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Activity of ceftazidime-avibactam against isolates of Enterobacteriaceae and Pseudomonas aeruginosa collected in Europe as part of the INFORM global surveillance programme, 2015

Krystyna Kazmierczak*[1], Mark Estabrook[1], Boudewijn De Jonge[2], Gregory Stone[2], Daniel Sahm[3]

[1]*International Health Management Associates, Inc.*

[2]*Astrazeneca Pharmaceuticals*

[3]*Ihma; Microbiology*

Background: Avibactam is a non-β-lactam β-lactamase inhibitor that restores the *in vitro* activity of ceftazidime against class A, class C, and some class D β-lactamases, including extended-spectrum β-lactamases (ESBL), serine carbapenemases, and the chromosomal AmpC of *Pseudomonas aeruginosa*. Ceftazidime-avibactam has been approved in Europe and the US for several indications. This study evaluated the *in vitro* activity of ceftazidime-avibactam and comparators against *Enterobacteriaceae* and *P. aeruginosa* collected in Europe in 2015 as part of the INFORM surveillance program.
Material/methods: Non-duplicate isolates were collected from 67 medical centers in 17 European countries. Susceptibility testing was performed by broth microdilution and interpreted using EUCAST breakpoints (ceftazidime-avibactam; ≤8 mg/L, susceptible; ≥16 mg/L, resistant). Avibactam was tested at a fixed concentration of 4 mg/L with doubling dilutions of ceftazidime. Multidrug resistant (MDR) was defined as resistant by EUCAST breakpoints to sentinel agents from three or more drug classes, including cefepime, aztreonam, piperacillin-tazobactam, meropenem, levofloxacin, amikacin, tigecycline, and colistin. *P. aeruginosa* isolates with a meropenem MIC >2 mg/L and *Enterobacteriaceae* isolates positive for ESBL activity, testing with a ceftazidime MIC >8 mg/L, and those with a meropenem MIC >1 mg/L were screened for acquired β-lactamase genes by PCR and sequencing.
Results: Susceptibility data are provided in the table. Ceftazidime-avibactam showed potent *in vitro* activity against the overall population of *Enterobacteriaceae* (MIC_{90}, 0.5 mg/L; 99.1% susceptible) and against ceftazidime-nonsusceptible (MIC >1 mg/L), colistin-resistant (MIC >2 mg/L), and MDR isolates, with >94% of these resistant subsets testing with MICs ≤8 mg/L. Reduced activity against meropenem-nonsusceptible (MIC >2 mg/L) *Enterobacteriaceae* was attributable to the presence of class B metallo-β-lactamases (MBL) because 99.5% of meropenem-nonsusceptible, MBL-negative isolates were susceptible to ceftazidime-avibactam. Ceftazidime-avibactam also showed good activity

against the majority of *P. aeruginosa* isolates (MIC_{90}, 8 mg/L; 92.2% susceptible). Activity was reduced against ceftazidime-nonsusceptible (MIC >8 mg/L), colistin-resistant (MIC >4 mg/L), meropenem-nonsusceptible (MIC >2 mg/L), meropenem-nonsusceptible, MBL-negative, and MDR subsets (67.3–83.0% susceptible) but exceeded the activity of ceftazidime and meropenem by 28.0–83.0%.

Species/Phenotype (n)	Drug (MIC_{90}/% Susceptible)					
	CAZ-AVI		CAZ		MER	
Enterobacteriaceae, All (6449)	0.5	99.1%	64	75.2%	0.12	96.2%
CAZ-NS (1602)	2	96.3%	>128	0.0%	>8	85.0%
MER-NS (248)	>128	79.4%	>128	2.8%	>8	0.0%
MER-NS, MBL-negative (194)	4	99.5%	>128	3.6%	>8	0.0%
CST-R (125)[a]	2	97.6%	>128	24.8%	>8	51.2%
MDR (1029)[c]	2	94.7%	>128	5.3%	>8	77.2%
P. aeruginosa, All (1835)	8	92.2%	64	76.0%	>8	71.8%
CAZ-NS (440)	64	67.3%	>128	0.0%	>8	35.9%
MER-NS (518)	64	73.6%	>128	45.6%	>8	0.0%
MER-NS, MBL-negative (459)	32	83.0%	128	51.4%	>8	0.0%
CST-R (5)[a]	NA[b]	80.0%	NA	40.0%	NA	40.0%
MDR (479)[c]	64	69.9%	>128	23.2%	>8	27.4%

CAZ-AVI, ceftazidime-avibactam; CAZ, ceftazidime; MER, meropenem; CST, colistin; MDR, multidrug resistant; MBL, metallo-β-lactamase. EUCAST breakpoints were used to define non-susceptible (NS) and resistant (R) subsets.

[a] Excludes isolates of Proteeae and *Serratia* spp.

[b] NA, MIC_{90} was not calculated for n <10

[c] MDR, resistant to sentinel agents from 3 or more drug classes by EUCAST breakpoints.

Conclusions: Ceftazidime-avibactam provides a valuable therapeutic option for treating infections caused by *Enterobacteriaceae* and *P. aeruginosa* isolates resistant to commonly used and last-in-line agents.