Fetroja® – Comparison to Aztreonam–Avibactam (including Aztreonam plus Ceftazidime–Avibactam)

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Summary | Prospective Study | Retrospective Study | Surveillance Studies | Relevant Prescribing Information | Literature Search | Abbreviations & References

Summary

- **Falcone et al (2024)** conducted a prospective observational cohort study in 343 patients infected with MBL-producing Enterobacterales, including 328 (96%) NDM and 15 (4%) VIM isolates[1]
  - The 30-day mortality rate in patients who received cefiderocol-containing regimens was 33% and AEs occurred in 3 (9.1%) patients (*Clostridioides difficile*, allergic reaction, and thrombocytopenia)
- **Larcher et al (2022)** performed a retrospective observational cohort study in 27 patients (30 treatment courses) who received ≥72 h of treatment with cefiderocol, ceftazidime–avibactam–aztreonam, or imipenem–relebactam at Nimes University Hospital in France. Cefiderocol was mainly utilized for DTR *Pseudomonas aeruginosa*, and ceftazidime–avibactam–aztreonam was utilized for NDM-1 producing *Klebsiella pneumoniae*[2]
  - The infection-free survival rates for cefiderocol and ceftazidime–avibactam–aztreonam were 48% (95% CI, 10.4–73.5) and 33.3% (95% CI, 6.7–100), respectively. AEs occurred in 3 (13%) patients who received cefiderocol (eosinophilia, diarrhea, and hepatitis)
- **Kung et al (2024)** assessed the *in vitro* activity of cefiderocol and comparator agents, including aztreonam–avibactam, against non-fermenter, Gram-negative bacterial isolates from hospitalized patients in the US and Europe with pneumonia as part of the SENTRY Antimicrobial Surveillance Program between 2020 and 2022[3]
  - Overall, against *P. aeruginosa* isolates, cefiderocol $MIC_{50/90}$ was 0.06/0.25 mg/L, while $MIC_{50/90}$ for aztreonam–avibactam was 4/>16 mg/L
  - Against CR isolates, cefiderocol $MIC_{50/90}$ was 0.12/0.5 mg/L and aztreonam–avibactam $MIC_{50/90}$ was 16/>16 mg/L
- **Mendes et al (2024)** studied the *in vitro* activity of cefiderocol and comparator agents, including aztreonam–avibactam, against carbapenem-NS isolates of *P. aeruginosa*, including those carrying MBL genes, collected in the US and Europe between 2020 and 2023 as part of the SENTRY Antimicrobial Surveillance Program[4]
  - $MIC_{50/90}$ of cefiderocol against 2236 carbapenem-NS *P. aeruginosa* isolates was 0.12/0.5 mg/L and was 8/>16 mg/L for aztreonam–avibactam
  - In the MBL-producing isolates (n=126), $MIC_{50/90}$ for cefiderocol and aztreonam–avibactam was 0.25/2 mg/L and 8/>16 mg/L, respectively
- **Sader et al (2024)** evaluated the activity of cefiderocol, aztreonam–avibactam, and other agents against Enterobacterales isolates collected from patients in the ICU and non-ICU of 72 US hospitals between 2020 and 2022. Susceptibility results were presented for cefiderocol and aztreonam–avibactam against 192 CRE isolates[5]
  - According to CLSI/FDA breakpoints, susceptibility to cefiderocol was 92.3% in isolates collected in the ICU and 94.9% in the non-ICU setting, while aztreonam–avibactam susceptibility ranged from 96.6 to 100%

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Summary (Cont.)

- **Sader et al (2024)** compared the activity of cefiderocol and comparator agents against 4802 Enterobacterales isolates, including MBL-producers, in BSIs collected from 72 US hospitals between 2020 and 2022. MICs and susceptibility results were presented for cefiderocol and aztreonam–avibactam against CRE and carbapenemase-producers[6]
  - According to CLSI breakpoints, cefiderocol susceptibility was 87.8% against CRE (n=49), while aztreonam–avibactam susceptibility was 98% (breakpoint of ≤8 mg/L)
  - Against carbapenemase-producers (n=43), including KPC, OXA-48, and MBLs, susceptibility was 90.7% and 100% for cefiderocol and aztreonam–avibactam, respectively
- **Henriksen et al (2024)** performed separate *in vitro* analyses of Enterobacterales and *P. aeruginosa* and *Acinetobacter* spp. isolates collected from 6 European countries between January and December 2020. Susceptibility to cefiderocol, aztreonam–avibactam, and other agents were described using CLSI, FDA, and/or EUCAST breakpoints[7,8]
  - Against 1909 Enterobacterales isolates, both cefiderocol and aztreonam–avibactam were active, with MIC_{90} of 2 and ≤1 mg/L, respectively
  - Against 950 *P. aeruginosa* isolates, cefiderocol MIC_{90} was 1 mg/L and aztreonam–avibactam MIC_{90} was 32 mg/L
    - In the CR subset, susceptibility for cefiderocol and aztreonam–avibactam was 97.8% and 41.7%, according to EUCAST breakpoints, respectively
  - Against 501 *Acinetobacter* spp. isolates, cefiderocol MIC_{90} was 2 mg/L and susceptibility was 92.4% (against the CR subset, susceptibility was 85%)
    - Limited data were available for aztreonam–avibactam
- **Wise et al (2023)** performed an *in vitro* analysis of meropenem-NS Enterobacterales, *P. aeruginosa*, and *Acinetobacter baumannii* complex isolates from the multinational SIDERO-WT 2014–2019 surveillance studies. CLSI 2022 susceptibility breakpoints were used. Aztreonam–avibactam (fixed combination of 4 mg/L) was tested against carbapenem-NS Enterobacterales isolates between 2018 and 2019[9]
  - Against the MBL-producing Enterobacterales isolates, $MIC_{50/90}$ were 2/4 and 0.25/1 mg/L, for cefiderocol and aztreonam–avibactam, respectively
  - Against the MBL-producing *P. aeruginosa* isolates, $MIC_{50/90}$ were 0.25/2 and >8/>8 mg/L, for cefiderocol and aztreonam–avibactam, respectively
- **Huang et al (2024)** evaluated the susceptibility of cefiderocol and aztreonam–avibactam against 350 MDR non-fermenter isolates between 2019 and 2021 in Taiwan. Isolates included *A. baumannii*, *P. aeruginosa* (including DTR, CR, and NS strains), and levofloxacin– and trimethoprim–sulfamethoxazole-NS *Stenotrophomonas maltophila*[10]
  - MICs for cefiderocol were low against most pathogens in the study, with an MIC_{50} range of ≤0.06 to >32 mg/L; the MIC_{50} range for aztreonam was 4 to >32 mg/L

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Prospective Study

Falcone et al (2023) performed a prospective observational cohort study in 343 adult patients with monomicrobial infections caused by MBL-producing Enterobacterales consecutively hospitalized at The University Hospital of Pisa in Italy between January 2019 and October 2022. The purpose of this study was to evaluate the clinical and safety outcomes and compare the different antibiotic approaches of patients with MBL-producing Enterobacterales.[1]

Results[1]

- BSI (58%) was the most frequent source of MBL infection followed by HABP/VABP and UTI at 17.5% each
- Of the 343 patients analyzed, 33 (9.6%) received cefiderocol-containing regimens and 215 (62.7%) received ceftazidime–avibactam–aztreonam-containing regimens
- Out of the 343 patients, there were 328 (96%) NDM- and 15 (4%) VIM-producing isolates
- MICs for cefiderocol were determined using disk diffusion methods and interpreted using the EUCAST breakpoints
  - Ceftazidime–avibactam and aztreonam were screened for synergy using a double synergy test followed by an evaluation using a gradient-test superposition method
- Susceptibility of the isolates against cefiderocol was 33.2% and synergy with the combination of ceftazidime–avibactam and aztreonam was 99.7%
- The full antibiotic regimen details with 30-day mortality of the patients treated for MBL-producing Enterobacterales infections can be found in **Table 1**
  - The unadjusted 30-day mortality rate for cefiderocol-containing regimens was 33% (11/33), and 22.3% (48/215) for ceftazidime–avibactam–aztreonam
- After excluding patients who did not receive active *in vitro* antibiotic treatment, a Cox regression model was constructed to evaluate risk factors for mortality and revealed the aHR for 30-day mortality compared to colistin – results are presented in **Table 2**
- AEs occurred in 3/33 (9.1%) patients who received cefiderocol (1 *C. difficile* infection, 1 allergic reaction, and 1 thrombocytopenia). AEs were observed in 9/214 (4.2%) patients who received ceftazidime–avibactam–aztreonam (4 increases in liver function tests, 2 allergy reactions, 2 pancytopenia, and 1 seizure)

