P1295

Activity of ceftazidime-avibactam against isolates of *Enterobacteriaceae* and *Pseudomonas aeruginosa* collected in Europe as part of the INFORM global surveillance program, 2015

IHMA, Inc.
2122 Palmer Drive
Schaumburg, IL 60173 USA
Phone: +1.847.303.5003
Fax: +1.847.303.5601
www.ihmainc.com

K. Kazmierczak[1], M. Estabrook[1], B. L. M. de Jonge[2], G. Stone[2], D. Sahm[1] [1]International Health Management Associates, Schaumburg, IL, USA [2]Formerly of AstraZeneca Pharmaceuticals, Waltham, MA, USA

Abstract

Background: Avibactam is a non-β-lactam β-lactamase inhibitor that restores the *in vitro* activity of ceftazidime against class A, class C, and some class D β-lactamases, including extended-spectrum β-lactamases (ESBL), serine carbapenemases, and the chromosomal AmpC of *Pseudomonas aeruginosa*. Ceftazidime-avibactam has been approved in Europe and the US for several indications. This study evaluated the *in vitro* activity of ceftazidime-avibactam and comparators against *Enterobacteriaceae* and *P. aeruginosa* collected in Europe in 2015 as part of the INFORM surveillance program. **Materials/methods:** Non-duplicate isolates were collected from 67 medical centers in 17 European countries. Susceptibility testing was performed by broth microdilution and interpreted using EUCAST breakpoints (ceftazidime-avibactam: ≤8 mg/L, susceptible; >8 mg/L, resistant). Avibactam was tested at a fixed concentration of 4 mg/L with doubling dilutions of ceftazidime. Multidrug resistant (MDR) was defined as resistant by EUCAST breakpoints to sentinel agents from three or more drug classes, including cefepime, aztreonam, piperacillin-tazobactam, meropenem, levofloxacin, amikacin, tigecycline, and colistin. *P. aeruginosa* isolates with a meropenem MIC >2 mg/L and *Enterobacteriaceae* isolates positive for ESBL activity, testing with a ceftazidime MIC >8 mg/L, and those with a meropenem MIC >1 mg/L were screened for acquired β-lactamase genes by PCR and sequencing. **Results:** Susceptibility data are provided in the table. Ceftazidime-avibactam showed potent *in vitro* activity against the overall population of *Enterobacteriaceae* (MIC_{90}, 0.5 mg/L; 99.1% susceptible) and against ceftazidime-nonsusceptible (MIC >1 mg/L), colistin-resistant (MIC >2 mg/L), and MDR isolates, with >94% of these resistant subsets testing with MICs ≤8 mg/L. Reduced activity against meropenem-nonsusceptible (MIC >2 mg/L) *Enterobacteriaceae* was attributable to the presence of class B metallo-β-lactamases (MBL) because 99.5% of meropenem-nonsusceptible, MBL-negative isolates were susceptible to ceftazidime-avibactam. Ceftazidime-avibactam also showed good activity against the majority of *P. aeruginosa* isolates (MIC_{90}, 8 mg/L; 92.2% susceptible). Activity was reduced against ceftazidime-nonsusceptible (MIC >8 mg/L), colistin-resistant (MIC >2 mg/L), meropenem-nonsusceptible (MIC >2 mg/L), meropenem-nonsusceptible, MBL-negative, and MDR subsets (67.3–85.7% susceptible) but exceeded the activity of ceftazidime and meropenem by 23.8–83.0%.

	Drug (MIC_{90}/% Susceptible)					
Species/Phenotype (n)	CAZ-AVI		CAZ		MER	
Enterobacteriaceae, All (6449)	0.5	99.1%	64	75.2%	0.12	96.2%
CAZ-NS (1602)	2	96.3%	>128	0.0%	>8	85.0%
MER-NS (248)	>128	79.4%	>128	2.8%	>8	0.0%
MER-NS, MBL-negative (194)	4	99.5%	>128	3.6%	>8	0.0%
CST-R (125)[a]	2	97.6%	>128	24.8%	>8	51.2%
MDR (1029)[c]	2	94.7%	>128	5.3%	>8	77.2%
P. aeruginosa, All (1835)	8	92.2%	64	76.0%	>8	71.8%
CAZ-NS (440)	64	67.3%	>128	0.0%	>8	35.9%
MER-NS (518)	64	73.6%	>128	45.6%	>8	0.0%
MER-NS, MBL-negative (459)	32	83.0%	128	51.4%	>8	0.0%
CST-R (21)	16	85.7%	64	61.9%	>8	57.1%
MDR (479)[c]	64	69.9%	>128	23.2%	>8	27.4%

