# P1293

# Activity of Ceftazidime-Avibactam and Comparators Against Carbapenemase-Producing *Enterobacteriaceae* Isolated in Sampled Countries of the European Union: 2013 INFORM Surveillance Program

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## Abstract

**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 ≤8 mg/L was used for comparative purposes. **Results:** The $MIC_{90}$/% S for CAZ-AVI and comparative antimicrobial agents for all CRE isolates and those with identified carbapenemase enzymes are shown in the table:

| | $MIC_{90}$ (mg/L)/%S | | | | | |
|---|---|---|---|---|---|---|
| Phenotype/genotype (n) | 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 MICs ≤ 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.

## Introduction

• 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 (carbapenemase-producing *Enterobacteriaceae*, or CPE).

• Ceftazidime-avibactam, a combination of ceftazidime with the novel non-β-lactam β-lactamase-inhibitor avibactam, has promising activity against *Enterobacteriaceae*, including those that are resistant to carbapenems.

• Here we assessed the *in vitro* activity of ceftazidime-avibactam and comparator agents against molecularly characterised CRE isolated from member states of the European Union in the 2013 INFORM surveillance program.

## Materials & Methods

- MICs were determined by the Clinical and Laboratory Standards Institute (CLSI) recommended broth microdilution testing method [1]. MIC interpretive criteria followed EUCAST guidelines [2].
- An isolate of *Enterobacteriaceae* was defined as CRE if it was not susceptible to meropenem, using EUCAST interpretive criteria [2].
- The presence of genes encoding β-lactamases (OXA-48, KPC and MBLs) was assessed via multiplex PCR, followed by sequencing.
- No breakpoints have been defined for ceftazidime-avibactam and a reference value of MIC ≤8 mg/L (based upon PK/PD target attainment) was used for comparative purposes.

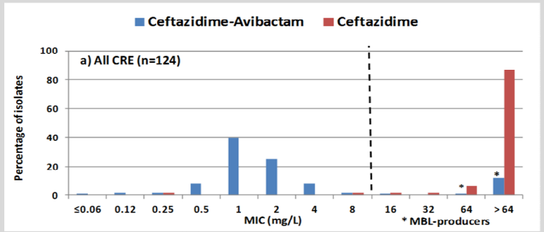
## Results

**Table 1. *In Vitro* Activity of Ceftazidime-Avibactam and Comparator Agents Tested Against *Enterobacteriaceae***

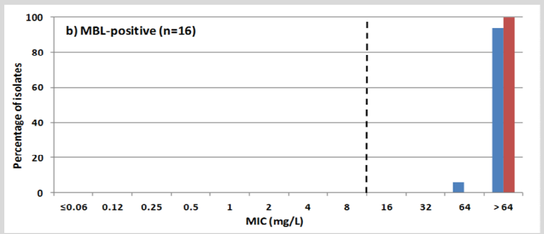
| Group (n)/Drug | $MIC_{90}$ (mg/L) | % Susceptible | % Resistant |
|---|---|---|---|
| **All *Enterobacteriaceae* (5,737)** | | | |
| Ceftazidime-avibactam[a] | 0.5 | 98.2 | - |
| Ceftazidime | 64 | 77.6 | 19.2 |
| Meropenem | 0.12 | 97.8 | 1.5 |
| Doripenem | 0.25 | 97.5 | 1.8 |
| Imipenem | 2 | 93.2 | 1.7 |
| Colistin | > 4 | 81.1 | 18.9 |
| Amikacin | 8 | 94.2 | 3.0 |
| Levofloxacin | > 4 | 78.5 | 19.4 |
| **All CRE (124)[b]** | | | |
| Ceftazidime-avibactam[a] | 128 | 86.3 | - |
| Ceftazidime | > 128 | 1.6 | 98.4 |
| Meropenem | > 8 | 0.0 | 71.0 |
| Doripenem | > 4 | 0.0 | 80.7 |
| Imipenem | > 8 | 1.6 | 73.4 |
| Colistin | > 4 | 71.8 | 28.2 |
| Amikacin | > 32 | 26.6 | 59.7 |
| Levofloxacin | >4 | 13.7 | 85.5 |
| **Non-MBL CRE (108)[c]** | | | |
| Ceftazidime-avibactam[a] | 4 | 99.1 | - |
| Ceftazidime | > 128 | 1.9 | 98.2 |
| Meropenem | > 8 | 0.0 | 72.2 |
| Doripenem | > 4 | 0.0 | 78.7 |
| Imipenem | > 8 | 1.9 | 74.1 |
| Colistin | > 4 | 71.3 | 28.7 |
| Amikacin | > 32 | 26.9 | 60.2 |
| Levofloxacin | > 4 | 13.0 | 86.1 |

[a] % susceptibility of ceftazidime-avibactam was interpreted based on a PK/PD cutoff of ≤8 mg/L and a dash indicates that no applied breakpoints were used for resistance.
[b] Includes KPC (87), MBL (13), OXA-48 (7), MBL + KPC (2), MBL + OXA-48 (1), no carbapenemases detected (14).
[c] MBL = Metallo-beta-lactamases were not detected.

