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In vitro Activity of Ceftazidime-avibactam against *Enterobacteriaceae* Causing Intra-abdominal, Urinary Tract and Lower Respiratory Tract Infections Collected in Latin America as Part of the INFORM Global Surveillance Program, 2012-2016

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Introduction

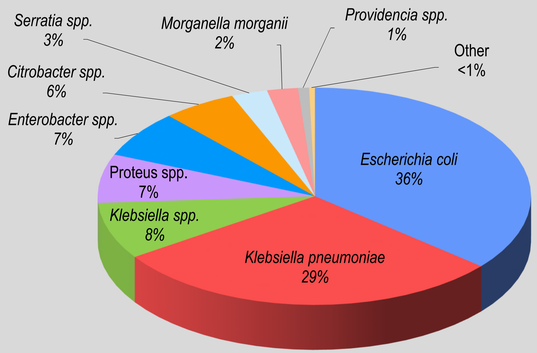
The dissemination of multidrug-resistant *Enterobacteriaceae* threatens the effective treatment of Gram-negative infections. Ceftazidime-avibactam (CAZ-AVI) is a novel antimicrobial with activity against *Enterobacteriaceae* producing Class A, C and some Class D β-lactamases. This study evaluated the *in vitro* activity of CAZ-AVI against *Enterobacteriaceae* isolates from urinary tract infections (UTI), intra-abdominal infections (IAI) and lower respiratory tract infections (LRTI) collected in Latin America as a part of the International Network for Optimal Resistance Monitoring (INFORM) global surveillance study from 2012-2016.

Materials & Methods

- 7,037 non-duplicate *Enterobacteriaceae* isolates were collected from UTI, IAI or LRTI in 26 sites in Argentina, Brazil, Chile, Colombia, Mexico and Venezuela.
- Susceptibility testing of ceftazidime-avibactam and comparator agents was by broth microdilution using CLSI 2018 breakpoints (1,2). Resistance to colistin was determined using EUCAST 2018 breakpoints (3). Ceftazidime-avibactam was tested with a fixed concentration of 4 µg/mL avibactam.
- Meropenem non-susceptibility prompted β-lactamase screening by multiplex PCR for bla_{SHV}, bla_{TEM}, bla_{CTX-M}, bla_{VEB}, bla_{PER}, bla_{GES}, bla_{ACC}, bla_{ACT}, bla_{CMY}, bla_{DHA}, bla_{FOX}, bla_{MIR}, bla_{MOX}, bla_{KPC}, $bla_{OXA-48-like}$, bla_{IMP}, bla_{VIM}, bla_{NDM} and bla_{SPM} followed by Sanger sequencing (4).
- Multidrug-resistance (MDR) was defined as resistance to sentinel drugs from ≥3 classes comprised of cephalosporins (cefepime), monobactams (aztreonam), β-lactam/β-lactamase inhibitor combinations (piperacillin-tazobactam), carbapenems (meropenem), fluoroquinolones (levofloxacin), aminoglycosides (amikacin), glycylcyclines (tigecycline) and polymyxins (colistin).

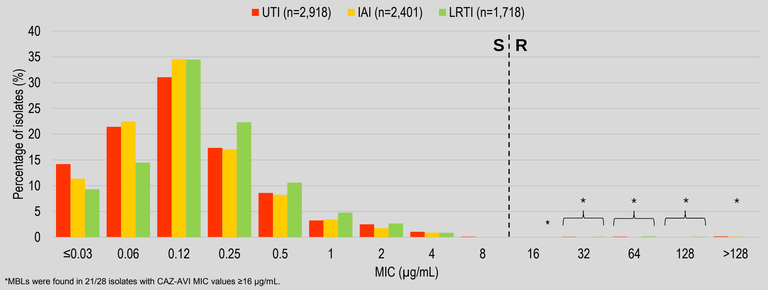
Results

Figure 1: Species distribution of *Enterobacteriaceae* (n=7,037)