CAZ-AVI, ceftazidime-avibactam; CAZ, ceftazidime; MER, meropenem; CST, colistin; MDR, multidrug resistant; MBL, metallo-β-lactamase. EUCAST breakpoints were used to define non-susceptible (NS) and resistant (R) subsets.
[a] Excludes isolates of Proteae and *Serratia* spp.
[b] NA, MIC_{90} was not calculated for n <10
[c] MDR: resistant to sentinel agents from 3 or more drug classes by EUCAST breakpoints.

Conclusions: Ceftazidime-avibactam provides a valuable therapeutic option for treating infections caused by *Enterobacteriaceae* and *P. aeruginosa* isolates resistant to commonly used and last-in-line agents.

Introduction

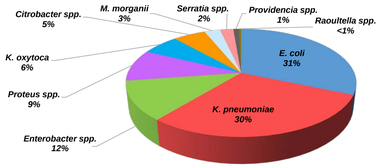
Avibactam is a non-β-lactam β-lactamase inhibitor that restores the *in vitro* activity of ceftazidime against class A, class C, and some class D β-lactamases, including extended-spectrum β-lactamases (ESBL), serine carbapenemases, and the chromosomal AmpC of *Pseudomonas aeruginosa*. Ceftazidime-avibactam has been approved in Europe and the US for several indications. This study evaluated the *in vitro* activity of ceftazidime-avibactam and comparators against *Enterobacteriaceae* and *P. aeruginosa* collected in Europe in 2015 as part of the INFORM surveillance program.

Materials & Methods

- Non-duplicate isolates (6,449 *Enterobacteriaceae* and 1,835 *P. aeruginosa*) were collected from 67 medical centers in 17 European countries.
- Susceptibility testing was performed by broth microdilution following Clinical and Laboratory Standards Institute guidelines [1] and interpreted using EUCAST 2017 breakpoints (ceftazidime-avibactam; ≤8 mg/L, susceptible; >8 mg/L, resistant) [2].
- Avibactam was tested at a fixed concentration of 4 mg/L with doubling dilutions of ceftazidime.
- Multidrug resistant (MDR) was defined as resistant by EUCAST breakpoints to sentinel agents from three or more drug classes, including cefepime, aztreonam, piperacillin-tazobactam, meropenem, levofloxacin, amikacin, tigecycline, and colistin.
- *P. aeruginosa* isolates with a meropenem MIC >2 mg/L and *Enterobacteriaceae* isolates positive for ESBL activity, testing with a ceftazidime MIC >8 mg/L, and those with a meropenem MIC >1 mg/L were screened for acquired β-lactamase genes by PCR and sequencing as described previously [3, 4].

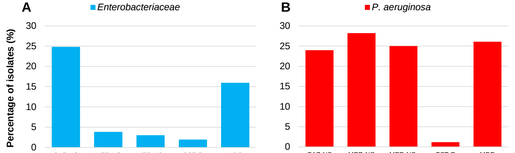
Results

Figure 1. Species distribution of *Enterobacteriaceae* isolates collected in Europe (n=6,449).



