

Activity of ceftazidime-avibactam against carbapenem-non-susceptible *Enterobacteriaceae* isolated from patients in Europe 2012–2014

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Revised Abstract

Objectives: Increasing resistance in Gram-negative pathogens, including resistance to carbapenems, has been reported worldwide, seriously limiting treatment options in some regions. Avibactam is a novel non-β-lactam β-lactamase inhibitor that restores the *in vitro* activity of ceftazidime against *Enterobacteriaceae* that produce class A (including KPC), class C, and some class D β-lactamases. In this study we evaluated the *in vitro* activity of ceftazidime-avibactam and comparator agents against a collection of carbapenem-non-susceptible *Enterobacteriaceae* isolated from European countries participating in the 2012–2014 INFORM surveillance program. **Methods:** MICs were determined using CLSI broth microdilution guidelines. The percent susceptible was assessed using the FDA breakpoint of ≤8 mg/L for ceftazidime-avibactam and EUCAST guidelines for other comparators. Carbapenem-non-susceptible *Enterobacteriaceae* were defined as non-susceptible to meropenem using the EUCAST breakpoint of ≥4 mg/L. **Results:** 448 out of 18,377 *Enterobacteriaceae* (2.4%) were meropenem-non-susceptible. The percent susceptible (%S) for ceftazidime-avibactam and comparative antimicrobial agents are shown in the table. Ceftazidime-avibactam provided activity against 99.6% of all *Enterobacteriaceae*, and against 85.5% of meropenem-non-susceptible isolates from Europe, and was the most active drug tested. Ceftazidime-avibactam showed potent activity against meropenem-non-susceptible *Klebsiella pneumoniae*, where the most common mechanism of carbapenem resistance was KPC production, but showed reduced activity against other meropenem-non-susceptible *Enterobacteriaceae*, where resistance was mainly due to the presence of metallo-β-lactamases (MBLs). Country differences were apparent, with lower activity in countries that showed higher incidence of MBLs.

Organism (N)	Percent Susceptible			
	Europe	Greece	Russia	Romania
<i>Enterobacteriaceae</i>	N=18,377	N=1,110	N=1,961	N=697
CAZ-AVI	99.6	99.9	99.6	98.0
CAZ	74.7	75.1	46.8	69.4
MEM	97.6	86.0	96.6	95.0
COL	82.2	76.4	84.3	80.6
TGC	81.6	79.0	80.4	81.4
<i>Enterobacteriaceae</i> , MEM NS	N=448	N=155	N=67	N=35
CAZ-AVI	85.5	82.6	91.0	62.9
CAZ	2.5	0.7	6.0	0.0
COL	72.4	65.2	96.4	35.3
TGC	66.3	63.9	64.2	88.6
<i>Klebsiella pneumoniae</i> , MEM NS	N=390	N=139	N=64	N=28
CAZ-AVI	90.8	89.2	92.2	78.6
CAZ	2.3	0.0	6.3	0.0
COL	71.3	64.1	96.3	35.7
TGC	66.9	64.8	65.6	92.9
Other <i>Enterobacteriaceae</i> , MEM NS	N=58	N=16	N=3	N=7
CAZ-AVI	50.0	25.0	66.7	0.0
CAZ	3.5	6.3	0.0	0.0
COL	81.8	80.0	100	33.3
TGC	62.1	56.3	33.3	71.4

CAZ-AVI, ceftazidime-avibactam; CAZ, ceftazidime; MEM, meropenem; COL, colistin; TGC, tigecycline; MEM-NS, meropenem non-susceptible
Conclusions: Ceftazidime-avibactam demonstrated good *in vitro* potency against meropenem-non-susceptible *Enterobacteriaceae* isolates from Europe. It was the most active agent tested, but activity was diminished by the presence of MBLs. The incidence of these amongst different countries explains the different degrees of activity observed in these countries.

