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Activity of Ceftazidime-Avibactam and Comparators against Colistin Non-Susceptible *Enterobacteriaceae* and *Pseudomonas aeruginosa* Isolated in 2012: The International Network For Optimal Resistance Monitoring (INFORM) Study

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Introduction

Due to the increase in multidrug resistance in Gram-negative bacteria, colistin, also known as polymyxin E, is increasingly being used to treat serious Gram-negative infections. While resistance to polymyxins is low, trends towards increasing resistance are being reported. Moreover, intrinsic resistance to colistin is present in *Proteus* spp., *Providencia* spp., *Morganella morganii* and *Serratia marcescens*. Avibactam, a novel non-β-lactam β-lactamase inhibitor, is being developed for use in combination with the β-lactams, ceftazidime, ceftaroline fosamil and aztreonam. Avibactam protects β-lactams from hydrolysis in Gram-negative bacteria that produce Ambler class A β-lactamases including extended-spectrum enzymes (ESBLs) and *Klebsiella pneumoniae* carbapenemases (KPCs), class C β-lactamases, and some class D enzymes. In this study, we evaluated the activity of ceftazidime-avibactam and comparators against colistin non-susceptible isolates from the 2012 INFORM global surveillance study.

Materials and Methods

- Non-duplicate isolates were collected from 132 medical centres in 32 countries in a 2012 global surveillance program. Each site collected and identified consecutive fresh clinical isolates from various sources. Only one isolate of any one species per patient was included.
- Isolates were sent to a central lab, International Health Management Associates, Inc., Schaumburg, IL, USA (IHMA) for susceptibility testing and confirmation of identification.
- Minimum inhibitory concentrations (MICs) were determined by CLSI recommended broth microdilution testing method using panels prepared at IHMA. Avibactam was tested at a set concentration of 4 mg/L. Colistin was supplemented with 0.002% polysorbate-80. MIC interpretive criteria followed EUCAST 2013 guidelines. Since no breakpoints are available for ceftazidime-avibactam, the percent of isolates with an MIC of ≤8 mg/L is reported (based on the 2g q8h dose of ceftazidime infused over 2h).
- Quality controls (QC) were performed on each day of testing using appropriate ATCC control strains, following CLSI guidelines.

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Results

- 9,278 *Enterobacteriaceae* (8,046 from species without intrinsic resistance to colistin, 1,232 from species with intrinsic colistin resistance including *Proteus* spp., *Providencia* spp., *Morganella morganii* and *Serratia marcescens*) and 1,558 *Pseudomonas aeruginosa*
- Of the isolates collected, 70 *Enterobacteriaceae* without intrinsic colistin resistance (0.9%) and 16 *P. aeruginosa* (1.0%) were colistin non-susceptible.

Table 1. *In vitro* activity of ceftazidime-avibactam and comparators against all *Enterobacteriaceae*, *Enterobacteriaceae* species with and without intrinsic colistin resistance, and colistin non-susceptible isolates.

Phenotype	Antimicrobial	%S	mg/L MIC_{50}	mg/L MIC_{90}
All *Enterobacteriaceae* (9567)	Amikacin	94	2	8
	Cefepime	78	≤0.12	> 16
	Ceftazidime	74	0.25	64
	Ceftazidime-avibactam[a]	99[a]	0.12	0.5
	Colistin	84	≤0.12	> 4
	Doripenem	98	0.06	0.25
	Ertapenem	96	0.015	0.25
	Imipenem	93	0.25	2
	Levofloxacin	73	0.06	> 4
	Meropenem	98	0.03	0.12
	Piperacillin-tazobactam	78	2	128
	Tigecycline	79	0.5	2
Enterobacteriaceae, species without intrinsic colistin resistance (8046)	Amikacin	94	2	8
	Cefepime	76	≤0.12	> 16
	Ceftazidime	71	0.25	64
	Ceftazidime-avibactam[a]	99[a]	0.12	0.5
	Colistin	99	≤0.12	0.25
	Doripenem	98	0.03	0.12
	Ertapenem	96	0.015	0.25
	Imipenem	97	0.25	1
	Levofloxacin	73	0.06	> 4
	Meropenem	98	0.03	0.06
	Piperacillin-tazobactam	75	4	128
	Tigecycline	90	0.5	1
Enterobacteriaceae, intrinsically colistin resistant[b] (1521)	Amikacin	95	2	8
	Cefepime	91	≤0.12	1
	Ceftazidime	90	0.06	2
	Ceftazidime-avibactam[a]	100[a]	0.06	0.25
	Colistin	0	> 4	> 4
	Doripenem	99	0.25	0.5
	Ertapenem	99	0.03	0.06
	Imipenem	73	2	4
	Levofloxacin	77	0.12	> 4
	Meropenem	100	0.06	0.25
	Piperacillin-tazobactam	96	0.5	2
	Tigecycline	21	2	8
Enterobacteriaceae, no intrinsically resistant species, colistin NS (70)	Amikacin	91	2	8
	Cefepime	77	≤0.12	> 16
	Ceftazidime	69	0.5	> 128
	Ceftazidime-avibactam[a]	99[a]	0.25	1
	Colistin	0	> 4	> 4
	Doripenem	**90**[c]	0.06	0.5
	Ertapenem	**90**	0.12	0.5
	Imipenem	**89**	1	4
	Levofloxacin	76	0.12	> 4
	Meropenem	**90**	0.06	0.25
	Piperacillin-tazobactam	77	2	64
	Tigecycline	**76**	1	2