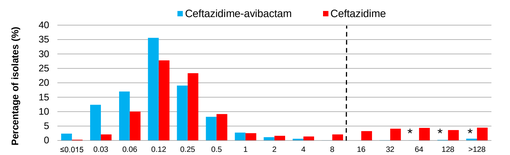
Enterobacter spp. includes *Enterobacter cloacae* (n=451), *Enterobacter aerogenes* (n=263), *Enterobacter asburiae* (n=28), *Enterobacter kobei* (n=12) and *Enterobacter ludwigii* (n=2); *Proteus* spp. includes *Proteus mirabilis* (n=384), *Proteus vulgaris* (n=217) and *Proteus penneri (n=11)*; *Citrobacter* spp. includes *Citrobacter freundii* (n=191), *Citrobacter koseri* (n=129), *Citrobacter braakii* (n=19), *Citrobacter amalonaticus* (n=5), *Citrobacter sedlakii* (n=4) and *Citrobacter farmeri* (n=2); *Serratia* spp. includes *Serratia marcescens* (n=143) and *Serratia liquefaciens* (n=1); *Providencia* spp. includes *Providencia stuartii* (n=31), *Providencia rettgeri* (n=25) and *Providencia alcalifaciens* (n=3); *Raoultella* spp. includes *Raoultella ornithinolytica* (n=17) and *Raoultella planticola* (n=8).

Figure 2A and 2B. Percentages of *Enterobacteriaceae* (n=6,449) and *P. aeruginosa* (n=1,835) isolates with drug-resistant phenotypes collected in Europe.



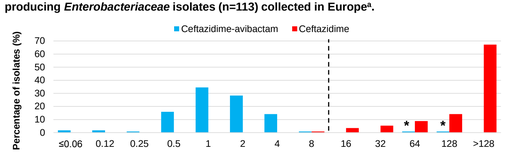
CAZ, ceftazidime; MER, meropenem; MBL, metallo-β-lactamase; CST, colistin; MDR, multidrug resistant. EUCAST breakpoints were used to define non-susceptible (NS) and resistant (R) subsets. MDR, resistant to sentinel agents from 3 or more drug classes by EUCAST breakpoints.

Figure 3A. Ceftazidime and ceftazidime-avibactam MIC distributions against *Enterobacteriaceae* (n=6,449) collected in Europe.



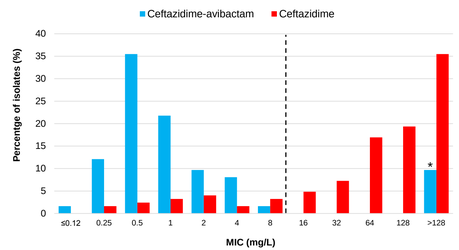
Dashed line represents the EUCAST susceptibility breakpoint of ≤8 mg/L for ceftazidime-avibactam. * Includes isolates carrying MBLs. Not visible due to low numbers and scale of graph: isolates with ceftazidime-avibactam MIC values of 64 and 128 mg/L (0.05% and 0.19%, respectively).

Figure 3B. Ceftazidime and ceftazidime-avibactam MIC distributions against all KPC-producing *Enterobacteriaceae* isolates (n=113) collected in Europe[a].



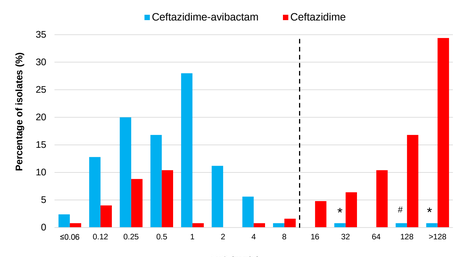
[a]Includes two isolates carrying KPC and MBL.
Dashed line represents the EUCAST susceptibility breakpoint of ≤8 mg/L for ceftazidime-avibactam. * Includes isolates carrying KPC-2 and VIM-26.

Figure 3C. Ceftazidime and ceftazidime-avibactam MIC distributions against all OXA-48-like-producing *Enterobacteriaceae* isolates (n=124) collected in Europe[a].



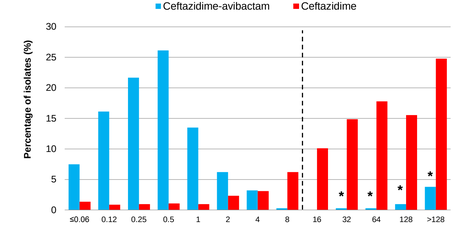
[a]Includes 17 isolates carrying OXA-48-like β-lactamases and MBL.
Dashed line represents the EUCAST susceptibility breakpoint of ≤8 mg/L for ceftazidime-avibactam. * Includes 12 isolates carrying OXA-48 and NDM-1. Five isolates carrying OXA-48 and VIM-31 tested with ceftazidime-avibactam MICs ≤8 mg/L.

