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Activity of ceftazidime-avibactam against carbapenem non-susceptible *Enterobacteriaceae* isolated from respiratory infections as part of the INFORM global surveillance program, 2014–2015

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Abstract

Background: Carbapenem-resistant *Enterobacteriaceae* (CRE) pose a growing health threat worldwide. Carbapenem resistance can be mediated through production of Class A or D serine carbapenemases (KPC, GES, OXA-48-like), Class B metallo-β-lactamases (MBLs), or Class A or C β-lactamases combined with impaired compound permeability. Ceftazidime-avibactam is a β-lactam/β-lactamase inhibitor combination with activity against Class A, C, and some D β-lactamases developed to treat infections caused by CRE. We evaluated the *in vitro* activity of ceftazidime-avibactam against carbapenem non-susceptible respiratory isolates collected in 2014–2015 through the INFORM surveillance program.
Materials/ methods: 5686 non-duplicate respiratory *Enterobacteriaceae* isolates were collected from 147 sites in 37 countries. Susceptibility testing was performed by CLSI broth microdilution and interpreted using EUCAST breakpoints (ceftazidime-avibactam; ≤8 mg/L, susceptible; >8 mg/L, resistant). Ceftazidime-avibactam was tested at a fixed concentration of 4 mg/L avibactam. CRE were defined as isolates with meropenem MIC >2 mg/L and were screened for the presence of β-lactamase genes by PCR and sequencing.
Results: 220 CRE isolates were identified (193 isolates of *Klebsiella pneumoniae* and 27 isolates of 7 other species) of which 90% carried carbapenemases (KPC, n=112; OXA-48-like, n=40; MBL, n=45; GES, n=1). Ceftazidime-avibactam showed potent activity against carbapenemase-positive MBL-negative isolates (100% susceptible) and carbapenemase-negative isolates (85.7–100% susceptible). Ceftazidime-avibactam was not active against MBL-positive isolates (<6% susceptible), as expected. As a result, ceftazidime-avibactam showed diminished activity in regions where MBLs were more frequently encountered in CRE (Asia/Pacific and Middle East/Africa). No regional differences in activity against CRE subgroups were observed, with the exception of slightly diminished activity against carbapenemase-negative isolates collected in Europe and the Asia/Pacific region.

Percentage of respiratory isolates susceptible to ceftazidime-avibactam according to enzyme type

Phenotype/Enzyme content[b] (n)	CAZ-AVI %S (n)[a]				
	Global[c]	EUR	LA	AP	MEA
All RTI (5686)	99.0 (5686)	99.3 (3350)	99.0 (761)	98.4 (1092)	98.6 (483)
All CRE (220)	79.1 (220)	85.7 (133)	88.5 (52)	46.2 (26)	22.2 (9)
CRE, Carbapenemase- (22)	90.9 (22)	87.5 (8)	100 (7)	85.7 (7)	NA[d] (0)
CRE, KPC+, MBL- (112)	100 (112)	100 (69)	100 (38)	100 (5)	NA (0)
CRE, GES+, MBL- (1)	100 (1)	NA (0)	NA (0)	100 (1)	NA (0)
CRE, OXA-48-like+, MBL- (40)	100 (40)	100 (37)	100 (1)	NA (0)	100 (2)
CRE, MBL+ (45)	2.2 (45)	5.3 (19)	0.0 (6)	0.0 (13)	0.0 (7)

[a] CAZ-AVI, ceftazidime-avibactam; %S, percent susceptible (MIC ≤8 mg/L); n, number of isolates.
[b] Includes isolates that co-carry Class A original spectrum β-lactamases and extended-spectrum β-lactamases and Class C AmpC β-lactamases.
[c] Global, all; EUR, Europe; LA, Latin America; AP, Asia/Pacific; MEA, Middle East/Africa.
[d] NA, not applicable (no isolates collected).

Conclusions: Ceftazidime-avibactam provides a new treatment option against CRE from respiratory infections that possess serine carbapenemases or non-carbapenemase-mediated mechanisms. Regional differences in the incidence of MBL-mediated resistance are important to consider when assessing the value of ceftazidime-avibactam.