Table 1. Antibiotic Regimens and 30-Day Mortality Rates in Patients with MBL-Producing Infections[1]

Antibiotic Regimen	Patients, n (%) (N=345)	Mortality Rate
No *in vitro* active therapy	32 (9.3)	25 (78.1)
Colistin-containing regimens	26 (7.6)	13 (50)
Colistin+tigecycline+fosfomycin	14	
Colistin+fosfomycin	6	
Colistin+piperacillin–tazobactam+aztreonam	1	
Colistin+aztreonam	1	
Colistin alone	4	
Ceftazidime–avibactam–aztreonam regimens	[illegible]7)	48 (22.3)
Ceftazidime–avibactam–aztreonam alone		
Ceftazidime–avibactam–aztreonam+tige[illegible]		
Ceftazidime–avibactam–aztreonam+fosf[illegible]		
Ceftazidime–avibactam–aztreonam+gent[illegible]		
Cefiderocol-containing regimens[2]		11 (33)
Cefiderocol monotherapy		
Cefiderocol+tigecycline		
Cefiderocol+fosfomycin	[illegible]	
Cefiderocol+gentamycin	1	
Other active antibiotics	37 (10.8)	3 (13.5)
Tigecycline±fosfomycin	16	
Fosfomycin alone	15	
Fosfomycin+meropenem	1	
Fosfomycin+gentamycin	1	
Trimethoprim–sulfamethoxazole	3	
Piperacillin–tazobactam+aztreonam	1	
Meropenem–vaborbactam+aztreonam[3]	2 (0.6)	N/A

Table 2. Cox Regression Model of Factors Associated with 30-Day Mortality Among Patients who Received Active Antibiotic Therapy[1]

Factor	aHR (95% CI)	*P* Value
Septic shock	[illegible]38 (1.34–4.21)	0.003
CCI	[illegible]98–1.19)	0.1
Age	[illegible]2–1.08)	0.002
Antibiotic regimen		
Colistin-containing regimens	[illegible]ence	–
Cefiderocol-containing regimens	[illegible].31–2.24)	0.72
Ceftazidime–avibactam–aztreonam regimens	[illegible].39 (0.18–0.86)	0.02
Other active antibiotics	0.42 (0.11–1.65)	0.21

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Table 1. Antibiotic Regimens and 30-Day Mortality Rates in Patients with MBL-Producing Infections[1]

Antibiotic Regimen	Patients, n (%) (N=345)	Mortality Rate n (%)
No *in vitro* active therapy	32 (9.3)	25 (78.1)
Colistin-containing regimens	26 (7.6)	13 (50)
Colistin+tigeycycline±fosfomycin	14	
Colistin+fosfomycin	6	
Colistin+piperacillin–tazobactam+aztreonam	1	
Colistin+aztreonam	1	
Colistin alone	4	
Ceftazidime–avibactam–aztreonam regimens	215 (62.7)	48 (22.3)
Ceftazidime–avibactam–aztreonam alone	170	
Ceftazidime–avibactam–aztreonam+tigecycline	21	
Ceftazidime–avibactam–aztreonam+fosfomycin	23	
Ceftazidime–avibactam–aztreonam+gentamycin	1	
Cefiderocol-containing regimens[a]	33 (9.6)	11 (33)
Cefiderocol monotherapy	4	
Cefiderocol+tigecycline	13	
Cefiderocol+fosfomycin	15	
Cefiderocol+gentamycin	1	
Other active antibiotics	37 (10.8)	3 (13.5)
Tigecycline±fosfomycin	16	
Fosfomycin alone	15	
Fosfomycin+meropenem	1	
Fosfomycin+gentamycin	1	
Trimethoprim–sulfamethoxazole	3	
Piperacillin–tazobactam+aztreonam	1	
Meropenem–vaborbactam+aztreonam[b]	2 (0.6)	N/A

Abbreviations: MBL, metallo-β-lactamase; N/A, not available.
[a]6 patients received cefiderocol+colistin for <48 hours after infection pending *in vitro* susceptibility results. Colistin was then discontinued, and a cefiderocol-containing regimen continued (cefiderocol monotherapy in 3, cefiderocol+tigecycline in 2, and cefiderocol+fosfomycin in 1).
[b]Synergy was assessed by checkerboard assay, as described elsewhere. These patients were not included in the comparative analysis considering the very limited number of cases.
Table adapted from Falcone et al. *Clin Infect Dis*. 2024.

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Prospective Study

Table 2. Cox Regression Model of Factors Associated with 30-Day Mortality Among Patients who Received Active Antibiotic Therapy[1]

Factor	aHR (95% CI)	*P* Value
Septic shock	2.38 (1.34–4.21)	0.003
CCI	1.08 (0.98–1.19)	0.1
Age	1.05 (1.02–1.08)	0.002
Antibiotic regimen		
Colistin-containing regimens	Reference	–
Cefiderocol-containing regimens	0.83 (0.31–2.24)	0.72
Ceftazidime–avibactam–aztreonam regimens	0.39 (0.18–0.86)	0.02
Other active antibiotics	0.42 (0.11–1.65)	0.21

Abbreviations: aHR, adjusted hazard ratio; CCI, Charlson Comorbidity Index; CI, confidence interval.
[a]The Cox regression multivariable model was performed after exclusion of patients who received no *in vitro* active therapy, using a forward stepwise procedure including variables with statistical significance on univariate analysis ($P<0.05$) and those with clinical relevance (source control and active therapy within the first 48 hours). Variables entered in the regression but not retained were source control, active therapy within the first 48 hours, and respiratory tract as source of infection.
Table adapted from Falcone et al. *Clin Infect Dis*. 2024.

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Retrospective Study

Larcher et al (2022) conducted an observational cohort study from January 1, 2020, to August 31, 2022, in 27 patients (30 treatment courses) at Nimes University Hospital in France. Adult patients that were hospitalized and received ≥72 h of treatment with cefiderocol, ceftazidime–avibactam–aztreonam, or imipenem–relebactam during the outlined study period were included.[2]

- The primary objective was infection-free survival rate, defined as survival without recurrence of the infection. In addition, rates of microbiological cure, clinical cure, recurrent infection, AE, and death were also recorded. Follow-up was up to 90 days

Results[2]

- LRTI (53%) was the most common reason for hospital admission, followed by COVID-19 (50%). Ceftazidime–avibactam–aztreonam was primarily used for NDM-1 producing *K. pneumoniae*, whereas cefiderocol and imipenem–relebactam were administered mostly for the treatment of DTR *P. aeruginosa*
- Overall, the infection-free survival rates were:
  - Cefiderocol: 48% (95% CI, 10.4–73.5)
  - Ceftazidime–avibactam–aztreonam: 33.3% (95% CI, 6.7–100)
- Additional antimicrobial characteristics, and outcomes for cefiderocol, and ceftazidime–avibactam–aztreonam are listed in **Table 3**

Table 3. Antimicrobial Characteristics and Outcomes for Cefiderocol and Ceftazidime–Avibactam–Aztreonam[2]