Figure 3D. Ceftazidime and ceftazidime-avibactam MIC distributions against colistin-resistant (n=125) *Enterobacteriaceae* isolates collected in Europe [a].



[a] Excludes Proteeae and *Serratia* spp. intrinsically resistant to colistin. Dashed line represents the EUCAST susceptibility breakpoint of ≤8 mg/L for ceftazidime-avibactam. * *K. pneumoniae* isolate carrying NDM-1, CTX-M-15, and an SHV-OSBL with or without a TEM-OSBL. # *K. pneumoniae* isolate carrying SHV-12 and a TEM-OSBL

Figure 3E. Ceftazidime and ceftazidime-avibactam MIC distributions against multidrug resistant (MDR) *Enterobacteriaceae* isolates (n=1,029) collected in Europe.



Dashed line represents the EUCAST susceptibility breakpoint of ≤8 mg/L for ceftazidime-avibactam. * Includes isolates carrying MBLs.

Table 1. *In vitro* activity of ceftazidime-avibactam and comparator agents tested against *Enterobacteriaceae* and *P. aeruginosa* collected in Europe.

Species/phenotype/genotype (n)[a]	MIC (mg/L)[b] Range	MIC_{50}	MIC_{90}	%Susceptible[c]
***Enterobacteriaceae* All (6,449)**				
Ceftazidime-avibactam	≤0.015 - >128	0.12	0.5	**99.1**
Ceftazidime	≤0.015 - >128	0.25	64	75.2
Cefepime	≤0.12 - >16	≤0.12	>16	79.1
Meropenem	≤0.004 - >8	0.06	0.12	**96.2**
Colistin	≤0.06 - >8	0.5	>8	83.0
Amikacin	≤0.25 - >32	2	8	**93.4**
Tigecycline	≤0.015 - 8	0.5	2	88.3
Levofloxacin	≤0.004 - >8	0.06	>8	72.2
Ceftazidime-NS (1,602)				
Ceftazidime-avibactam	≤0.015 - >128	0.25	2	**96.3**
Ceftazidime	2 - >128	32	>128	0.0
Cefepime	≤0.12 - >16	>16	>16	21.6
Meropenem	0.008 - >8	0.06	>8	85.0
Colistin	0.12 - >8	0.5	8	87.8
Amikacin	≤0.25 - >32	4	32	79.0
Tigecycline	≤0.015 - 8	0.5	2	86.4
Levofloxacin	0.008 - >8	8	>8	29.4
Meropenem-NS (248)				
Ceftazidime-avibactam	≤0.015 - >128	1	>128	79.4
Ceftazidime	0.25 - >128	>128	>128	2.8
Cefepime	≤0.12 - >16	>16	>16	3.2
Meropenem	4 - >8	>8	>8	0.0
Colistin	0.25 - >8	1	>8	75.4
Amikacin	0.5 - >32	32	>32	33.5
Tigecycline	0.12 - 8	1	2	76.2
Levofloxacin	0.06 - >8	>8	>8	6.5
Meropenem-NS, MBL-negative (194)				
Ceftazidime-avibactam	≤0.015 - 128	1	4	**99.5**
Ceftazidime	0.25 - >128	>128	>128	3.6
Cefepime	≤0.12 - >16	>16	>16	3.6
Meropenem	4 - >8	>8	>8	0.0
Colistin	0.25 - >8	1	>8	77.1