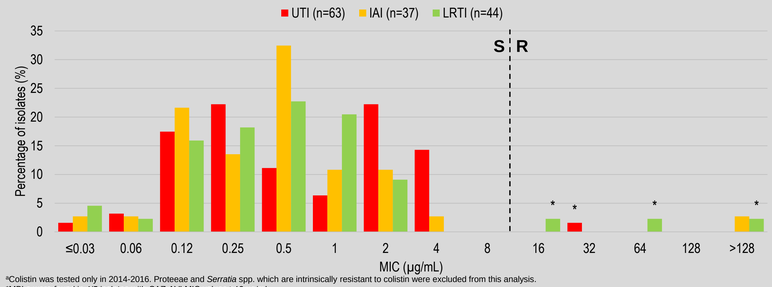
Genus	Species	Count
Escherichia	*Escherichia coli*	2,543
Klebsiella	*Klebsiella pneumoniae*	2,070
Klebsiella	*Klebsiella oxytoca*	307
	Klebsiella aerogenes	263
	Klebsiella variicola	25
Proteus	*Proteus mirabilis*	385
	Proteus vulgaris	109
	Proteus hauseri	9
	Proteus penneri	7
	Proteus rettgeri	1
Enterobacter	*Enterobacter cloacae*	419
	Enterobacter asburiae	55
	Enterobacter kobei	15
	Enterobacter ludwigii	2
Citrobacter	*Citrobacter freundii*	261
	Citrobacter koseri	100
	Citrobacter braakii	19
	Citrobacter amalonaticus	6
	Citrobacter farmeri	2
Serratia	*Serratia marcescens*	185
	Serratia liquefaciens	2
	Serratia rubidaea	1
	Serratia ureilytica	1
Morganella	*Morganella morgannii*	162
Providencia	*Providencia rettgeri*	29
	Providencia stuartii	26
	Providencia alcalifeciens	3
Other	*Raoultella ornithinolytica*	24
	Pluralibacter gergoviae	2
	Cronobacter sakazakii	1
	Escherichia vulneris	1
	Kluyvera ascorbata	1
	Leliottia amnigena	1

Figure 2: Activity of ceftazidime-avibactam against all *Enterobacteriaceae*, by infection source



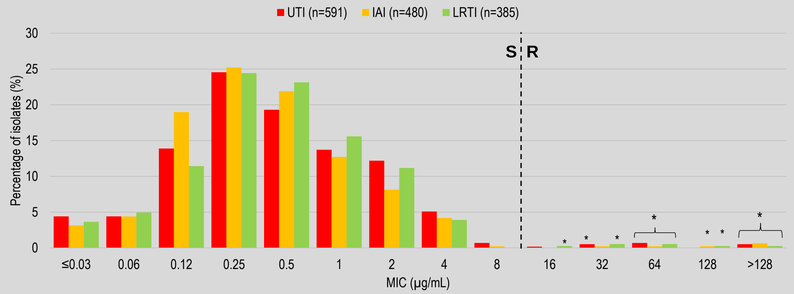
[a]MBLs were found in 21/28 isolates with CAZ-AVI MIC values ≥16 µg/mL.

Figure 3a: Activity of ceftazidime-avibactam against colistin-resistant *Enterobacteriaceae*, by infection source[a]



[a]Colistin was tested only in 2014-2016. Proteeae and *Serratia* spp. which are intrinsically resistant to colistin were excluded from this analysis.
[b]MBLs were found in 4/5 isolates with CAZ-AVI MIC values ≥16 µg/mL.

Figure 3b: Activity of ceftazidime-avibactam against multidrug-resistant *Enterobacteriaceae*, by infection source[a]



[a]Multidrug-resistant is defined as resistant to ≥3 classes of drugs.
[b]MBLs were found in 19/24 isolates with CAZ-AVI MIC values ≥16 µg/mL.

Table 1: Activity of ceftazidime-avibactam and comparator agents against *Enterobacteriaceae*, by infection source[a]