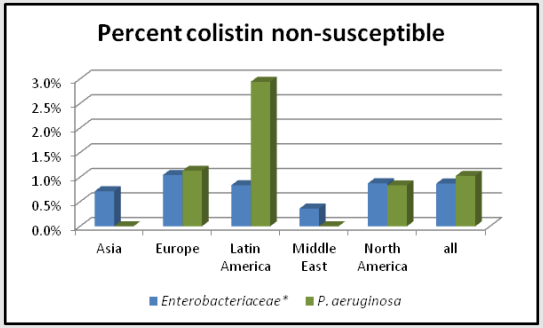
[a] Percent of isolates with a ceftazidime-avibactam MIC of ≤8 mg/L.
[b] *Morganella morganii* (289), *Proteus mirabilis* (676), *P. penneri* (11), *P. rettgeri* (2), *P. vulgaris* (238), *Providencia alcalifaciens* (7), *P. rettgeri* (32), *P. stuartii* (40), *Serratia marcescens* (226).
[c] Bolded numbers show significant decrease in percent susceptible compared to all *Enterobacteriaceae* species without intrinsic colistin resistance.

Table 2. *In vitro* activity of ceftazidime-avibactam and comparators against *P. aeruginosa* and colistin non-susceptible isolates.

Phenotype	Antimicrobial	%S	mg/L MIC_{50}	mg/L MIC_{90}
All *P. aeruginosa* (1558)	Amikacin	89	4	16
	Cefepime	83	4	16
	Ceftazidime	82	2	32
	Ceftazidime-avibactam[a]	97[a]	2	8
	Colistin	99	0.25	2
	Doripenem	70	0.5	> 4
	Imipenem	74	2	> 8
	Levofloxacin	65	0.5	> 4
	Meropenem	75	0.5	> 8
	Piperacillin-tazobactam	76	8	128
P. aeruginosa, colistin NS (16)	Amikacin	75	8	32
	Cefepime	94	1	8
	Ceftazidime	75	2	128
	Ceftazidime-avibactam[a]	94[a]	2	8
	Colistin	0	> 8	> 8
	Doripenem	56	1	> 4
	Imipenem	56	4	> 8
	Levofloxacin	38	4	> 4
	Meropenem	63	0.5	> 8
	Piperacillin-tazobactam	69	4	> 128

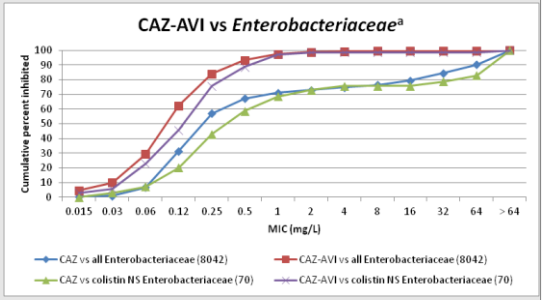
[a] percent of isolates with a ceftazidime-avibactam MIC of ≤8 mg/L

Figure 1. Percent of isolates non-susceptible to colistin by region.



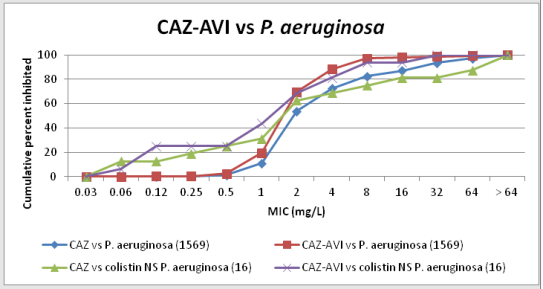
* *Enterobacteriaceae* species without intrinsic colistin resistance.

Figure 2. Cumulative frequency distribution of ceftazidime and ceftazidime-avibactam MICs vs 8,042 European *Enterobacteriaceae* and 70 European colistin non-susceptible *Enterobacteriaceae*[a].



[a]Does not include intrinsically resistant species.

Figure 3. Cumulative frequency distribution of ceftazidime and ceftazidime-avibactam MICs vs 1,569 European *P. aeruginosa* and 16 European colistin non-susceptible *P. aeruginosa*.



Conclusions

- Ceftazidime-avibactam demonstrated potent activity against colistin non-susceptible isolates of *Enterobacteriaceae* and *P. aeruginosa* from a global population, with an MIC of ≤8 mg/L in >99% and 94%, respectively. There was no significant difference in ceftazidime-avibactam susceptibility between colistin-susceptible and -non-susceptible isolates.
- The carbapenems and tigecycline were significantly less active against the colistin non-susceptible isolates. These results may reflect selective pressure as colistin is increasingly used empirically to treat KPC and metallo-β-lactamase producing isolates.
- These *in vitro* results suggest that ceftazidime-avibactam may be a valuable option for the treatment of increasingly difficult to treat serine β-lactamase-producing pathogens.