Amikacin	0.5 - >32	32	>32	37.1
Tigecycline	0.12 - 8	1	2	78.4
Levofloxacin	0.06 - >8	>8	>8	5.7
Colistin-R (125)				
Ceftazidime-avibactam	≤0.015 - >128	0.5	2	**97.6**
Ceftazidime	0.06 - >128	128	>128	24.8
Cefepime	≤0.12 - >16	>16	>16	30.4
Meropenem	0.015 - >8	1	>8	51.2
Colistin	4 - >8	>8	>8	0.0
Amikacin	0.5 - >32	8	>32	51.2
Tigecycline	0.12 - 8	1	2	84.0
Levofloxacin	0.015 - >8	>8	>8	30.4
MDR (1,029)				
Ceftazidime-avibactam	≤0.015 - >128	0.5	2	**94.7**
Ceftazidime	0.03 - >128	64	>128	5.3
Cefepime	≤0.12 - >16	>16	>16	6.8
Meropenem	0.008 - >8	0.06	>8	77.2
Colistin	0.12 - >8	0.5	>8	82.1
Amikacin	0.5 - >32	8	>32	68.5
Tigecycline	≤0.015 - 8	0.5	4	80.0
Levofloxacin	0.03 - >8	>8	>8	8.2
ESBL-positive (880)[d]				
Ceftazidime-avibactam	≤0.015 - 128	0.25	0.5	**99.9**
Ceftazidime	0.25 - >128	32	128	5.1
Cefepime	≤0.12 - >16	>16	>16	3.5
Meropenem	0.008 - >8	0.06	0.12	**98.3**
Colistin	0.12 - >8	0.5	1	**95.1**
Amikacin	≤0.25 - >32	4	16	84.4
Tigecycline	0.06 - 8	0.5	1	**92.0**
Levofloxacin	0.015 - >8	8	>8	21.9
AmpC-positive (48)[e]				
Ceftazidime-avibactam	0.03 - 2	0.25	1	**100**
Ceftazidime	0.25 - >128	32	128	6.3
Cefepime	≤0.12 - 16	0.5	8	70.8
Meropenem	0.015 - 8	0.06	2	**91.7**
Colistin	0.12 - >8	0.5	>8	75.0
Amikacin	0.5 - >32	4	8	**91.7**
Tigecycline	0.12 - 8	0.5	8	83.3
Levofloxacin	0.03 - >8	4	>8	29.2
ESBL-positive + AmpC-positive (16)				
Ceftazidime-avibactam	0.12 - 4	0.5	2	**100**
Ceftazidime	16 - >128	64	>128	0.0
Cefepime	0.5 - >16	>16	>16	6.3
Meropenem	0.03 - >8	0.06	0.5	**93.8**
Colistin	0.25 - >8	1	>8	68.8
Amikacin	1 - >32	8	>32	56.3
Tigecycline	0.25 - 4	0.5	2	87.5
Levofloxacin	0.5 - >8	>8	>8	6.3
KPC-positive (111)[f]				
Ceftazidime-avibactam	≤0.015 - 8	1	4	**100**
Ceftazidime	8 - >128	>128	>128	0.0
Cefepime	2 - >16	>16	>16	0.0
Meropenem	4 - >8	>8	>8	0.0
Colistin	0.25 - >8	1	>8	65.8
Amikacin	0.5 - >32	32	>32	23.4
Tigecycline	0.25 - 8	1	2	75.7
Levofloxacin	0.12 - >8	>8	>8	3.6
OXA-48-like-positive (107)[g]				
Ceftazidime-avibactam	0.12 - 8	0.5	2	**100**
Ceftazidime	0.25 - >128	64	>128	8.4
Cefepime	≤0.12 - >16	>16	>16	7.5
Meropenem	0.12 - >8	4	>8	41.1
Colistin	0.25 - >8	1	>8	82.2
Amikacin	0.5 - >32	8	>32	66.4
Tigecycline	≤0.015 - 8	0.5	2	81.3
Levofloxacin	0.03 - >8	>8	>8	6.5