Introduction

Increasing resistance in Gram-negative pathogens, including resistance to carbapenems, has been reported worldwide, seriously limiting treatment options in some regions. To help meet this challenge the β-lactam/β-lactamase inhibitor combination ceftazidime-avibactam has been developed to treat infections caused by carbapenem-resistant *Enterobacteriaceae* (CRE), specifically those expressing serine carbapenemases (e.g. KPCs, OXA-48), and ESBLs or class C β-lactamases combined with carbapenem permeability defects. In this study we evaluated the *in vitro* activity of ceftazidime-avibactam and comparator agents against a collection of CRE isolated from European countries participating in the 2012–2014 INFORM surveillance program.

Materials & Methods

- MICs were determined by the Clinical and Laboratory Standards Institute (CLSI) recommended broth microdilution testing method [1]. MIC interpretive criteria followed EUCAST guidelines [2] where available. The FDA breakpoint was used for ceftazidime-avibactam [3].
- An isolate of *Enterobacteriaceae* was defined as CRE if it was not susceptible to meropenem using EUCAST interpretive criteria [2].
- The presence of genes encoding OXA-48-like, KPC, and metallo-β-lactamase (GES, NDM, IMP, VIM, SPM, and GIM) carbapenemases was assessed via multiplex PCR, followed by amplification of the full-length genes and sequencing.

Results

- Ceftazidime-avibactam showed the highest percent of susceptibility of all antimicrobials tested in this study against *Enterobacteriaceae* isolated from Europe, with 99.6% of all isolates susceptible.
- 98.0% of non-MBL CRE from all Europe were susceptible to ceftazidime-avibactam, including isolates positive for KPC (96.9%), and OXA-48-like (97.8%) genes.
- Ceftazidime-avibactam was active against 95.7% of CRE from all Europe in which carbapenem resistance was not mediated by known carbapenemases, such as changes in drug efflux levels, modifications of PBPs, or other β-lactamases.
- High percentages of susceptibility for ceftazidime-avibactam were seen across all countries, with the exception of countries with a high number of MBL-positive isolates (Greece and Romania).
- Overall, 0.3% of *Enterobacteriaceae* in Europe were MBL-positive; 70% (40/58) of MBL isolates came from two countries (Greece and Romania) (Figure 3). Ceftazidime-avibactam only had decreased activity in countries with higher numbers of MBL-producing isolates, which is consistent with avibactam's lack of activity against MBLs.

Figure 1. Distribution of 259 KPC-positive CRE Isolates from Europe (N).

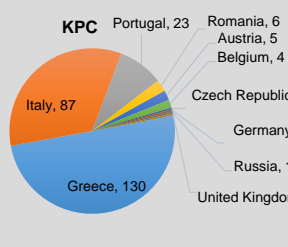


Figure 2. Distribution of 89 OXA-48-like CRE Isolates from Europe (N).

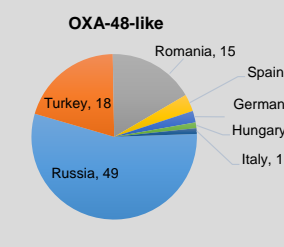


Figure 3. Distribution of 58 MBL-positive CRE Isolates from Europe (N).

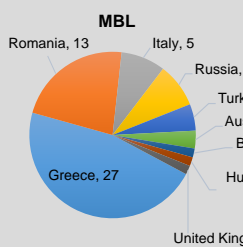


Figure 4. Distribution of 46 CRE with No Carbapenemase Identified (N).

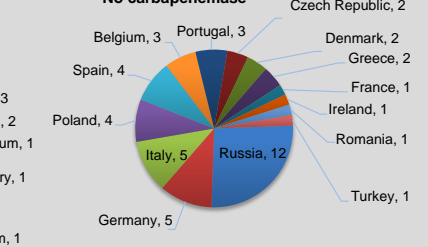


Table 1. *In Vitro* Activity of Ceftazidime-Avibactam and Comparator Agents Tested Against *Enterobacteriaceae*, Carbapenem-resistant *Enterobacteriaceae* (CRE), Non-MBL CRE, KPC-positive CRE, OXA-48-positive CRE, MBL-positive CRE, and CRE with Other Mechanisms of Resistance collected in Europe in 2012-2014.