	Cefiderocol (n=24)	Ceftazidime–Avibactam–Aztreonam (n=3)
	n (%) or Median (IQR)	
Infection Site		
Pneumonia	17 (71)	2 (67)
VABP	17 (71)	1 (33)
BSI	5 (21)	1 (33)
CR-BSI	3 (13)	1 (33)
BJI		0
IAI		0
UTI		0
Meningitis		0
Reason for Antibiotic Initiation		
DTR *P. aeruginosa*		0
NDM *K. pneumoniae*		3 (100)
Other		1 (33)
Antimicrobial Therapy Characteristics		
Duration (days)		14 (12–18)
Daily dose (grams)		6/1.5/6
Daily regimen		TID
Infusion time (hours)		2 (2–7)
Combination Therapy		3 (100)
Outcomes		
Death (all-cause)	5 (21)	2 (67)
Sepsis-related	3 (13)	1 (33)
WLS	2 (8)	1 (33)
Clinical failure	7 (29)	2 (66)
Microbiological failure	10 (42)	0
Recurrent infection	5 (21)	0
AEs[a]	3 (13)	0

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Retrospective Study

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	Cefiderocol (n=24)	Ceftazidime–Avibactam–Aztreonam (n=3)
	n (%) or Median (IQR)	
Infection Site		
Pneumonia	17 (71)	2 (67)
VABP	17 (71)	1 (33)
BSI	5 (21)	1 (33)
CR-BSI	3 (13)	1 (33)
BJI	2 (8)	0
IAI	2 (8)	0
UTI	1 (4)	0
Meningitis	1 (4)	0
Reason for Antibiotic Initiation		
DTR *P. aeruginosa*	19 (79)	0
NDM *K. pneumoniae*	1 (4)	3 (100)
Other	6 (25)	1 (33)
Antimicrobial Therapy Characteristics		
Duration (days)	14 (12–31)	14 (12–18)
Daily dose (grams)	6	6/1.5/6
Daily regimen	TID	TID
Infusion time (hours)	3 (3–4)	2 (2–7)
Combination Therapy	13 (54)	3 (100)
Outcomes		
Death (all-cause)	5 (21)	2 (67)
Sepsis-related	3 (13)	1 (33)
WLS	2 (8)	1 (33)
Clinical failure	7 (29)	2 (66)
Microbiological failure	10 (42)	0
Recurrent infection	5 (21)	0
AEs[a]	3 (13)	0

Abbreviations: AEs, adverse events; BJI, bone and joint infection; BSI, bloodstream infection; CR-BSI, catheter-related bloodstream infection; DTR, difficult-to-treat resistant; IAI, intra-abdominal infection; IQR, interquartile range; NDM, New Delhi metallo-β-lactamase; TID, 3 times daily; UTI, urinary tract infection; WLS, withdrawal of life support; VABP, ventilator-associated bacterial pneumonia.
[a]Details of AEs, eosinophilia (cefiderocol n=1), diarrhea (cefiderocol n=1), hepatitis (cefiderocol n=1).
Table adapted from Larcher et al. *Front Cell Infect Microbiol*. 2022.

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Surveillance Studies

Several studies evaluated the *in vitro* susceptibility of cefiderocol and aztreonam–avibactam. ID-CAMHB was used in the MIC determination for cefiderocol and CAMHB for aztreonam–avibactam. Susceptibilities were evaluated according to CLSI, FDA, and/or EUCAST breakpoints.

Aztreonam–Avibactam

Kung et al (2024) assessed the *in vitro* activity of cefiderocol and comparator agents, including aztreonam–avibactam, against non-fermenter Gram-negative bacterial isolates from hospitalized patients with pneumonia as part of the SENTRY Antimicrobial Surveillance Program between 2020 and 2022 collected in the US and Europe.[3]

Results[3]

- A total of 5995 bacterial isolates were collected, with the most common being *P. aeruginosa* (3809 [64%]), of which, 588 were CR
- Cefiderocol showed high susceptibility, which was maintained against CR *P. aeruginosa* isolates
- For information on MIC_{50} and MIC_{90} for cefiderocol compared to aztreonam–avibactam against *P. aeruginosa* isolates, see **Table 4**

Table 4. *In Vitro* Activity of Cefiderocol and Aztreonam–Avibactam against *P. aeruginosa* Isolates from Patients with Pneumonia from 2020–2022[3]

Agent	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC Range (mg/L)	CLSI[a] (%S)	FDA[a] (%S)	EUCAST[a] (%S)
P. aeruginosa **(n=3809)**						
Cefiderocol	0.06	0.25	≤0.004 to >64	99.7	98.3	99.3
Aztreonam–avibactam	4	>16	≤0.03 to >16	NA	NA	NA
CR *P. aeruginosa* **(n=588)**						
Cefiderocol	0.12	0.5	≤0.004 to >16	99.3	96.1	98.6
Aztreonam–avibactam	16	>16	0.12 to >16	NA	NA	NA

Abbreviations: CLSI, Clinical and Laboratory Standards Institute; CR, carbapenem-resistant; EUCAST, European Committee on Antimicrobial Susceptibility Testing; FDA, US Food and Drug Administration; MIC, minimum inhibitory concentration; MIC_{50}, minimum inhibitory concentration to inhibit 50% of growth; MIC_{90}, minimum inhibitory concentration to inhibit 90% of growth; NA, not applicable; S, susceptible.
[a]Criteria as published by CLSI (2024), EUCAST (2024), and FDA (2024).
Table adapted from Kung et al. IDWeek. 2024.

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Surveillance Studies (Cont.)

Mendes et al (2024) assessed the *in vitro* activity of cefiderocol and comparator agents, including aztreonam–avibactam, against carbapenem-NS *P. aeruginosa* isolates, including those harboring MBL genes, collected in the US and Europe between 2020 and 2023 as part of the SENTRY Antimicrobial Surveillance Program.[4]

- 9572 *P. aeruginosa* isolates were collected from hospitalized patients from 36 medical centers in the US and 43 sites across Europe (including Tukey and Israel)

Results[4]

- Of the 9572 isolates collected, 2236 (23.4%) were determined to be carbapenem-NS
  - A total of 5.6% (126/2236) carried MBL genes
- Against the overall population of carbapenem-NS isolates, cefiderocol had a MIC_{50} of 0.12 mg/L and a MIC_{90} of 0.5 mg/L (96–99.4% susceptible), including against both US and European isolates – Table 5
- Cefiderocol demonstrated activity against the MBL-carrying *P. aeruginosa* isolates with a MIC_{50} of 0.25 mg/L and a MIC_{90} of 2 mg/L (85–96% susceptible) – Table 5
- See Table 5 for additional information on *in vitro* activity of cefiderocol and aztreonam–avibactam against *P. aeruginosa* isolates

Table 5. *In Vitro* Activity of Cefiderocol and Aztreonam–Avibactam against Carbapenem-NS *P. aeruginosa* Isolates (and MBL-Carrying Subsets)[4]

Phenotype/Genotype[a] (n)	$MIC_{50/90}$ in mg/L (%S)[b]	
	Cefiderocol	Aztreonam–Avibactam
Carbapenem-NS (2236)	0.12/0.5 (99.2/98.6/96.3)	8/>16 (–)
US (980)		16/>16 (–)
Europe (1256)		8/>16 (–)
MBL-positive[c] (126)		8/>16 (–)
bla$_{IMP}$ (11)		16/>16 (–)
bla$_{NDM}$ (14)	(64.3/57.1/14.3)	4/>16 (–)
bla$_{VIM}$ (99)	0.12/1 (100/99/93.9)	8/>16 (–)

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Surveillance Studies (Cont.)