Species/phenotype/genotype (n)[a]	MIC (mg/L)[b] Range	MIC_{50}	MIC_{90}	%Susceptible[c]
MBL-positive (60)[h]				
Ceftazidime-avibactam	4 - >128	>128	>128	10.0
Ceftazidime	64 - >128	>128	>128	0.0
Cefepime	1 - >16	>16	>16	3.3
Meropenem	0.25 - >8	>8	>8	10.0
Colistin	0.25 - >8	0.5	1	**96.7**
Amikacin	1 - >32	32	>32	28.3
Tigecycline	0.12 - 4	0.5	2	70.0
Levofloxacin	0.3 - >8	>8	>8	10.0
***P. aeruginosa* All (1,835)**				
Ceftazidime-avibactam	0.03 - >128	2	8	**92.2**
Ceftazidime	0.12 - >128	4	64	76.0
Cefepime	≤0.12 - >16	4	>16	76.7
Meropenem	0.015 - >8	0.5	>8	71.8
Colistin	0.25 - >8	1	2	**98.9**
Amikacin	≤0.25 - >32	4	32	85.2
Levofloxacin	0.015 - >8	1	>8	58.7
Ceftazidime-NS (440)				
Ceftazidime-avibactam	0.12 - >128	8	64	67.3
Ceftazidime	16 - >128	64	>128	0.0
Cefepime	1 - >16	16	>16	16.6
Meropenem	0.06 - >8	8	>8	35.9
Colistin	0.25 - >8	1	2	**98.2**
Amikacin	≤0.25 - >32	8	>32	56.6
Levofloxacin	0.06 - >8	>8	>8	22.5
Meropenem-NS (518)				
Ceftazidime-avibactam	0.5 - >128	4	64	73.6
Ceftazidime	1 - >128	16	>128	45.6
Cefepime	0.5 - >16	16	>16	43.6
Meropenem	4 - >8	>8	>8	0.0
Colistin	0.25 - >8	1	2	**98.3**
Amikacin	≤0.25 - >32	8	>32	63.1
Levofloxacin	0.06 - >8	8	>8	21.4
Meropenem-NS, MBL-negative (459)				
Ceftazidime-avibactam	0.5 - >128	4	32	83.0
Ceftazidime	1 - >128	8	128	51.4
Cefepime	0.5 - >16	16	>16	49.0
Meropenem	4 - >8	>8	>8	0.0
Colistin	0.25 - >8	1	2	**98.0**
Amikacin	≤0.25 - >32	8	>32	69.7
Levofloxacin	0.06 - >8	8	>8	23.7
Colistin-R (21)				
Ceftazidime-avibactam	0.25 - 32	2	16	85.7
Ceftazidime	0.5 - >128	4	64	61.9
Cefepime	1 - >16	4	>16	57.1
Meropenem	0.12 - >8	1	>8	57.1
Colistin	4 - >8	4	>8	0.0
Amikacin	2 - >32	8	>32	66.7
Levofloxacin	0.25 - >8	4	>8	47.6
MDR (479)				
Ceftazidime-avibactam	0.12 - >128	8	64	69.9
Ceftazidime	0.5 - >128	32	>128	23.2
Cefepime	1 - >16	16	>16	17.1
Meropenem	0.06 - >8	>8	>8	27.4
Colistin	0.25 - >8	1	2	**97.7**
Amikacin	0.5 - >32	8	>32	53.4
Levofloxacin	0.06 - >8	>8	>8	11.9
ESBL-positive (25)[i]				
Ceftazidime-avibactam	4 - 128	32	128	12.0
Ceftazidime	64 - >128	>128	>128	0.0
Cefepime	16 - >16	>16	>16	0.0
Meropenem	4 - >8	>8	>8	0.0
Colistin	1 - >8	1	2	**96.0**
Amikacin	2 - >32	>32	>32	8.0
Levofloxacin	0.5 - >8	>8	>8	4.0
MBL-positive (59)[h]				
Ceftazidime-avibactam	16 - >128	64	>128	0.0
Ceftazidime	16 - >128	64	>128	0.0
Cefepime	8 - >16	>16	>16	0.0
Meropenem	8 - >8	>8	>8	0.0
Colistin	0.5 - 2	1	2	**100**
Amikacin	2 - >32	>32	>32	11.9
Levofloxacin	0.5 - >8	>8	>8	3.4
No acquired β-lactamase (426)[j]				
Ceftazidime-avibactam	0.5 - >128	4	16	87.1
Ceftazidime	1 - >128	8	64	55.4
Cefepime	0.5 - >16	8	>16	52.8
Meropenem	4 - >8	>8	>8	0.0
Colistin	0.25 - >8	1	2	**98.1**
Amikacin	≤0.25 - >32	4	>32	74.4
Levofloxacin	0.06 - >8	8	>8	25.4
GES carbapenemase (7)				
Ceftazidime-avibactam	4 - 16	-	-	85.7
Ceftazidime	16 - 128	-	-	0.0
Cefepime	16 - >16	-	-	0.0
Meropenem	>8 - >8	-	-	0.0
Colistin	1 - 2	-	-	**100**
Amikacin	32 - >32	-	-	0.0
Levofloxacin	>8 - >8	-	-	0.0

