

New data on new cephalosporin/beta-lactamase inhibitor combinations

Activity of ceftazidime-avibactam and comparators against carbapenemase-producing *Enterobacteriaceae* isolated in sampled countries of the European Union: 2013 INFORM surveillance programmeD. Biedenbach¹, B. deJonge², W.W. Nichols², D. Sahn¹¹International Health Management Associates- Inc., Schaumburg- IL, USA²AstraZeneca Pharmaceuticals, Waltham- MA, USA

Objectives: Carbapenem-resistant *Enterobacteriaceae* (CRE) are becoming a global threat. Resistance in these organisms is mainly driven by production of carbapenemases, which are being disseminated among these species worldwide. Ceftazidime-avibactam (CAZ-AVI) is a combination of ceftazidime (CAZ) with the novel non- β -lactam β -lactamase-inhibitor avibactam (AVI) that has promising activity against *Enterobacteriaceae*, including those that are increasingly becoming resistant to advanced cephalosporins and carbapenems. Here we assessed the *in vitro* activity of CAZ-AVI and comparator agents against a collection of CRE isolated from member states of the European Union available from the 2013 INFORM surveillance program. **Methods:** A total of 124 CRE were defined as non-susceptible to meropenem using EUCAST breakpoints. Presence of β -lactamase genes for OXA-48, KPC and MBLs was assessed via multiplex PCR, followed by sequencing. MICs were determined using CLSI broth microdilution methods. The percent susceptible (S) was assessed according to EUCAST guidelines. No breakpoints have been defined for CAZ-AVI and a reference value of MIC \leq 8 mg/L was used for comparative purposes. **Results:** The MIC₉₀/% S for CAZ-AVI and comparative antimicrobial agents for all CRE isolates and those with identified carbapenemase enzymes are shown in the table:

Phenotype/ genotype (n)	MIC ₉₀ (mg/L)/%S					
	CAZ-AVI*	CAZ	CEP	IMP	MEM	COL
All CRE (124)	128/86.3	>128/1.6	>16/1.6	>8/1.6	>8/0.0	>4/71.8
OXA-48+ (7)	-/85.7	-/0.0	-/0.0	-/0.0	-/0.0	-/14.3
KPC+(87)	4/100	>128/0.0	>16/1.1	>8/0.0	>8/0.0	>4/72.4
MBL+ (13)	>128/0.0	>128/0.0	>16/0.0	>8/0.0	>8/0.0	>4/84.6
No enzymes (14)	2/100	>128/14.3	>16/7.1	>8/14.3	>8/0.0	1/92.9

CAZ-AVI, ceftazidime-avibactam; CAZ, ceftazidime; MEM, meropenem; CEP, cefepime; IMP, imipenem; COL, colistin; KPC+, MBL+, OXA 48+ indicates populations containing the indicated enzyme type.

Two isolates contained a MBL and a KPC, and one isolate contained an MBL and an OXA-48 (not included in the Table). Two of these three strains were resistant to all drugs, and one was resistant to all drugs except colistin. Overall, 84.7% of the CRE were *K. pneumoniae*.

Conclusions: Based on CAZ-AVI MIC \leq 8 mg/L, CAZ-AVI provided activity against 86% of the CRE isolates (99% against the non-MBL CRE isolates), and was the most active drug, and the only agent active against OXA-48, tested against this European Union collection. CAZ-AVI was strongly active against KPC, OXA-48, and enzyme-negative strains, but did not have activity against the MBL-producing isolates. Based on these *in vitro* results CAZ-AVI has strong potential as a therapeutic option for the treatment infections caused by a spectrum of CRE.