Table 5. ***In Vitro*** **Activity of Cefiderocol and Aztreonam–Avibactam against Carbapenem-NS** ***P. aeruginosa*** **Isolates (and MBL-Carrying Subsets)**[4]

Phenotype/Genotype[a] (n)	$MIC_{50/90}$ in mg/L (%S)[b]	
	Cefiderocol	Aztreonam–Avibactam
Carbapenem-NS (2236)	0.12/0.5 (99.2/98.6/96.3)	8/>16 (–)
US (980)	0.12/0.5 (99.4/98.9/96.6)	16/>16 (–)
Europe (1256)	0.12/0.5 (99/98.3/96)	8/>16 (–)
MBL-positive[c] (126)	0.25/2 (96/94.4/85)	8/>16 (–)
bla$_{IMP}$ (11)	0.5/1 (100/100/90.9)	16/>16 (–)
bla$_{NDM}$ (14)	2/16 (64.3/57.1/14.3)	4/>16 (–)
bla$_{VIM}$ (99)	0.12/1 (100/99/93.9)	8/>16 (–)

Abbreviations: CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; FDA, US Food and Drug Administration; MBL, metallo-β-lactamases; MIC, minimum inhibitory concentration; $MIC_{50/90}$, minimum inhibitory concentration to inhibit 50% and 90% of growth; NS, non-susceptible; S, susceptibility.

[a]Carbapenem-NS isolates were those NS to imipenem and/or meropenem based on CLSI criteria (MIC values ≥4 mg/L).

[b]Cefiderocol MIC results were interpreted according to the CLSI/EUCAST/FDA criteria for susceptibility (≤4 mg/L, ≤2 mg/L, and ≤1 mg/L, respectively). MIC values for comparator agents interpreted based on the CLSI criteria, except for colistin where the EUCAST susceptible breakpoint was applied.

[c]Includes class B *bla*$_{DIM-1}$ (2), *bla*$_{IMP-1}$ (2), *bla*$_{IMP-7}$ (4), *bla*$_{IMP-8}$ (1), *bla*$_{IMP-10}$ (1), *bla*$_{IMP-13}$ (3), *bla*$_{NDM-1}$ (14), *bla*$_{VIM-1}$ (8), *bla*$_{VIM-1}$ and *bla*$_{HMB-1}$ (1), *bla*$_{VIM-2}$ (80), *bla*$_{VIM-4}$ (7), *bla*$_{VIM-20}$ (2), and *bla*$_{VIM-43}$ (1) genes.

Table adapted from Mendes et al. IDWeek. 2024.

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Surveillance Studies (Cont.)

Sader et al (2024) assessed *in vitro* activity of cefiderocol, aztreonam–avibactam, and other agents against CRE isolates collected in 72 US hospitals from patients in the ICU and non-ICU setting as part of the INFORM program.[5]

- Overall, 21,996 Enterobacterales isolates were collected, of which 195 (0.89%) were CRE
  - Of the 195 CRE isolates, 78 (40.0%) were from ICU patients and 117 (60.0%) were from non-ICU patients
- Pneumonia (52.8%) and UTI (53.6%) were the most common infection sites in the ICU and non-ICU patients, respectively

Results[5]

- Cefiderocol and aztreonam–avibactam were among the most active agents against CRE isolates
- Susceptibility of CRE isolates to cefiderocol and aztreonam–avibactam can be found in **Table 6**

Table 6. Susceptibility of CRE Isolates from ICU and Non-ICU Patients[5]

Agent	Susceptibility (%)[a]	
	ICU (n=78)	Non-ICU (n=117)
Cefiderocol	92.3	94.9
Aztreonam–avibactam	100/98.7[b]	98.3/96.6[b]

Abbreviations: CLSI, Clinical and Laboratory Standards Institute; CRE, carbapenem-resistant Enterobacterales; EUCAST, European Committee on Antimicrobial Susceptibility Testing; FDA, US Food and Drug Administration; ICU, intensive care unit; PD, pharmacodynamic; PK, pharmacokinetic.
[a]Susceptibility per CLSI and/or FDA criteria.
[b]Percent inhibited at ≤8/≤4 mg/L (PK/PD EUCAST susceptible breakpoints, respectively).
Table adapted from Sader et al. *Antibiotics (Basel)*. 2024.

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Surveillance Studies (Cont.)

In an additional analysis, **Sader et al (2024)** analyzed the *in vitro* activity of cefiderocol and comparator agents, including aztreonam–avibactam, against 4802 Enterobacterales isolates collected from BSIs in 72 US hospitals between 2020 and 2022 as part of the INFORM program.[6]

- Susceptibility rates and $MIC_{50/90}$ for cefiderocol and aztreonam–avibactam were available for CRE (n=49) and carbapenemase-producing isolates (n=43)

Results[6]

- Of the 49 CRE isolates, the most common carbapenemase genes were KPC (57.1%), OXA-48-like (16.3%; this also included 1 isolate with OXA-181 and NDM-1), NDM (14.3%; including the isolate also harboring OXA-181), and IMP (2.0%)
- Cefiderocol and aztreonam–avibactam were the most active agents against both the CRE isolates and the carbapenemase-producing isolates – **Table 7**
- Susceptibility of cefiderocol and aztreonam–avibactam against specific carbepenemases can be seen in **Table 8**

Table 7. Activity of Cefiderocol and Aztreonam–Avibactam against Enterobacterales Isolates Collected from BSIs[6]

Agent	MIC_{50} (mg/L)	MIC_{90} (mg/L)	CLSI[a] %S	%I	%R
CRE (n=49)					
Cefiderocol	1			6.1	6.1
Aztreonam–avibactam	0.25			–	–
Carbapenemase-producers (n=43)					
Cefiderocol	1		90.7	4.7	4.7
Aztreonam–avibactam	0.25	0.5	100[b]	–	–

Table 8. Susceptibility Rates of Cefiderocol and Aztreonam–Avibactam against CRE (N=49)[6]

Agent	Susceptibility (%) KPC-Producers (n=28)	MBL-Producers (n=8)	No Carbapenemase (n=6)
Cefiderocol	96.4	62.5	66.7
Aztreonam–avibactam	100	100	66.7

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Surveillance Studies (Cont.)

Table 7. Activity of Cefiderocol and Aztreonam–Avibactam against Enterobacterales Isolates Collected from BSIs[6]

Agent	MIC_{50} (mg/L)	MIC_{90} (mg/L)	CLSI[a]		
			%S	%I	%R
CRE (n=49)					
Cefiderocol	1	8	87.8	6.1	6.1
Aztreonam–avibactam	0.25	1	98[b]	–	–
Carbapenemase-producers (n=43)					
Cefiderocol	1	4	90.7	4.7	4.7
Aztreonam–avibactam	0.25	0.5	100[b]	–	–

Abbreviations: BSI, bloodstream infection; CLSI, Clinical and Laboratory Standards Institute; CRE, carbapenem-resistant Enterobacterales; I, intermediate; MIC_{50}, minimum inhibitory concentration to inhibit 50% of bacterial growth; MIC_{90}, minimum inhibitory concentration to inhibit 90% of bacterial growth; R, resistant; S, susceptible.

[a]According to CLSI (2023).

[b]% inhibited at ≤8 mg/L.

Table adapted from Sader et al. *BMC Infect Dis*. 2024.

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Surveillance Studies (Cont.)

Table 8. Susceptibility Rates of Cefiderocol and Aztreonam–Avibactam against CRE (N=49)[6]

Agent	Susceptibility (%)			
	KPC-Producers (n=28)	OXA-48-Producers (n=7)	MBL-Producers (n=8)	No Carbapenemase (n=6)
Cefiderocol	96.4	100	62.5	66.7
Aztreonam–avibactam	100	100	100	66.7

Abbreviations: CRE, carbapenem-resistant Enterobacterales; KPC, *Klebsiella pneumoniae* carbapenemase; MBL, metallo-β-lactamase; OXA, oxacillinase.
Table adapted from Sader et al. *BMC Infect Dis*. 2024.

- Susceptibility of cefiderocol and aztreonam–avibactam against specific carbepenemases can be seen in **Table 8**

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Surveillance Studies (Cont.)

