➢ **CAZ-AVI represents a valuable option for targeted treatment of infections caused by non-MBL-producing Enterobacterales and *Pseudomonas aeruginosa* isolates.**

In vitro activity of ceftazidime-avibactam against ceftazidime-non-susceptible Gram-negative pathogens recovered from hospitalized patients from Germany, Austria and Switzerland, 2019-2020

Background

The combination of ceftazidime (CAZ) plus avibactam (AVI) possesses potent activity against Gram-negative bacteria producing different classes of β-lactamases, with exception of metallo-β-lactamases (MBL).[1] This study investigates the *in vitro* activity of CAZ-AVI against Gram-negative bacteria recovered from patients during a multicentre surveillance study conducted in 2019/20.

Results

- CAZ-resistance was confirmed in 215 Enterobacterales and 104 *P. aeruginosa* isolates. Susceptibility to CAZ-AVI (MIC ≤ 8 mg/L) was observed in 98.6% of CAZ-resistant Enterobacterales and 80.8% of CAZ-resistant *P. aeruginosa* (Table).
- Isolates from Austria (n=27) and Switzerland (n=18) were susceptible to CAZ-AVI, with three isolates from each country showing MIC = 8 mg/L, which is close to the EUCAST breakpoint (>8 mg/L).

Table: Number and percent of ceftazidime-avibactam (CAZ-AVI)-susceptible and CAZ-AVI-resistant Enterobacterales and *P. aeruginosa* isolates

Group / subgroup (n, number of isolates)	CAZ-AVI-susceptible		CAZ-AVI-resistant	
	n	%	n	%
Enterobacterales				
All (n=261)	258	98.9	3	1.1
Ceftazidime-resistant Enterobacterales				
All (n=215)	212	98.6	3[§]	1.4
ESBL-producer (without CP) (n=92)	92	100.0	0	0.0
CP-/ESBL-producer (n=8)[*]	6	75.0	2	25.0
Pseudomonas aeruginosa				
All (n=154)	134	87.0	20	13.0
Ceftazidime-resistant *P. aeruginosa*				
All (n=104)	84	80.8	20	19.2
MBL-producer (n=5)[#]	0	0.0	5	100.0

CP, carbapenemase; ESBL, extended-spectrum-β-lactamase; MBL, metallo-β-lactamase. [§] In one CAZ-AVI-resistant *K. pneumoniae* isolate there was neither a CP nor an ESBL detected. [*]Five *K. pneumoniae* isolates encoded either OXA-232 together with CTX-M-1 (n=3), KPC-2 in combination with CTX-M-1 (n=1) or NDM-1 together with CTX-M-1 and OXA-48. In addition, one *K. variicola* isolate encoded VIM-1 together with CTX-M-9 and two *E. coli* isolates encoded OXA-244 together with CTX-M-9. [#]MBL-positive *P. aeruginosa* encoded GIM-1 (n=1), IMP-1 (n=1) or VIM-2 (n=3).

- Various β-lactamase genes were detected, including CTX-M-group1/9, OXA-48-like, KPC-2, NDM-1 and VIM-1 in Enterobacterales isolates and VIM-2, IMP-1 or GIM-1 in *P. aeruginosa* isolates.
- Non-MBL-producing CAZ-resistant isolates revealed CAZ-AVI-susceptibility rates of 99.5% for Enterobacterales and 84.8% for *P. aeruginosa*.

Methods

In total, 415 Enterobacterales and *Pseudomonas aeruginosa* isolates were collected at 23 laboratories across Germany, Austria and Switzerland as part of the resistance study of the Paul-Ehrlich-Society. At one reference laboratory verification of species identification and antimicrobial susceptibility testing were performed; and the in vitro activity of CAZ-AVI and CAZ was determined by broth microdilution. Presence of beta-lactamase genes was investigated by PCR and/or whole genome sequencing at the Robert Koch-Institute and the National Reference Centre for multidrug-resistant Gram-negative Bacteria.

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Funding & Disclosures

This project was sponsored by Pfizer Pharma GmbH. EW is a general partner and CEO of Antiinfectives Intelligence GmbH, which provides research services for pharmaceutical companies.

Paul-Ehrlich-Gesellschaft für Infektionstherapie e.V.