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Paper Poster Session VI

New data on new cephalosporin/beta-lactamase inhibitor combinations

Comparative *in vitro* activity of ceftazidime-avibactam against Gram-negative pathogens from hospital-acquired lower respiratory tract infections in the European union: 2013 INFORM surveillance programme

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Objectives: Treatment options are limited in hospital-acquired lower respiratory tract infections (HA-LRTI) because of high resistance rates due to extended-spectrum β-lactamases (ESBL) and other resistance mechanisms. As a non-β-lactam β-lactamase inhibitor capable of inhibiting Ambler class A, C, and some class D β-lactamases, avibactam combined with ceftazidime may represent an additional therapeutic option. Therefore, the *in vitro* activity of ceftazidime-avibactam was tested against European clinical isolates from HA-LRTI collected in 2013 as part of the International Network For Optimal Resistance Monitoring (INFORM) global surveillance program.

Methods: 65 sites in 17 countries in the European Union (Austria, Belgium, Czech Republic, Denmark, France, Germany, Greece, Hungary, Ireland, Italy, Netherlands, Poland, Portugal, Romania, Spain, Sweden, United Kingdom) collected 1,196 clinically relevant Gram-negative isolates from patients with hospital-acquired (isolates collected ≥48 hours post-admission) LRTI in 2013. One strain per patient infection episode was included. Susceptibility was determined using the CLSI broth microdilution method and EUCAST breakpoints. Isolates phenotypically positive for ESBL or non-susceptible to a carbapenem were analysed for β-lactamases via multiplex PCR, followed by sequencing.

Results: MIC_{90} values (mg/L) of ceftazidime-avibactam and comparators against selected Gram-negative species and genera (including molecularly characterized ESBL+ subsets and ceftazidime-non-susceptible phenotypes) are shown below.

Organisms (n) / S|R Breakpoints†	CAZ-AVI na	CAZ ≤1/≥8	FEP ≤1/≥8	ATM ≤1/≥8	TZP ≤8/≥32	MEM ≤2/≥16	LVX ≤1/≥4	AMK ≤8/≥32
Klebsiella spp. (373)	1	128	>16	128	>128	0.25	>4	8
ESBL+ (95)	2	>128	>16	>128	>128	>8	>4	32
Escherichia coli (238)	0.25	16	16	16	32	0.03	>4	8
ESBL+ (37)	0.25	64	>16	128	>128	0.06	>4	>32
Enterobacter spp. (179)	1	128	4	64	128	0.12	1	4
CAZ-NS (79)	1	>128	8	64	>128	0.5	>4	4
Citrobacter spp. (66)	0.5	128	1	32	64	0.06	1	4
CAZ-NS (17)	1	>128	>16	128	128	0.12	>4	16
S|R Breakpoints†	**na**	**≤8/≥16**	**≤8/≥16**	**≤1/≥32**	**≤16/≥32**	**≤2/≥16**	**≤1/≥4**	**≤8/≥32**
Pseudomonas aeruginosa (250)	8	64	16	64	>128	>8	>4	16
CAZ-NS (60)	32	128	>16	128	>128	>8	>4	>32

CAZ-AVI, ceftazidime-avibactam; CAZ, ceftazidime; FEP, cefepime; ATM, aztreonam; TZP, piperacillin-tazobactam; MEM, meropenem; LVX, levofloxacin; AMK, amikacin; na, not available; NS, non-susceptible.

† EUCAST v3.1 breakpoints.

68% of CAZ-non-susceptible *P. aeruginosa* had CAZ-AVI MICs ≤8 mg/L (used as reference value for comparative purposes in the absence of a CAZ-AVI breakpoint), compared to 73% susceptible to amikacin and 25% to meropenem. The MIC_{90} values for 90 *A. baumannii* isolates were 128 and >128 mg/L for ceftazidime-avibactam and ceftazidime, respectively. The most commonly found ESBL enzymes in *Klebsiella* spp. were CTX-M-15 (70 of 95) and SHV-12 (18 of 95), whereas in *E. coli* they were CTX-M-15 (26 of 37) and CTX-M-14 (4 of 37).

Conclusions:

- MIC_{90} values of ceftazidime-avibactam were reduced at least 64-fold for *Enterobacteriaceae* and 8-fold for *P. aeruginosa* compared to ceftazidime alone. The *in vitro* activity of ceftazidime-avibactam was excellent against ESBL+ and ceftazidime-non-susceptible *Enterobacteriaceae* (MIC_{90} ≤2), subsets for which the MIC_{90} values of most other tested agents were in the resistant range.
- Not surprisingly, ESBL+ rates were high in these hospital-acquired LRTI isolates from the European Union (16% in *E. coli* and 25% in *Klebsiella* spp.), and will have to be considered when selecting therapeutic agents.
- Even in this collection of pathogens with high resistance levels to several classes of antimicrobials, ceftazidime-avibactam showed very promising activity against Gram-negative pathogens, except *A. baumannii.*