Henriksen et al (2024) performed 2 separate *in vitro* analyses of cefiderocol and comparator agents, including aztreonam–avibactam, against Enterobacterales and *P. aeruginosa* and *Acinetobacter* spp. isolates collected in 6 European countries in 2020.[7,8]

Enterobacterales[7]

- Overall, 1909 Enterobacterales isolates were collected
  - The most common pathogens were *Klebsiella* spp. (n=970), *Escherichia coli* (n=382), and *Enterobacter* spp. (n=244)
  - The most common infections sites were the bloodstream (43.6%), respiratory tract (22.6%), and skin (16%)
  - Of the 1909 isolates collected, 148 (7.8%) were CRE, with various β-lactamases identified, including MBLs
- Cefiderocol and aztreonam–avibactam demonstrated strong activity against the Enterobacterales isolates and remained highly active against the CR isolates (Table 9)
- Activity was higher with aztreonam–avibactam against isolates harboring β-lactamase genes (Table 10)

P. aeruginosa and *Acinetobacter* spp.[8]

- Overall, 1451 isolates were collected (950 [65.5%] *P. aeruginosa*, and 501 [34.5%] *Acinetobacter* spp.)
  - The most common infection sites for both pathogens was respiratory tract, bloodstream, and skin
  - In total, 139/950 (14.6%) of the *P. aeruginosa* isolates and 227/501 (45.3%) of the *Acinetobacter* spp. isolates were CR
  - Cefiderocol susceptibility rates were determined using CLSI or FDA breakpoints, depending on availability
- Susceptibility rates of cefiderocol and aztreonam–avibactam were high against *P. aeruginosa* isolates. Limited susceptibility data were available for aztreonam–avibactam in *Acinetobacter* spp. isolates (Table 11)
- Against CR strains of both *P. aeruginosa* and *Acinetobacter*, cefiderocol susceptibility retained activity

Table 9. *In Vitro* Activity of Cefiderocol and Aztreonam–Avibactam against Enterobacterales Isolates[7]

Isolate (n)	Cefiderocol		Aztreonam–Avibactam	
		%S	MIC_{90} (mg/L)	%S
Enterobacterales (1909)		98.1	≤1	99.1
CRE (148)		87.8	≤1	98.6
CR+ceftazidime–avibactam-resistant (42)		61.9	1	97.6
CR+meropenem–vaborbactam-resistant (43)		65.1	1	97.7
CR+imipenem–relebactam-resistant (44)	8	65.9	≤1	95.5

Table 10. *In Vitro* Activity of Cefiderocol and Aztreonam–Avibactam against CRE Isolates Harboring β-Lactamase Genes[7]

Isolate (n)	Cefiderocol			Aztreonam–Avibactam		
	MIC_{90} (mg/L)	%S		MIC_{90} (mg/L)	%S	
		EUCAST	CLSI		EUCAST	CLSI
OXA (18)	16	44.4		<1	94.4	94.4
NDM (27)	16			<1	100	100
VIM (8)	32			1	100	100
KPC (110)	2			1	100	100
SHV (122)	2	95		<1	97.5	97.5
TEM (71)	2	93		<1	98.6	98.6
CTX-M (37)	8	89.2	89.2	<1	97.3	97.3
AmpC[b] (20)	16	55	70	<1	95	95

Table 11. Susceptibility Rates of Cefiderocol and Aztreonam–Avibactam against *P. aeruginosa* and *Acinetobacter* spp. Isolates[8]

Isolate (n)	Cefiderocol		Aztreonam–Avibactam	
	MIC	%S[b]	MIC_{90} (mg/L)	%S[b]
P. aeruginosa (950)			32	86.2
CR *P. aeruginosa* (139)			–	41.7
CR+ceftazidime–avibactam-resistant (60)			–	45
CR+ceftolozane–tazobactam-resistant (62)			–	54.8
Acinetobacter spp.[c] (501)		92.4	N/A	N/A
CR *Acinetobacter* spp. (227)	–	85	–	N/A

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Surveillance Studies (Cont.)

Table 9. ***In Vitro*** **Activity of Cefiderocol and Aztreonam–Avibactam against Enterobacterales Isolates**[7]

Isolate (n)	Cefiderocol		Aztreonam–Avibactam	
	MIC_{90} (mg/L)	%S	MIC_{90} (mg/L)	%S
Enterobacterales (1909)	2	98.1	≤1	99.1
CRE (148)	4	87.8	≤1	98.6
CR+ceftazidime–avibactam-resistant (42)	8	61.9	1	97.6
CR+meropenem–vaborbactam-resistant (43)	8	65.1	1	97.7
CR+imipenem–relebactam-resistant (44)	8	65.9	≤1	95.5

Abbreviations: CR, carbapenem-resistant; CRE, carbapenem-resistant Enterobacterales; MIC_{90}, minimum inhibitory concentration at which growth is inhibited in 90% of isolates; S, susceptible.
[a]Results are not reported for isolates tested against antibiotics to which they had an expected resistance phenotype. Susceptibility was assessed according to EUCAST breakpoints (including high dosage breakpoints and breakpoints for the agent without inhibitor, where necessary). Data are shown where n≥20 isolates were available.
Table adapted from Henriksen et al. *Microbiol Spectr*. 2024;12(8):e0418123.

P. aeruginosa, and 501 [34.5%] *Acinetobacter* spp.)

- The most common infection sites for both pathogens was respiratory tract, bloodstream, and skin
- In total, 139/950 (14.6%) of the *P. aeruginosa* isolates and 227/501 (45.3%) of the *Acinetobacter* spp. isolates, were CR
- Cefiderocol susceptibility rates were determined used CLSI or FDA breakpoints, depending on availability

- Susceptibility rates of cefiderocol and aztreonam–avibactam were high against *P. aeruginosa* isolates. Limited susceptibility data were available for aztreonam–avibactam in *Acinetobacter* spp. isolates (**Table 11**)
- Against CR strains of both *P. aeruginosa* and *Acinetobacter*, cefiderocol susceptibility retained activity

Table 11. Susceptibility Rates of Cefiderocol and Aztreonam–Avibactam against *P. aeruginosa* and *Acinetobacter* spp. Isolates[8]

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Surveillance Studies (Cont.)

Table 10. *In Vitro* Activity of Cefiderocol and Aztreonam–Avibactam against CRE Isolates Harboring β-Lactamase Genes[7]

Isolate (n)	Cefiderocol			Aztreonam–Avibactam		
	MIC_{90} (mg/L)	%S		MIC_{90} (mg/L)	%S	
		EUCAST	CLSI		EUCAST	CLSI
OXA (18)	16	44.4	61.1	<1	94.4	94.4
NDM (27)	16	48.1	70.4	<1	100	100
VIM (8)	32	87.5	87.5	<1	100	100
KPC (110)	2	97.3	99.1	<1	100	100
SHV (122)	2	95.9	97.5	<1	97.5	97.5
TEM (71)	2	93	97.2	<1	98.6	98.6
CTX-M (37)	8	89.2	89.2	<1	97.3	97.3
AmpC[b] (20)	16	55	70	<1	95	95

Abbreviations: AmpC, ampicillinase C; CLSI, Clinical and Laboratory Standards Institute; CR, carbapenem-resistant; CRE, carbapenem-resistant Enterobacterales; CTX, cefotaximase; EUCAST, European Committee on Antimicrobial Susceptibility Testing; KPC, *Klebsiella pneumoniae* carbapenemase; MBL, metallo-β-lactamase; MIC_{90}, minimum inhibitory concentration at which growth is inhibited in 90% of isolates; NDM, New Delhi metallo-β-lactamase; OXA, oxacillinase; S, susceptible; SHV, sulfhydryl variable; TEM, Temoneira; VIM, Verona integron-borne metallo-β-lactamase.
[a]Resistant phenotypes were defined according to EUCAST breakpoints. Susceptibility was assessed according to EUCAST and CLSI breakpoints. Of the 148 meropenem-resistant Enterobacterales isolates, 147 harbored at least 1 acquired β-lactamase.
[b]Includes CMY, DHA, ACT, and MIR genes.
Table adapted from Henriksen et al. *Microbiol Spectr*. 2024;12(8):e0418123.

