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In Vitro Activities of Ceftazidime-avibactam and Comparator Agents against *Enterobacteriaceae* and *Pseudomonas aeruginosa* from Turkey Collected Through the ATLAS Global Surveillance Program 2012-2017

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Introduction

Avibactam is a non-β-lactam, β-lactamase inhibitor that can restore the activity of ceftazidime against organisms that possess Class A, C, and some Class D enzymes. This study examined the *in vitro* activity of ceftazidime-avibactam and comparators against Enterobacterales and *Pseudomonas aeruginosa* collected in Turkey through the ATLAS global surveillance program from 2012 to 2017.

Materials & Methods

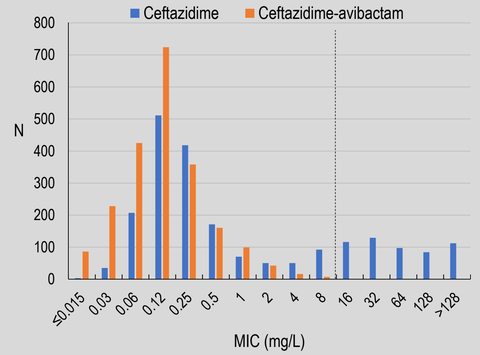
A total of 2,177 non-duplicate, clinically isolated Enterobacterales and 563 *P. aeruginosa* were collected from five sites in four cities in Turkey during 2012-2017 (two sites in Ankara, one site each in Antalya, Trabzon, and Istanbul). Infection sources included (N/percent of total) urinary tract (868/31.7%), lower respiratory tract (727/26.5%), skin and soft tissue (618/22.6%), intra-abdominal (375/13.7%), and blood (152/5.5%). The distribution of Enterobacterales species is shown in Table 1. Susceptibility testing was done by broth microdilution according to CLSI guidelines [1] and interpreted using EUCAST 2018 breakpoints [2]. Ceftazidime-avibactam was tested with a fixed concentration of 4 mg/L avibactam. The presence of genes encoding resistance mechanisms was previously assessed via multiplex PCR, followed by amplification of the full-length genes and sequencing.

Results

Table 1. Distribution of 2,177 Enterobacterales from Turkey by species

Organism	N	% of total
Citrobacter braakii	5	0.2
Citrobacter freundii	72	3.3
Citrobacter koseri	23	1.1
Citrobacter, non-speciated	1	<0.1
Enterobacter asburiae	32	1.5
Enterobacter cloacae	137	6.3
Enterobacter hormaechi	1	<0.1
Enterobacter kobei	5	0.2
Enterobacter ludwigii	1	<0.1
Enterobacter, non-speciated	1	<0.1
Escherichia coli	746	34.3
Klebsiella aerogenes	79	3.6
Klebsiella oxytoca	142	6.5
Klebsiella pneumoniae	618	28.4
Klebsiella variicola	1	<0.1
Morganella morganii	61	2.8
Proteus hauseri	1	0.0
Proteus mirabilis	131	6.0
Proteus vulgaris	33	1.5
Providencia alcalifaciens	1	<0.1
Providencia rettgeri	20	0.9
Providencia stuartii	8	0.4
Raoultella ornithinolytica	3	0.1
Raoultella planticola	3	0.1
Serratia marcescens	52	2.4

Figure 1. Ceftazidime and ceftazidime-avibactam MIC distribution against 2,145 non-MBL Enterobacterales from Turkey, 2012-2017



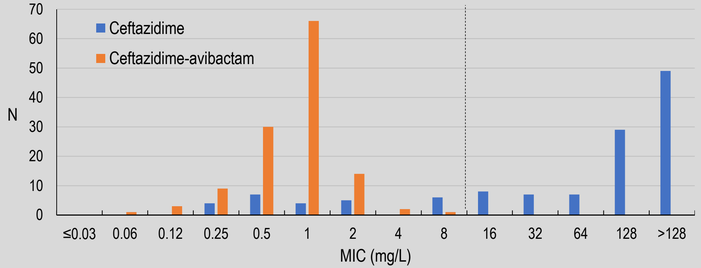
Dashed line represents the EUCAST 2018 breakpoint of 8 mg/L for ceftazidime-avibactam

Table 2. *In vitro* activity of ceftazidime-avibactam and comparators agents against Enterobacterales and *P. aeruginosa* from Turkey