Introduction

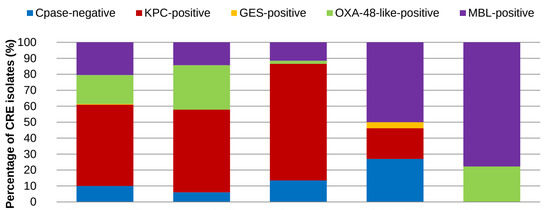
Carbapenem-resistant *Enterobacteriaceae* (CRE) pose a growing health threat worldwide. Carbapenem resistance can be mediated through production of Class A or D serine carbapenemases (KPC, GES, OXA-48-like), Class B metallo-β-lactamases (MBLs), or Class A or C β-lactamases combined with impaired compound permeability. Ceftazidime-avibactam is a β-lactam/β-lactamase inhibitor combination with *in vitro* activity against Gram-negative isolates expressing Class A, C, and some D β-lactamases, developed to treat infections caused by CRE. We evaluated the *in vitro* activity of ceftazidime-avibactam against carbapenem non-susceptible respiratory isolates collected in 2014–2015 through the INFORM surveillance program.

Materials & Methods

- 5,686 non-duplicate respiratory *Enterobacteriaceae* isolates were collected from 147 medical centres in 37 countries. Infection sources included sputum (n=2,510), endotracheal aspirate (n=1,764), bronchoalveolar lavage (n=708), bronchial brushing (n=455), thoracentesis (n=84), throat (n=36), lungs (n=17), bronchials (n=1), and not specified (n=111).
- Organism identification and susceptibility testing were performed at a central laboratory using CLSI broth microdilution [1] and interpreted using EUCAST 2017 breakpoints (ceftazidime-avibactam; ≤8 mg/L, susceptible; >8 mg/L, resistant) [2]. Ceftazidime-avibactam was tested at a fixed concentration of 4 mg/L avibactam.
- CRE were defined as isolates with meropenem MIC >2 mg/L and were screened for the presence of β-lactamase genes encoding carbapenemases (KPC, OXA-48-like, GES, NDM, IMP, VIM, SPM, GIM), extended-spectrum β-lactamases (ESBLs; TEM, SHV, CTX-M, VEB, PER, GES), and AmpC cephalosporinases (ACC, ACT, CMY, DHA, FOX, MIR, MOX) by PCR and sequencing as described previously [3].

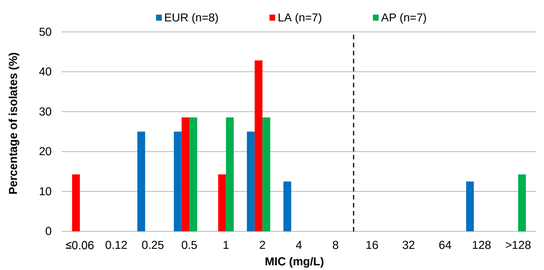
Results

Figure 1. Distribution of CRE isolates with different resistance mechanisms collected from patients with respiratory tract infections (RTI) in 2014-2015, by region[a]



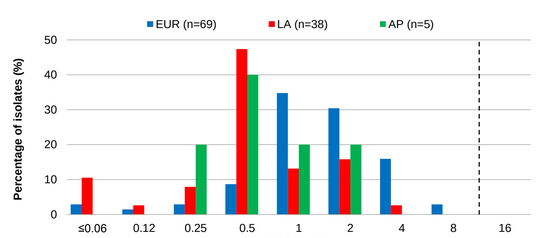
[a]The 220 CRE isolates were composed of *Klebsiella pneumoniae* (n=193), *Enterobacter cloacae* (n=9), *Escherichia coli* (n=6), *Klebsiella oxytoca* (n=4), *Citrobacter freundii* (n=3), *Enterobacter aerogenes* (n=2), *Serratia marcescens* (n=2), and *Raoultella ornithinolytica* (n=1).
Cpase, carbapenemase; MBL, metallo-β-lactamase; Global, all regions, excluding North America; EUR, Europe; LA, Latin America; AP, Asia/Pacific; MEA, Middle East/Africa. Isolates carrying both MBL and OXA-48-like carbapenemases were collected in Europe (n=9) and the Asia/Pacific region (n=3).