- Susceptibility rates of cefiderocol and aztreonam–avibactam were high against *P. aeruginosa* isolates. Limited susceptibility data were available for aztreonam–avibactam in *Acinetobacter* spp. isolates (**Table 11**)
- Against CR strains of both *P. aeruginosa* and *Acinetobacter*, cefiderocol susceptibility retained activity

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Surveillance Studies (Cont.)

Table 11. Susceptibility Rates of Cefiderocol and Aztreonam–Avibactam against *P. aeruginosa* and *Acinetobacter* spp. Isolates[8]

Isolate (n)	Cefiderocol		Aztreonam–Avibactam	
	MIC_{90} (mg/L)	%S[b]	MIC_{90} (mg/L)	%S[b]
P. aeruginosa (950)	1	98.9	32	86.2
CR *P. aeruginosa* (139)	–	97.8	–	41.7
CR+ceftazidime–avibactam-resistant (60)	–	96.7	–	45
CR+ceftolozane–tazobactam-resistant (62)	–	98.4	–	54.8
Acinetobacter spp.[c] (501)	2	92.4	N/A	N/A
CR *Acinetobacter* spp. (227)	–	85	–	N/A

Abbreviations: CR, carbapenem-resistant; EUCAST, European Committee on Antimicrobial Susceptibility Testing; MIC_{90}, minimum inhibitory concentration at which growth is inhibited in 90% of isolates; N/A, not applicable; PD, pharmacodynamic; PK, pharmacokinetic; S, susceptible.
[a]Antimicrobials were tested against *P. aeruginosa* and/or *Acinetobacter* spp. based on expected use in a real-world setting. Results are not reported for isolates tested against antibiotics to which they had an expected resistance phenotype. Susceptibility was assessed according to EUCAST breakpoints (including non-species-specific PK/PD breakpoints, high dosage breakpoints, and breakpoints for the agent without inhibitor, where applicable). Data are shown where n≥20 isolates were available.
[b]Refers to susceptibility, or susceptibility with increased exposure for aztreonam–avibactam.
[c]Includes 458 *A. baumannii* complex isolates.
Table adapted from Henriksen et al. *Microbiol Spectr*. 2024;12(4):e0383623.

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Surveillance Studies (Cont.)

Wise et al (2023) evaluated the *in vitro* activity of cefiderocol against Gram-negative clinical isolates collected from North America and Europe in 5 multinational surveillance studies (SIDERO-WT-2014–2019).[9]

Methods[9]

- The collection of organisms, along with testing of isolates, and data analysis were independently conducted by IHMA
  - Specimens were obtained from patients with BSIs, SSTIs, LRTIs, UTIs, or IAIs
- Meropenem-NS isolates were screened by WGS or by multiplex PCR followed by Sanger sequencing for molecular characterization
- Aztreonam–avibactam was tested as a fixed combination of 4 mg/L against meropenem-NS Enterobacterales isolates between 2018 and 2019

Results[9]

- Susceptibility profiles of the meropenem-NS MBL-producing Enterobacterales and *P. aeruginosa* isolates from SIDERO-WT-2014–2019 against cefiderocol and aztreonam–avibactam are shown in Table 12 and Table 13

Table 12. Cumulative Antimicrobial Susceptibility Testing Results from SIDERO-WT-2014–2019 for Meropenem-NS MBL-Producing Enterobacterales Isolates (North America and Europe)[9]

Isolate Type	MIC (mg/L)				CLSI MIC Interpretation		
	Antimicrobial Agent	Range	MIC_{50}	MIC_{90}	%S	%I	%R
MBL n=211[a]	Cefiderocol	0.06 to 128	2	4	91.5	5.7	2.8
	Aztreonam–avibactam (n=92)[b]			1	N/A[c]	N/A	N/A
VIM n=113[a]	Cefiderocol			4	96.5	1.8	1.8
	Aztreonam–avibactam (n=39)[b]			2	N/A	N/A	N/A
NDM n=96[a]	Cefiderocol		2	8	85.4	10.4	4.2
	Aztreonam–avibactam (n=51)[b]	≤0.12 to >8	0.25	1	N/A	N/A	N/A

Table 13. Cumulative Antimicrobial Susceptibility Testing Results from SIDERO-WT-2014–2019 for Meropenem-NS MBL-Producing *P. aeruginosa* Isolates (North America and Europe)[9]

Isolate Type	MIC (mg/L)				CLSI MIC Interpretation		
	Antimicrobial Agent	Range	MIC_{50}	MIC_{90}	%S	%I	%R
MBL n=227[a]	Cefiderocol	0.008 to 4	0.25	2	100	0	0
	Aztreonam–avibactam (n=76)[b]			>8	N/A[d]	N/A	N/A
VIM n=200[a]	Cefiderocol			1	100	0	0
	Aztreonam–avibactam (n=65)[b]			>8	N/A	N/A	N/A
IMP n=25[a]	Cefiderocol		2	4	100	0	0
	Aztreonam–avibactam (n=9)[b]	8 to >8	ND[c]	ND	N/A	N/A	N/A

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Surveillance Studies (Cont.)

Table 12. Cumulative Antimicrobial Susceptibility Testing Results from SIDERO-WT-2014–2019 for Meropenem-NS MBL-Producing Enterobacterales Isolates (North America and Europe)[9]

Isolate Type	MIC (mg/L)				CLSI MIC Interpretation		
	Antimicrobial Agent	Range	MIC_{50}	MIC_{90}	%S	%I	%R
MBL n=211[a]	Cefiderocol	0.06 to 128	2	4	91.5	5.7	2.8
	Aztreonam–avibactam (n=92)[b]	≤0.12 to >8	0.25	1	N/A[c]	N/A	N/A
VIM n=113[a]	Cefiderocol	0.12 to 16	1	4	96.5	1.8	1.8
	Aztreonam–avibactam (n=39)[b]	≤0.12 to >8	≤0.12	2	N/A	N/A	N/A
NDM n=96[a]	Cefiderocol	0.12 to 128	2	8	85.4	10.4	4.2
	Aztreonam–avibactam (n=51)[b]	≤0.12 to >8	0.25	1	N/A	N/A	N/A

Abbreviations: AmpC, ampicillinase C; ESBL, extended-spectrum β-lactamase; I, intermediate; MBL, metallo-β-lactamase; MIC, minimum inhibitory concentration; MIC_{50}, minimum inhibitory concentration at which growth is inhibited in 50% of isolates; MIC_{90}, minimum inhibitory concentration at which growth is inhibited in 90% of isolates; NDM, New Delhi metallo-β-lactamase; R, resistant; S, susceptible; VIM, Verona integron-encoded metallo-β-lactamase.

[a]Isolates may also harbor serine carbapenemases, ESBLs, or AmpC-type enzymes.

[b]Aztreonam–avibactam was only tested in 2018 and 2019.

[c]N/A, MIC breakpoints are not available.

Table adapted from Wise et al. *Microb Drug Resist*. 2023.

Fetroja® – Comparison to Aztreonam–Avibactam (including Aztreonam plus Ceftazidime–Avibactam)

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Surveillance Studies (Cont.)

Table 13. Cumulative Antimicrobial Susceptibility Testing Results from SIDERO-WT-2014–2019 for Meropenem-NS MBL-Producing *P. aeruginosa* Isolates (North America and Europe)[9]

Isolate Type	MIC (mg/L)				CLSI MIC Interpretation		
	Antimicrobial Agent	Range	MIC_{50}	MIC_{90}	%S	%I	%R
MBL n=227[a]	Cefiderocol	0.008 to 4	0.25	2	100	0	0
	Aztreonam–avibactam (n=76)[b]	0.25 to >8	>8	>8	N/A[d]	N/A	N/A
VIM n=200[a]	Cefiderocol	0.008 to 4	0.25	1	100	0	0
	Aztreonam–avibactam (n=65)[b]	0.25 to >8	>8	>8	N/A	N/A	N/A
IMP n=25[a]	Cefiderocol	0.12 to 4	2	4	100	0	0
	Aztreonam–avibactam (n=9)[b]	8 to >8	ND[c]	ND	N/A	N/A	N/A

Abbreviations: AmpC, ampicillinase C; ESBL, extended-spectrum β-lactamase; I, intermediate; IMP, imipenemase; MBL, metallo-β-lactamase; MIC, minimum inhibitory concentration; MIC_{50}, minimum inhibitory concentration at which growth is inhibited in 50% of isolates; MIC_{90}, minimum inhibitory concentration at which growth is inhibited in 90% of isolates; ND, not determined; R, resistant; S, susceptible; VIM, Verona integron-encoded metallo-β-lactamase.