Region	Compound	<i>Enterobacteriaceae</i>				CRE				CRE, non-MBL				CRE, KPC				CRE, OXA-48				CRE, other				CRE, MBL				
		N	%S	MIC ₅₀	Range	N	%S	MIC ₅₀	Range	N	%S	MIC ₅₀	Range	N	%S	MIC ₅₀	Range	N	%S	MIC ₅₀	Range	N	%S	MIC ₅₀	Range	N	%S	MIC ₅₀	Range	
Europe	CAZ-AVI	18377	99.6	0.5	≤0.015- >128	448	85.5	>128	≤0.015- >128	390	98.0	4	≤0.015- >128	259	96.9	4	≤0.015- >128	97	8	0.06-64	46	95.7	4	0.12-16	58	1.7	>128	8	>128	
	CAZ	18377	74.7	64	≤0.015- >128	448	2.5	>128	0.25- >128	390	2.8	>128	0.25- >128	259	0	>128	8	>128	0.06-64	46	0	0	0	0	0	0	0	0	0	0
	MEM	18377	97.6	0.12	≤0.004- >8	448	0	>8	4- >8	390	0	>8	4- >8	259	0	>8	4- >8	97	0	>8	4- >8	46	0	>8	4- >8	58	0	>8	4- >8	
	TGC	18377	81.6	2	≤0.015- >8	448	66.3	4	0.12- >8	390	66.7	4	0.12- >8	259	65.3	4	0.12- >8	97	71.9	4	0.25- >4	46	60.9	4	0.25- >4	58	63.8	4	0.25- >8	
Austria	CAZ-AVI	789	99.6	0.25	≤0.015- >128	7	71.4	0	0.06- >128	5	100	0	0.06- >4	5	100	0	0.06- >4	0	NA	NA	NA	NA	NA	NA	2	0	0	>128- >128		
	CAZ	789	85.2	16	≤0.015- >128	7	0	0	32- >128	5	0	0	32- >128	5	0	0	32- >128	0	NA	NA	NA	NA	NA	2	0	0	>128- >128			
	MEM	789	99.1	0.12	≤0.004- >8	7	0	0	8- >8	5	0	0	8- >8	5	0	0	8- >8	0	NA	NA	NA	NA	NA	2	0	0	8- >8			
	TGC	789	81.5	2	0.06- >8	7	14.3	0	1-8	5	20	0	1-4	5	20	0	1-4	0	NA	NA	NA	NA	NA	2	0	0	4- >8			
Belgium	CAZ-AVI	1136	99.8	0.5	≤0.015- >128	8	87.5	0	0.03- >128	7	100	0	0.03- >4	4	100	0	0.03- >4	0	NA	NA	NA	NA	NA	3	100	0	0	>128- >128		
	CAZ	1136	62.0	32	≤0.015- >128	8	0	0	8- >128	7	0	0	8- >128	4	0	0	32- >128	0	NA	NA	NA	NA	3	0	0	8- >128				
	MEM	1136	99.3	0.12	0.008- >8	8	0	0	4- >8	7	0	0	4- >8	4	0	0	8- >8	0	NA	NA	NA	NA	3	0	0	4- >8				
	TGC	1136	82.1	2	≤0.015- >8	8	75.0	0	0.5- >2	7	85.7	0	0.5- >2	4	100	0	0.5- >1	0	NA	NA	NA	NA	3	66.7	0	0	1-2			
Czech Republic	CAZ-AVI	867	100	0.5	≤0.015- >4	3	100	0	0.5- >4	3	100	0	0.5- >4	3	100	0	0.5- >1	0	NA	NA	NA	NA	2	100	0	0	1-1			
	CAZ	867	75.0	64	≤0.015- >128	3	0	0	16- >128	3	0	0	16- >128	1	0	0	16- >16	0	NA	NA	NA	NA	2	0	0	>128- >128				
	MEM	867	99.7	0.12	0.015- >8	3	0	0	4- >8	3	0	0	4- >8	1	0	0	4- >4	0	NA	NA	NA	NA	2	0	0	8- >8				
	TGC	867	78.3	2	0.06- >8	3	66.7	0	0.5- >2	3	66.7	0	0.5- >2	1	0	0	2- >2	0	NA	NA	NA	NA	2	100	0	0	0.5- >0.5			
Denmark	CAZ-AVI	629	100	0.25	≤0.015- >8	2	100	0	0.25- >0.5	2	100	0	0.25- >0.5	2	100	0	0.25- >0.5	0	NA	NA	NA	NA	2	100	0	0	0.25- >0.5			
	CAZ	629	90.6	1	≤0.015- >128	2	0	0	32- >64	2	0	0	32- >64	0	NA	NA	NA	NA	NA	NA	NA	NA	2	0	0	32- >64				
	MEM	629	99.7	0.12	0.008- >4	2	0	0	4- >4	2	0	0	4- >4	0	NA	NA	NA	NA	NA	NA	NA	NA	2	0	0	4- >4				
	TGC	629	86.3	2	0.03- >8	2	50.0	0	1-2	2	50.0	0	1-2	0	NA	NA	NA	NA	NA	NA	NA	NA	2	50	0	0	1-2			
France	CAZ-AVI	1338	100	0.25	≤0.015- >4	1	100	0	4- >4	1	100	0	4- >4	0	NA	NA	NA	NA	NA	NA	NA	NA	1	100	0	0	4- >4			
	CAZ	1338	80.3	32	≤0.015- >128	1	0	0	>128- >128	1	0	0	>128- >128	0	NA	NA	NA	NA	NA	NA	NA	NA	1	0	0	>128- >128				
	MEM	1338	99.9	0.12	0.008- >8	1	0	0	>8- >8	1	0	0	>8- >8	0	NA	NA	NA	NA	NA	NA	NA	NA	1	0	0	>8- >8				
	TGC	1338	80.3	2	≤0.015- >8	1	100	0	0.5- >0.5	1	100	0	0.5- >0.5	0	NA	NA	NA	NA	NA	NA	NA	NA	1	0	0	0.5- >0.5				