Figure 2B. Ceftazidime-avibactam MIC distributions against carbapenemase-negative CRE isolates collected from patients with RTI (n=22).



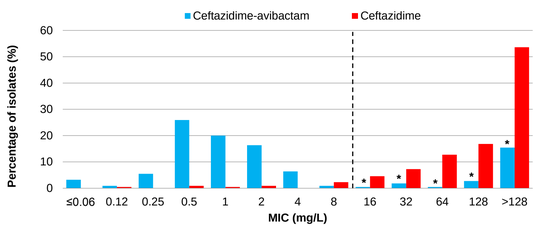
Dashed line represents the EUCAST susceptibility breakpoint of ≤8 mg/L for ceftazidime-avibactam.
Two *Klebsiella pneumoniae* isolates with ceftazidime-avibactam MIC values >8 mg/L carried ESBLs (SHV-12 (n=1) and CTX-M-15 (n=1)).

Figure 2C. Ceftazidime-avibactam MIC distributions against KPC-positive CRE isolates collected from patients with RTI (n=112).



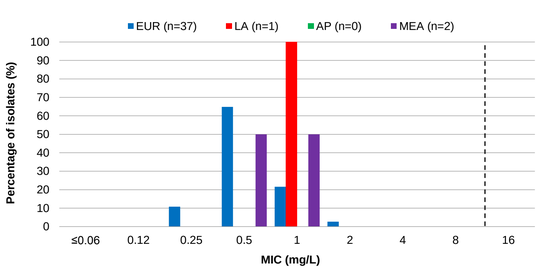
Dashed line represents the EUCAST susceptibility breakpoint of ≤8 mg/L for ceftazidime-avibactam.

Figure 2A. Ceftazidime and ceftazidime-avibactam MIC distributions against all CRE collected globally from patients with RTI (n=220).



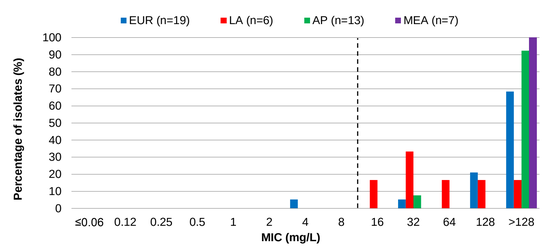
Dashed line represents the EUCAST susceptibility breakpoint of ≤8 mg/L for ceftazidime-avibactam. * 44 of 46 isolates (95.6%) with ceftazidime-avibactam MIC values >8 mg/L carried MBLs.

Figure 2D. Ceftazidime-avibactam MIC distributions against OXA-48-like-positive CRE isolates collected from patients with RTI (n=40).



Dashed line represents the EUCAST susceptibility breakpoint of ≤8 mg/L for ceftazidime-avibactam. Includes isolates carrying OXA-48 (n=37), OXA-163 (n=1), OXA-181 (n=1), and OXA-232 (n=1).

Figure 2E. Ceftazidime-avibactam MIC distributions against MBL-positive CRE isolates collected from patients with RTI (n=45).



Dashed line represents the EUCAST susceptibility breakpoint of ≤8 mg/L for ceftazidime-avibactam. Eleven *Klebsiella pneumoniae* isolates co-carried NDM-1 and OXA-48 (n=8) or NDM-1 and OXA-232 (n=3). One *Citrobacter freundii* isolate co-carried VIM-31 and OXA-48 and tested with a ceftazidime-avibactam MIC value <8 mg/L.