[a] ESBL,extended-spectrum β-lactamase; OSBL, original-spectrum β-lactamase (includes TEM-1,TEM-2, SHV-1 and SHV-11); MBL, metallo-β-lactamase; NS, non-susceptible; R, resistant.
[b] MIC_{50} and MIC_{90} were not calculated for n <10 isolates.
[c] % Susceptibility was determined according to EUCAST 2017 breakpoints.
[d] ESBL-positive, isolates in which a β-lactamase gene encoding an ESBL was detected by PCR; includes isolates with and without OSBLs.
[e] AmpC-positive, includes isolates carrying acquired AmpC β-lactamases or the intrinsic, chromosomally-encoded AmpC common to *C. freundii, Enterobacter* spp., *P. stuartii*, and *S. marcescens*, with or without OSBLs.
[f] KPC-positive, isolates carrying KPC with or without ESBLs, OSBLs and/or AmpC β-lactamases. Does not include isolates carrying KPC and MBL β-lactamases.
[g] OXA-48-like-positive, isolates carrying OXA-48 (n=84), OXA-162 (n=3), OXA-181 (n=18) or OXA-244 (n=2), with or without ESBLs, OSBLs and/or AmpC β-lactamases. Does not include isolates carrying OXA-48-like and MBL β-lactamases.
[h] MBL-positive, isolates carrying a metallo-β-lactamase with or without serine carbapenemases, ESBLs, OSBLs, and/or AmpC β-lactamases.
[i] Assumed to carry the intrinsic, chromosomally-encoded AmpC β-lactamase common to *P. aeruginosa*.
[j] Includes isolates carrying VEB-1A (n=13), PER-1 (n=7), GES-1 (n=4), and SHV-2A (n=1).
[k] One isolate carried an SHV-5 (ESBL) and VIM-1.

Results Summary

- The activity of ceftazidime-avibactam was comparable to that of meropenem against the overall collection of *Enterobacteriaceae* (MIC_{90}, 0.5 mg/L; 99.1% susceptible) and exceeded the activity of all tested comparator agents against ceftazidime-NS, meropenem-NS MBL-negative, colistin-R, and MDR subsets of isolates (MIC_{90}, 2–4 mg/L; 94.7–99.5% susceptible) (Table 1, Figure 3A, 3D-E).
- Ceftazidime-avibactam showed potent activity against *Enterobacteriaceae* carrying ESBL, AmpC, KPC, and OXA-48-like serine β-lactamases in all observed combinations (MIC_{90}, 0.5–4 mg/L; 99.9-100% susceptible). As expected, ceftazidime-avibactam was not active against isolates carrying MBLs (10% susceptible) (Table 1, Figure 3B-C).
- Ceftazidime-avibactam showed good activity against all *P. aeruginosa* isolates (MIC_{90}, 8 mg/L; 92.2% susceptible).
- Activity was reduced against ceftazidime-NS, meropenem-NS MBL-negative, and MDR subsets of *P. aeruginosa* (67.3–83.0% susceptible) but exceeded the activity of all tested comparators except colistin. Ceftazidime-avibactam activity was superior to all other tested comparators against colistin-R isolates (Table 1).
- Ceftazidime-avibactam was active against *P. aeruginosa* carrying GES carbapenemases and isolates assumed to hyperproduce chromosomally-encoded AmpC combined with loss of OprD (85.7-87.1% susceptible) (Table 1).
- Activity was reduced against subsets of MBL-positive isolates and ESBL-positive *P. aeruginosa* isolates assumed to carry additional resistance mechanisms (Table 1).

Conclusions

- *Enterobacteriaceae* with varied genotypes and resistance phenotypes remained susceptible to ceftazidime-avibactam, except for isolates in which resistance was mediated by MBLs.
- Ceftazidime-avibactam demonstrated good *in vitro* activity against the majority of *P. aeruginosa* isolates, including isolates in which resistance was mediated by chromosomally-encoded mechanisms.
- Ceftazidime-avibactam provides a valuable therapeutic option for treating infections caused by *Enterobacteriaceae* and *P. aeruginosa* isolates resistant to commonly used and last-in-line agents.

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