Region	Compound	<i>Enterobacteriaceae</i>				CRE				CRE, non-MBL				CRE, KPC				CRE, OXA-48				CRE, other				CRE, MBL			
		N	%S	MIC ₅₀	Range	N	%S	MIC ₅₀	Range	N	%S	MIC ₅₀	Range	N	%S	MIC ₅₀	Range	N	%S	MIC ₅₀	Range	N	%S	MIC ₅₀	Range	N	%S	MIC ₅₀	Range
Germany	CAZ-AVI	1370	99.9	0.25	≤0.015- >128	8	100	0	0.5- >4	8	100	0	0.5- >4	1	100	0	2- >2	2	100	0	0.5- >1	5	100	0	0	1- >4			
	CAZ	1370	80.7	32	≤0.015- >128	8	0	0	8- >128	8	0	0	8- >128	1	0	0	128- >128	2	0	0	8- >16	5	0	0	16- >128				
	MEM	1370	99.4	0.12	0.008- >8	8	0	0	4- >8	8	0	0	4- >8	1	0	0	>8- >8	2	0	0	4- >8	5	0	0	4- >8				
	TGC	1370	80.6	2	0.03- >8	8	75.0	0	1-2	8	75.0	0	1-2	1	100	0	1-1	2	100	0	1-1	5	60	0	1-2				
Greece	CST	578	82.7	>4	≤0.12- >4	5	80.0	0	0.25- >4	5	80.0	0	0.25- >4	1	100	0	0.5- >0.5	2	50	0	1- >4	2	100	0	0.25- >1				
	CAZ-AVI	1110	96.9	1	≤0.015- >128	155	82.6	>128	0																				