Organism group (n)	%S	mg/L		
		MIC_{50}	MIC_{90}	Range
Enterobacterales (2,177)				
Ceftazidime-avibactam	98.8	0.12	0.5	≤0.015-> 128
Ceftazidime	65.0	0.25	128	≤0.015-> 128
Cefepime	68.9	≤0.12	> 16	≤0.12-> 16
Meropenem	92.8	0.03	0.5	≤0.004-> 8
Amikacin	92.4	2	8	≤0.25-> 32
Colistin (n=1,653)*	79.9	0.5	> 8	≤0.06-> 8
Piperacillin-tazobactam	67.1	4	> 128	≤0.25-> 128
Enterobacterales, MBL-negative (2,145)				
Ceftazidime-avibactam	100	0.12	0.5	≤0.015-8
Ceftazidime	66.0	0.25	64	≤0.015-> 128
Cefepime	69.8	≤0.12	> 16	≤0.12-> 16
Meropenem	94.1	0.03	0.25	≤0.004-> 8
Amikacin	93.3	2	8	≤0.25-> 32
Colistin (n=1,567)*	80.5	0.5	> 8	≤0.06-> 8
Piperacillin-tazobactam	68.1	4	> 128	≤0.25-> 128
CRE, MBL-negative (126)				
Ceftazidime-avibactam	100	1	2	0.06-8
Ceftazidime	11.9	128	> 128	0.25-> 128
Cefepime	7.1	> 16	> 16	≤0.12-> 16
Meropenem	0	> 8	> 8	4-> 8
Amikacin	73.8	4	> 32	0.5-> 32
Colistin (n=117)*	40.7	8	> 8	0.12-> 8
Piperacillin-tazobactam	0.8	> 128	> 128	2-> 128
Enterobacterales, OXA-48 (160)				
Ceftazidime-avibactam	98.8	1	2	0.03->128
Ceftazidime	18.8	64	>128	0.06->128
Cefepime	16.3	>16	>16	0.12->16
Meropenem	28.1	>8	>8	0.015->8
Amikacin	80.0	2	>32	0.5->32
Colistin (n=134)*	44.8	>8	>4	0.25->8
Piperacillin-tazobactam	0.6	>128	>128	4->128
***Escherichia coli* (746)**				
Ceftazidime-avibactam	99.9	0.12	0.25	≤0.015-64
Ceftazidime	59.9	0.25	64	0.06-> 128
Cefepime	59.5	≤0.12	> 16	≤0.12-> 16
Meropenem	99.1	0.03	0.06	0.008-> 8
Amikacin	90.4	4	8	1-> 32
Colistin (n=554)*	99.8	0.25	1	≤0.06-> 4
Piperacillin-tazobactam	70.4	4	> 128	≤0.25-> 128
***Klebsiella pneumoniae* (618)**				
Ceftazidime-avibactam	97.9	0.12	1	≤0.015-> 128
Ceftazidime	52.6	1	> 128	0.03-> 128
Cefepime	55.0	0.25	> 16	≤0.12-> 16
Meropenem	80.9	0.06	> 8	≤0.004-> 8
Amikacin	90.6	1	8	≤0.25-> 32
Colistin (n=495)*	82.0	0.5	> 8	0.12-> 8
Piperacillin-tazobactam	46.6	16	> 128	≤0.25-> 128
***Enterobacter* spp. (177)**				
Ceftazidime-avibactam	99.6	0.25	0.5	0.03-32
Ceftazidime	72.0	0.25	64	0.06-> 128
Cefepime	84.9	≤0.12	8	≤0.12-> 16
Meropenem	97.4	0.06	0.12	0.015-8
Amikacin	98.3	2	2	0.5-> 32
Colistin (n=129)*	95.6	0.5	1	0.12-> 8
Piperacillin-tazobactam	75.0	4	128	≤0.25-> 128
***Pseudomonas aeruginosa* (563)**				
Ceftazidime-avibactam	95.0	2	8	0.12-> 128
Ceftazidime	81.0	4	64	0.25-> 128
Cefepime	79.8	4	> 16	0.25-> 16
Meropenem	71.4	0.5	> 8	0.03-> 8
Amikacin	89.2	4	16	≤0.25-> 32
Colistin (n=461)*	95.9	1	2	0.25-8
Levofloxacin	65.7	0.5	> 4	0.03-> 8
Piperacillin-tazobactam	72.7	8	> 128	≤0.25-> 128

