoviae* (1), *Proteus hauseri* (2), *P. mirabilis* (392), *P. penneri* (5), *P. vulgaris* (25), *P. vulgaris* group (10), *Providencia rettgeri* (18), *P. stuartii* (25), *Raoultella ornithinolytica* (13), *R. planticola* (2), *Serratia liquefaciens* (5), *S. liquefaciens* complex (3), *S. marcescens* (331), *S. rubidaea* (1), unspeciated *Citrobacter* (2), unspeciated *Erwinia* (1), unspeciated *Klebsiella* (1), unspeciated *Pantoea* (5), unspeciated *Raoultella* (14), *Yersinia enterocolitica* (2).

CONCLUSIONS

- Contemporary Enterobacterales, *P. aeruginosa*, *A. baumannii-calcoaceticus* complex, and *S. maltophilia* causing BSIs, including carbapenem-nonsusceptible subsets for which treatment options are limited, were highly susceptible to cefiderocol.
- These data suggest that cefiderocol may be a valuable empiric and guided treatment option for BSI caused by Gram-negative pathogens in patients with risk factors for carbapenem resistance.

References

1. Fetroja (Cefiderocol). Prescribing Information. Shionogi Inc., Florham Park, NJ, USA. 2020.
2. Fetcroja (Cefiderocol). Summary of Product Characteristics. Shionogi BV, Amsterdam, The Netherlands. 2020.

Acknowledgments

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