Source/Phenotype (n [All]/n [Excl. Proteeae/*Serratia*])[b]	Drug (MIC$_{90}$ [µg/mL]/% Susceptible)							
	CAZ-AVI		CAZ		MEM		CST[b]	
All sources, All phenotypes (n=7,037/4,087)	0.5	99.6	64	70.0	0.12	94.7	1	96.5
CAZ-NS (n=2,110/1,361)	2	98.7	>128	0.0	8	83.4	1	93.8
MEM-NS (n=372/259)	4	93.8	>128	5.9	>8	0.0	>4	74.9
MEM-NS, MBL-negative (n=351/241)	4	99.4	>128	6.3	>8	0.0	>4	74.7
CST-R (n=144)	4	96.5	>128	41.0	>8	54.9	>4	0.0
MDR[c] (n=1,456/917)	2	98.4	>128	6.5	>8	76.0	2	90.5
UTI, All phenotypes (n=2,918/1,617)	0.5	99.6	64	72.7	0.12	95.0	1	96.1
CAZ-NS (n=797/495)	2	98.4	>128	0.0	4	82.3	1	92.7
MEM-NS (n=147/100)	4	93.2	>128	4.1	>8	0.0	>4	70.0
MEM-NS, MBL-negative (n=138/94)	4	99.3	>128	4.4	>8	0.0	>4	69.2
CST-R (n=63)	4	98.4	128	42.9	>8	52.4	>4	0.0
MDR[c] (n=591/358)	2	98.1	>128	8.1	8	76.1	>4	88.8
IAI, All phenotypes (n=2,401/1,419)	0.5	99.8	64	70.5	0.12	95.2	1	97.4
CAZ-NS (n=709/471)	1	99.2	>128	0.0	8	84.8	1	95.5
MEM-NS (n=116/83)	4	95.7	>128	6.9	>8	0.0	>4	80.7
MEM-NS, MBL-negative (n=112/79)	2	99.1	>128	7.1	>8	0.0	>4	79.8
CST-R (n=37)	2	97.3	>128	43.2	>8	56.8	>4	0.0
MDR[c] (n=480/315)	2	98.8	>128	5.8	>8	77.5	1	93.3
LRTI, All phenotypes (n=1,718/1,051)	0.5	99.5	128	64.8	0.25	93.7	1	95.8
CAZ-NS (n=604/395)	2	98.5	>128	0.0	8	83.3	1	92.9
MEM-NS (n=109/76)	4	92.7	>128	7.3	>8	0.0	>4	75.0
MEM-NS, MBL-negative (n=101/68)	2	100.0	>128	7.9	>8	0.0	>4	76.5
CST-R (n=44)	2	93.2	>128	36.4	>8	56.8	>4	0.0
MDR[c] (n=385/244)	2	98.2	>128	4.7	>8	74.0	4	89.3

[a]Abbreviations: CAZ-AVI, ceftazidime-avibactam; CAZ, ceftazidime; MEM, meropenem; CST, colistin; NS, non-susceptible; MBL, metallo-β-lactamase; R, resistant; MDR, multidrug-resistant.
[b]CST data excludes Proteeae and *Serratia* spp. intrinsically resistant to CST; CST was not tested in project years 2012-2013. CST breakpoints are by EUCAST 2018.
[c]MDR, resistant to agents from ≥3 classes.

Results

- Ceftazidime-avibactam exhibited potent *in vitro* activity against this collection of 7,037 *Enterobacteriaceae*.
- Among these isolates, 99.5-99.8% were susceptible across all infection sites (MIC$_{90}$ 0.5 µg/mL), with 21 of the 28 resistant isolates positive for a metallo-β-lactamase gene (Figure 2, Table 1).
- 93.2-98.4% of colistin-resistant isolates from all infection sites were susceptible to ceftazidime-avibactam (MIC$_{90}$ 2-4 µg/mL); in comparison, only 52.4-56.8% of these isolates were susceptible to meropenem (Figure 3a, Table 1).
- More multidrug-resistant isolates were susceptible to ceftazidime-avibactam (MIC$_{90}$ 2 µg/mL) than to meropenem or colistin (98.4%, 76.0% and 90.5% susceptible, respectively) (Table 1).
- The activity of ceftazidime-avibactam exceeded that of colistin against meropenem-nonsusceptible isolates in every specimen source (92.7-95.7% vs 70.0-80.7%). As expected, ceftazidime-avibactam demonstrated greater activity against meropenem-nonsusceptible isolates which were metallo-β-lactamase-negative (99.1-100% susceptible) (Table 1).

Conclusions

- Ceftazidime-avibactam demonstrated potent *in vitro* activity against this collection of *Enterobacteriaceae* isolated in Latin America from 2012-2016.
- More isolates from UTI, IAI and LRTI were susceptible to ceftazidime-avibactam than to meropenem or colistin.
- Ceftazidime-avibactam could provide a valuable alternative to other last resort agents for the treatment of infections caused by *Enterobacteriaceae* that are resistant to meropenem, colistin or presenting a multidrug-resistant phenotype.
- *Enterobacteriaceae* harboring metallo-β-lactamases compromise the activity of ceftazidime-avibactam and other agents currently in use and must continue to be monitored.

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Disclosures

This study was sponsored by AstraZeneca (AZ). AZ's rights to ceftazidime-avibactam were acquired by Pfizer in December 2016. IHMA received financial support from AZ in connection with the study and from Pfizer for the development of this poster. M. Estabrook, K. Kazmierczak, and D. Sahm are employees of IHMA. G. Stone, an employee of and shareholder in AZ at the time of the study, is currently an employee of Pfizer.

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