[a]Isolates may also harbor serine carbapenemases, ESBLs, or AmpC-type enzymes.

[b]Aztreonam–avibactam was only tested in 2018 and 2019.

[c]ND, not determined because isolate count was <10.

[d]N/A, MIC breakpoints were not available.

Table adapted from Wise et al. *Microb Drug Resist*. 2023.

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Surveillance Studies (Cont.)

Huang et al (2024) evaluated the susceptibility of cefiderocol, aztreonam–avibactam, and ceftazidime–avibactam against various isolates (N=350) of Gram-negative bacteria between 2019 and 2021 in Taiwan.[10]

- Isolates collected included:
  - 126 MDR *A. baumannii*
  - 110 imipenem-resistant *P. aeruginosa* (including 14 DTR isolates)
  - 47 levofloxacin- or trimethoprim–sulfamethoxazole-NS *S. maltophilia*
  - 45 ceftazidime- and meropenem-NS *Burkholderia cepacia* complex
  - 22 ciprofloxacin-NS *Elizabethkingia* spp. isolates

Results[10]

- Overall, MICs for cefiderocol were low against most pathogens in the study, with a MIC_{50} range of ≤0.06 to >32 mg/L
- Aztreonam–avibactam also demonstrated *in vitro* activity against these pathogens, with a MIC_{50} range of 4 to >32 mg/L
- See **Table 14** for additional information on *in vitro* activity of cefiderocol and aztreonam–avibactam

Table 14. MICs of Cefiderocol and Aztreonam–Avibactam against Gram-Negative Bacterial Isolates in Taiwan[10]

Bacteria	Antibiotic	MIC (mg/L)			Susceptibility (breakpoint, mg/L)
		MIC Range	MIC_{50}	MIC_{90}	
MDR *A. baumannii* (n=126)	Cefiderocol	≤0.06 to >32	0.25	2	94.4 (≤4)
	Aztreonam–avibactam	16 to >32	>32	>32	NA
Imipenem-resistant *P. aeruginosa* (n=110)	Cefiderocol	≤0.06 to 4	0.25	1	100 (≤4)
	Aztreonam–avibactam[a]	0.125 to >32	16	>32	12.7 (≤8/4)
Imipenem-resistant *P. aeruginosa*, excluding DTR strains (n=96)	Cefiderocol		0.25	1	100 (≤4)
	Aztreonam–avibac		16	>32	43.8 (≤8/4)
DTR *P. aeruginosa* (n=14)	Cefiderocol		0.25	1	100 (≤4)
	Aztreonam–avibac		32	>32	7.1 (≤8/4)
Ceftazidime- and meropenem-NS *B. cepacia* complex (n=45)[b]	Cefiderocol		≤0.06	≤0.06	100 (≤4)
	Aztreonam–avibactam	8 to >32	8	16	86.7 (≤8/4)
Levofloxacin- or trimethoprim–sulfamethoxazole-NS | *S. maltophilia* (n=47)	Cefiderocol	≤0.06 to 2	≤0.06	0.25	97.9 (≤1)
	Aztreonam–avibactam	1 to 16	4	8	NA
Ciprofloxacin-NS *Elizabethkingia* spp. isolates (n=22)	Cefiderocol	2 to >32	>32	>32	NA
	Aztreonam–avibactam	>32 to >32	>32	>32	NA

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Surveillance Studies (Cont.)

Table 14. MICs of Cefiderocol and Aztreonam–Avibactam against Gram-Negative Bacterial Isolates in Taiwan[10]

Bacteria	Antibiotic	MIC (mg/L)			Susceptibility (breakpoint, mg/L)
		MIC Range	MIC_{50}	MIC_{90}	
MDR *A. baumannii* (n=126)	Cefiderocol	≤0.06 to >32	0.25	2	94.4 (≤4)
	Aztreonam–avibactam	16 to >32	>32	>32	NA
Imipenem-resistant *P. aeruginosa* (n=110)	Cefiderocol	≤0.06 to 4	0.25	1	100 (≤4)
	Aztreonam–avibactam[a]	0.125 to >32	16	>32	12.7 (≤8/4)
Imipenem-resistant *P. aeruginosa*, excluding DTR strains (n=96)	Cefiderocol	≤0.06 to 4	0.25	1	100 (≤4)
	Aztreonam–avibactam[a]	0.125 to >32	16	>32	43.8 (≤8/4)
DTR *P. aeruginosa* (n=14)	Cefiderocol	0.125 to 4	0.25	1	100 (≤4)
	Aztreonam–avibactam[a]	4 to >32	32	>32	7.1 (≤8/4)
Ceftazidime- and meropenem-NS *B. cepacia* complex (n=45)[b]	Cefiderocol	≤0.06 to 0.125	≤0.06	≤0.06	100 (≤4)
	Aztreonam–avibactam	8 to >32	8	16	86.7 (≤8/4)
Levofloxacin- or trimethoprim–sulfamethoxazole-NS *S. maltophilia* (n=47)	Cefiderocol	≤0.06 to 2	≤0.06	0.25	97.9 (≤1)
	Aztreonam–avibactam	1 to 16	4	8	NA
Ciprofloxacin-NS *Elizabethkingia* spp. isolates (n=22)	Cefiderocol	2 to >32	>32	>32	NA
	Aztreonam–avibactam	>32 to >32	>32	>32	NA

Abbreviations: DTR, difficult-to-treat resistant; MDR, multidrug-resistant; MIC, minimum inhibitory concentration; MIC_{50}, minimum inhibitory concentration at which growth of 50% of isolates is inhibited; MIC_{90}, minimum inhibitory concentration at which growth of 90% of isolates is inhibited; NA, not applicable; NS, non-susceptible.

[a]Susceptibility interpretations of aztreonam–avibactam were based on CLSI aztreonam interpretive criteria against *P. aeruginosa* with a fixed concentration of avibactam at 4 mg/L.

[b]Susceptibility interpretations of cefiderocol, and aztreonam–avibactam were based on same interpretive criteria against *P. aeruginosa*.

Table adapted from Huang et al. *JAC Antimicrob Resist*. 2024.

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Relevant Prescribing Information

Fetroja® is indicated in patients 18 years of age or older for the treatment of:[11]

- Complicated urinary tract infections (cUTIs), including pyelonephritis caused by the following susceptible Gram-negative microorganisms:
  - *Escherichia coli*
  - *Klebsiella pneumoniae*
  - *Proteus mirabilis*
  - *Pseudomonas aeruginosa*
  - *Enterobacter cloacae* complex
- Hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP), caused by the following susceptible Gram-negative microorganisms:
  - *Acinetobacter baumannii* complex
  - *Escherichia coli*
  - *Enterobacter cloacae* complex
  - *Klebsiella pneumoniae*
  - *Pseudomonas aeruginosa*
  - *Serratia marcescens*

Fetroja is contraindicated in:[11]

- Patients with a known history of severe hypersensitivity to cefiderocol or other beta-lactam antibacterial drugs, or any other component of **Fetroja**

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Literature Search

As of June 2026, a computerized search of the published medical literature using internal and external databases (ie, Medline® and Embase®) has identified several additional relevant references regarding the comparison of cefiderocol to either ceftazidime–avibactam and aztreonam or aztreonam–avibactam For your review, these references are listed below:

- Castanheira M, Kimbrough JH, Morgan GM, Karr M, Sader HS. Activity of aztreonam-avibactam, cefiderocol, and cefepime-taniborbactam against a global collection of genetically characterized metallo-β-lactamase-producing Enterobacterales. *Antimicrob Agents Chemother*. 2026;70(1):e0084225. doi:10.1128/aac.00842-25 [Web Link]

- Sengupta M, Ammy K, Banik I, Ghoshal U, Banerjee S. Outstanding presence of New Delhi metallo-beta-lactamase in carbapenem-resistant Enterobacterales and exceptionally potent *in vitro* activity of cefiderocol and aztreonam-avibactam emphasises their immediate access in India. *Trans R Soc Trop Med Hyg*. 2026;120(5):575-581. [Web Link]

- Estabrook M, Dickson J, Stone G, Perez K, Sahm DF. P-1335. The *in vitro* activities of aztreonam-avibactam and cefiderocol against metallo-β-lactamase-producing Enterobacterales isolates collected as a part of the ATLAS Global Surveillance Program, 2021-2022. *Open Forum Infect Dis*. 2026;13(Suppl 1):ofaf695.1523. Published 2026 Jan 11. doi:10.1093/ofid/ofaf695.1523 [Web Link]

- Emeraud C, Dutkiewicz M, Dortet L. Comparative *in vitro* efficacy of aztreonam-avibactam and other alternatives (cefepime-taniborbactam, cefepime-zidebactam, and cefiderocol) against metallo-β-lactamase-producing Enterobacterales isolated in 2024 in France. *Antimicrob Agents Chemother*. 2026;70(5):e0017626. doi:10.1128/aac.00176-26 [Web Link]

- Meini S, Del Cesta R, Sbrana F, et al. Clinical outcomes of patients hospitalized in internal medicine wards adequately treated for bloodstream infections caused by NDM-producing *Klebsiella pneumoniae*. Results from a real-life retrospective multi-center study in an endemic area. *Infection*. 2025;53(5):1737-1744. doi:10.1007/s15010-025-02488-x [Web Link]

- Blanco AC, Sáez ABG, Cristobal CP, et al. Evaluating the susceptibility of MBL carbapenemase-producing Enterobacteriaceae and Pseudomonas spp. to ceftazidime/avibactam plus aztreonam and Cefiderocol: A synergy study and susceptibility profile. *J Microbiol Methods*. 2025;239:107311. doi:10.1016/j.mimet.2025.107311 [Web Link]

- Benyahia M, Magnan C, Jean-Pierre V, et al. TROJAN-MDR: *in vitro* activity of cefiderocol and comparators against multidrug-resistant Enterobacterales and *Pseudomonas aeruginosa* strains in Southern France, evaluation of available testing methods performances. *Ann Clin Microbiol Antimicrob*. 2025;24(1):20. Published 2025 Mar 19. doi:10.1186/s12941-025-00785-9 [Web Link]

- Sader HS, Mendes RE, Kimbrough JH, Papp-Wallace KM, Winkler ML, Castanheira M. Antimicrobial susceptibility of Enterobacterales causing infection in the elderly: focus on aztreonam-avibactam and recently approved β-lactamase inhibitor combinations. *JAC Antimicrob Resist*. 2025;7(5):dlaf189. Published 2025 Oct 22. doi:10.1093/jacamr/dlaf189 [Web Link]

- Sader HS, Kimbrough JH, Kockler Z, Debabov D, Mendes RE, Castanheira M. Antimicrobial activity of aztreonam-avibactam and molecular characterization of enterobacterales resistant to ceftazidime-avibactam and/or meropenem-vaborbactam from United States medical centers (2016–2024). Presented at: IDWeek; October 19-22, 2025: Atlanta, GA.

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Literature Search (Cont.)

- Sader HS, Mendes RE, Winkler ML, Debabov D, Kimbrough JH, Castanheira M. Activity of aztreonam-avibactam and comparators against difficult-to-treat resistant Enterobacterales from United States medical centers (2020–2024). Presented at: IDWeek; October 19-22, 2025: Atlanta, GA.

- Senchyna F, Murugesan K, Rotunno W, Nadimpalli SS, Deresinski S, Banaei N. Sequential treatment failure with aztreonam-ceftazidime-avibactam followed by cefiderocol due to preexisting and acquired mechanisms if a New Delhi metallo-β-lactamase-producing *Escherichia coli* causing fatal bloodstream infection. *Clin Infect Dis*. 2024;78(6):1425-1428. [Web Link]

- Yasmin M, Rojas LJ, Marshall SH, et al. Characterization of a novel pathogen in immunocompromised patients: *Elizabethkingia anophelis*-exploring the scope of resistance to contemporary antimicrobial agents and β-lactamase inhibitors. *Open Forum Infect Dis*. 2023;10(2):ofad014. [Web Link]

Please keep in mind that medical literature databases, while considered a major source of biomedical information, are selective in their sources, and the information derived from them should not be considered all-inclusive.

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Abbreviations

AE	adverse event	IQR	interquartile range
aHR	adjusted hazard ratio	KPC	*Klebsiella pneumoniae* carbapenemase
AmpC	ampicillinase C	LRTI	lower respiratory tract infection
BJI	bone and joint infection	MBL	metallo-β-lactamase
BSI	bloodstream infection	MDR	multidrug-resistant
CAMHB	cation-adjusted Mueller Hinton broth	MIC	minimum inhibitory concentration
CCI	Charlson Comorbidity Index	NA	not applicable
CI	confidence interval	N/A	not available
CLSI	Clinical and Laboratory Standards Institute	ND	not determined
CR	carbapenem-resistant	NDM	New Delhi metallo-β-lactamase
CR-BSI	catheter-related bloodstream infection	NS	non-susceptible
CRE	carbapenem-resistant Enterobacterales	OXA	oxacillinase
CTX	cefotaximase	PCR	polymerase chain reaction
cUTI	complicated urinary tract infection	R	resistant
DTR	difficult-to-treat resistant	S	susceptible
EUCAST	European Committee on Antimicrobial Susceptibility Testing	SHV	sulfhydryl variable
FDA	US Food and Drug Administration	TEM	Temoneira
h	hours	TID	3 times daily
HABP	hospital-acquired bacterial pneumonia	US	United States
I	intermediate	UTI	urinary tract infection
IAI	intra-abdominal infection	VABP	ventilator-associated bacterial pneumonia
ICU	intensive care unit	VIM	Verona integron-encoded metallo-β-lactamase
ID-CAMHB	iron-depleted cation-adjusted Mueller Hinton broth	WGS	whole genome sequencing
IHMA	International Health Management Associates	WLS	withdrawal of life support
INFORM	International Network for Optimal Resistant Monitoring		

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2. Larcher R, Laffont-Lozes P, Roger C, et al. Last resort beta-lactam antibiotics for treatment of New-Delhi metallo-beta-lactamase producing Enterobacterales and other difficult-to-treat resistance in Gram-negative bacteria: a real-life study. *Front Cell Infect Microbiol*. 2022;12:1048633. [Web Link]
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4. Mendes RE, Beekman D, Karr M, Kimbrough JH, Sader HS, Castanheira M. Cefiderocol activity against *Pseudomonas aeruginosa* clinical isolates carrying metallo-β-lactamase genes in United States and European hospitals (2020–2023). Poster presented at: IDWeek 2024; October 16-19, 2024; Los Angeles, CA.
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6. Sader HS, Kimbrough JH, Mendes RE, Castanheira M. Antimicrobial susceptibility of Enterobacterales causing bloodstream infection in United States medical centres: comparison of aztreonam-avibactam with beta-lactams active against carbapenem-resistant Enterobacterales. *BMC Infect Dis*. 2024;24(1):1242. [Web Link]
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11. Fetroja® (cefiderocol) for injection, for intravenous use [Prescribing Information]. Shionogi Inc.

Enclosure

Fetroja® (cefiderocol) for injection, for intravenous use [Prescribing Information]. Shionogi Inc.