Table 1. *In vitro* activity of ceftazidime-avibactam and comparator agents against CRE collected globally from patients with RTI

Region	Phenotype/enzyme content (n)	MIC (mg/L)			% Susceptible[a]
		Range	MIC_{50}	MIC_{90}	
Global	CRE All (220)				
	Ceftazidime-avibactam	≤0.015 - >128	1	>128	79.1
	Ceftazidime	0.12 - >128	>128	>128	1.8
	Cefepime	≤0.12 - >16	>16	>16	1.8
	Meropenem	4 - >8	>8	>8	0.0
	Colistin	0.25 - >8	1	8	72.7
	Amikacin	0.5 - >32	16	>32	41.4
	Tigecycline	0.25 - 8	1	2	71.4
	Levofloxacin	≤0.03 - >4	>4	>4	6.4
	CRE, MBL-negative (175)				
	Ceftazidime-avibactam	≤0.015 - >128	1	2	98.9
	Ceftazidime	0.12 - >128	128	>128	2.3
	Cefepime	≤0.12 - >16	>16	>16	1.1
	Meropenem	4 - >8	>8	>8	0.0
	Colistin	0.25 - >8	1	>8	68.0
	Amikacin	0.5 - >32	16	>32	45.1
	Tigecycline	0.25 - 8	1	4	68.6
	Levofloxacin	≤0.03 - >4	>4	>4	6.3
Europe	CRE All (133)				
	Ceftazidime-avibactam	≤0.015 - >128	1	128	85.7
	Ceftazidime	0.5 - >128	>128	>128	0.8
	Cefepime	0.5 - >16	>16	>16	2.3
	Meropenem	4 - >8	>8	>8	0.0
	Colistin	0.25 - >8	1	>8	68.4
	Amikacin	0.5 - >32	32	>32	30.8
	Tigecycline	0.25 - 8	1	2	70.7
	Levofloxacin	≤0.03 - >4	>4	>4	5.3
	CRE, MBL-negative (114)				
	Ceftazidime-avibactam	≤0.015 - 128	1	4	99.1
	Ceftazidime	0.5 - >128	>128	>128	0.9
	Cefepime	1 - >16	>16	>16	0.9
	Meropenem	4 - >8	>8	>8	0.0
	Colistin	0.25 - >8	1	>8	64.0
	Amikacin	0.5 - >32	32	>32	32.5
	Tigecycline	0.25 - 8	1	2	67.5
	Levofloxacin	≤0.03 - >4	>4	>4	5.3
Latin America	CRE All (52)				
	Ceftazidime-avibactam	0.03 - >128	0.5	16	88.5
	Ceftazidime	0.12 - >128	64	>128	5.8
	Cefepime	≤0.12 - >16	>16	>16	1.9
	Meropenem	4 - >8	>8	>8	0.0
	Colistin	0.5 - >8	1	8	67.3
	Amikacin	0.5 - >32	8	32	59.6
	Tigecycline	0.25 - 4	1	2	75.0
	Levofloxacin	0.06 - >4	>4	>4	13.5
	CRE, MBL-negative (46)				
	Ceftazidime-avibactam	0.03 - 4	0.5	2	100
	Ceftazidime	0.12 - >128	64	>128	6.5
	Cefepime	≤0.12 - >16	>16	>16	2.2
	Meropenem	4 - >8	>8	>8	0.0
	Colistin	0.5 - >8	1	>8	69.6
	Amikacin	0.5 - >32	4	32	67.4
	Tigecycline	0.25 - 4	1	2	78.3
	Levofloxacin	0.06 - >4	>4	>4	10.9
Asia/Pacific	CRE All (26)				
	Ceftazidime-avibactam	0.25 - >128	32	>128	46.2
	Ceftazidime	32 - >128	>128	>128	0.0
	Cefepime	16 - >16	>16	>16	0.0
	Meropenem	4 - >8	>8	>8	0.0
	Colistin	0.25 - 4	0.5	2	96.2
	Amikacin	1 - >32	8	>32	65.4
	Tigecycline	0.5 - 8	1	8	65.4
	Levofloxacin	1 - >4	>4	>4	0.0
	CRE, MBL-negative (13)				
	Ceftazidime-avibactam	0.25 - >128	1	2	92.3
	Ceftazidime	32 - >128	>128	>128	0.0
	Cefepime	16 - >16	>16	>16	0.0
	Meropenem	4 - >8	>8	>8	0.0
	Colistin	0.25 - 4	0.5	2	92.3
	Amikacin	1 - >32	8	16	84.6
	Tigecycline	0.5 - 8	2	8	46.2
	Levofloxacin	2 - >4	>4	>4	0.0
Middle East/ Africa	CRE All (9)				
	Ceftazidime-avibactam	0.5 - >128	--[b]	--[b]	22.2
	Ceftazidime	16 - >128	--	--	0.0
	Cefepime	>16 - >16	--	--	0.0
	Meropenem	8 - >8	--	--	0.0
	Colistin	0.25 - 2	--	--	100
	Amikacin	4 - >32	--	--	22.2
	Tigecycline	0.25 - 2	--	--	77.8
	Levofloxacin	2 - >4	--	--	0.0
	CRE, MBL-negative (2)				
	Ceftazidime-avibactam	0.5 - 1	--	--	100
	Ceftazidime	16 - >128	--	--	0.0
	Cefepime	>16 - >16	--	--	0.0
	Meropenem	>8 - >8	--	--	0.0
	Colistin	0.5 - 1	--	--	100
	Amikacin	>32 - >32	--	--	0.0
	Tigecycline	1 - 2	--	--	50.0
	Levofloxacin	>4 - >4	--	--	0.0