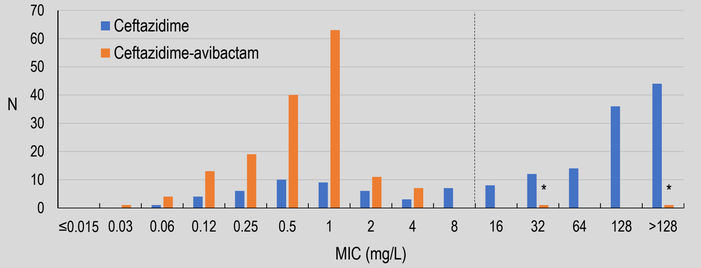
**colistin was not tested in 2012-2013
%S, percent susceptible defined using EUCAST 2018 breakpoints; CRE; carbapenem resistant Enterobacterales based on meropenem nonsusceptibility (MIC ≥4 mg/L); MBL, metallo-β-lactamase

Figure 2. Ceftazidime and ceftazidime-avibactam MIC distribution against 126 non-MBL carbapenem-nonsusceptible (CRE) Enterobacterales from Turkey, 2012-2017



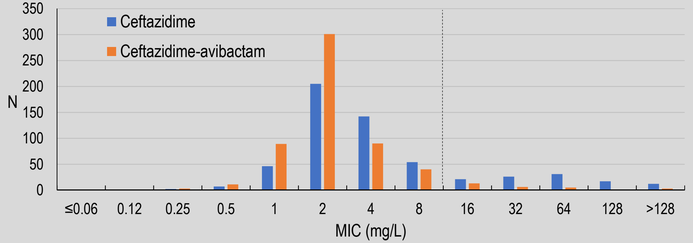
Dashed line represents the EUCAST 2018 breakpoint of 8 mg/L for ceftazidime-avibactam

Figure 3. Ceftazidime and ceftazidime-avibactam MIC distribution against 160 OXA-48-positive Enterobacterales from Turkey, 2012-2017



Dashed line represents the EUCAST 2018 breakpoint of 8 mg/L for ceftazidime-avibactam
*2 of 2 isolates with ceftazidime-avibactam MICs >8 also carry MBLs

Figure 4. Ceftazidime and ceftazidime-avibactam MIC distribution against 563 Pseudomonas aeruginosa from Turkey, 2012-2017



Dashed line represents the EUCAST 2018 breakpoint of 8 mg/L for ceftazidime-avibactam

Results

- Ceftazidime-avibactam exhibited potent activity against all Enterobacterales (MIC_{90}, 0.5 mg/L; 98.8% susceptible). When MBL-positive isolates were removed from analysis, susceptibility to ceftazidime-avibactam was 100% (Table 2, Figure 1).
- Ceftazidime-avibactam showed consistently higher % susceptibilities than all comparators against MBL-negative meropenem-nonsuscepible isolates (CRE) (Table 2).
- 27 Enterobacterales were non-susceptible to ceftazidime-avibactam. All were positive for MBL genes: 24 NDM-1 (MIC range 64->128 mg/L); one each NDM-1 plus VIM-1 (MIC=128 mg/L); VIM-31 (MIC=32 mg/L); and VIM-5 (MIC=32 mg/L).
- 158/160 isolates positive for OXA-48 were susceptible to ceftazidime-avibactam. The two non-susceptible isolates also produced an MBL (Figure 3).
- Ceftazidime-avibactam showed good activity against the majority of *P. aeruginosa* isolates (MIC_{90}, 8 mg/L; 95.0% susceptible), and was the most active of the drugs tested with the exception of colistin (Table 2, Figure 4).

Conclusions

- Ceftazidime-avibactam showed potent *in vitro* activity against Enterobacterales and *P. aeruginosa* collected in Turkey, including isolates resistant to last-in-line agents, with susceptibility of >95%.
- Ceftazidime-avibactam provides a valuable alternative to colistin and meropenem for infections caused by *P. aeruginosa* and Enterobacterales that do not carry MBLs.

References

1. CLSI. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard – Eleventh Edition*. CLSI document M07-A11. Wayne, PA.: Clinical and Laboratory Standards Institute; 2017.
2. The European Committee on Antimicrobial Susceptibility Testing. 2018. *Breakpoint tables for interpretation of MICs and zone diameters*. Version 8.1. http://www.eucast.org.

Disclosures

This study was sponsored by AstraZeneca (AZ). AZ's rights to ceftazidime-avibactam were acquired by Pfizer in December 2016. MH and DS are employees of IHMA, who received fees from Pfizer for the conduct of the study and were paid consultants to Pfizer in connection with the development of this abstract. GS, an employee of and shareholder in AZ at the time of the study, is currently an employee of Pfizer.

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