[a]MICs were interpreted according to EUCAST 2017 breakpoints.
[b]MIC_{50} and MIC_{90} were not calculated for n <10 isolates.

Results Summary

- The proportion of CRE from RTI with different resistance mechanisms varied among regions. Isolates carrying serine carbapenemases composed 75-80% of CRE collected in Latin America (LA) and Europe (EUR) but only ~20% of CRE collected in Asia/Pacific (AP) and the Middle East/Africa (MEA) (Figure 1).
- KPC-positive isolates were identified in all regions but MEA and composed the majority of CRE from EUR and LA. OXA-48-like enzymes were found in 22-28% of CRE from MEA and EUR but were rare (LA) or not found (AP) in other regions. MBL-positive isolates were found in all regions and composed the majority of CRE from MEA and AP. Isolates in which carbapenemases were not detected were most common in AP. Only one isolate carrying a GES carbapenemase (ceftazidime-avibactam MIC=1 mg/L) was identified (LA) (Figure 1).
- Ceftazidime-avibactam was active *in vitro* against 98.9% (MIC ≤8 mg/L) of CRE carrying KPC, OXA-48-like, GES, and isolates in which resistance was not mediated by known carbapenemases (Figure 2A-D).
- Ceftazidime-avibactam was not active *in vitro* against isolates carrying MBLs (Figure 2E).
- The *in vitro* activity of ceftazidime-avibactam was greater than that of comparator agents (ceftazidime, cefepime, meropenem, amikacin, levofloxacin, and tigecycline) against MBL-negative CRE from RTI collected in all regions (92.3–100% susceptible). The activity of ceftazidime-avibactam was comparable to that of colistin in AP and MEA and exceeded it in all other regions (Table 1).

Conclusions

- Ceftazidime-avibactam provides a new treatment option for respiratory infections caused by CRE that possess serine carbapenemases, or where resistance is mediated through non-carbapenemase-mediated mechanisms.
- Regional differences in the incidence of MBL-mediated resistance are important to consider when assessing the value of ceftazidime-avibactam.

References and Acknowledgments:

1. Clinical Laboratory Standards Institute. 2015. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standards -- Tenth Edition. CLSI document M07-910. Wayne, PA.

2. The European Committee on Antimicrobial Susceptibility Testing. 2017. Breakpoint tables for interpretation of MICs and zone diameters. Version 7.0. http://www.eucast.org.

3. Lob SH, Kazmierczak KM, Badal RE, Hackel MA, Bouchillon SK, Biedenbach DJ, Sahm, DF. 2015. Trends in susceptibility of *Escherichia coli* from intra-abdominal infections to ertapenem and comparators in the United States according to data from the SMART program, 2009 to 2013. *Antimicrob Agents Chemother* 59:3606-3610.

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