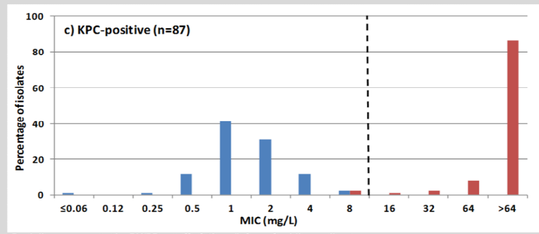
**Figure 3a-e. Ceftazidime and Ceftazidime-Avibactam MIC Distributions Against CRE Isolates From European Union Countries**



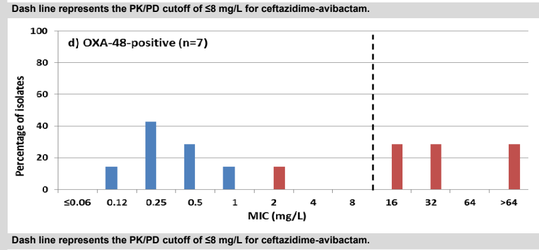

Dash line represents the PK/PD cutoff of ≤8 mg/L for ceftazidime-avibactam.
*16 isolates (12.9%) with ceftazidime-avibactam MIC values >8 mg/L contained MBLs



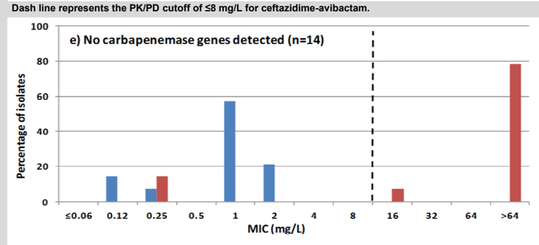

Dash line represents the PK/PD cutoff of ≤8 mg/L for ceftazidime-avibactam.




Dash line represents the PK/PD cutoff of ≤8 mg/L for ceftazidime-avibactam.




Dash line represents the PK/PD cutoff of ≤8 mg/L for ceftazidime-avibactam.




Dash line represents the PK/PD cutoff of ≤8 mg/L for ceftazidime-avibactam.

**Figure 1a and b. Country Distribution of CRE Isolates Collected From European Union**

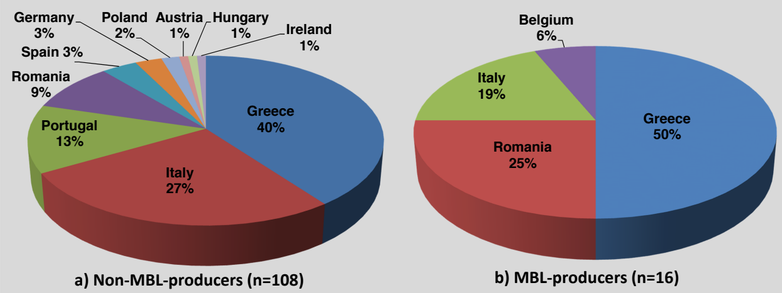
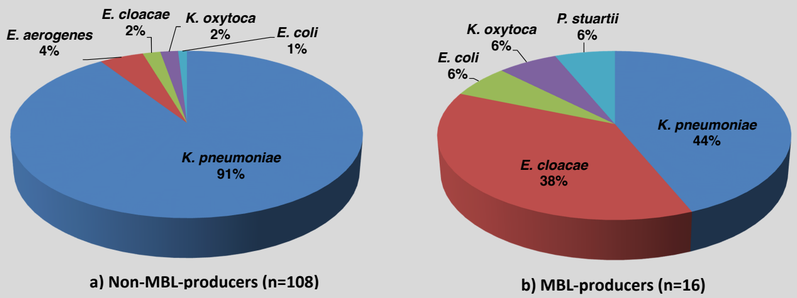



**Figure 2a and b. Species Distribution of CRE Isolates Collected From European Union**




## Conclusions

- Ceftazidime-avibactam was active *in vitro* against *Enterobacteriaceae* isolated from member states of the European Union in the 2013 INFORM surveillance program .
- Ceftazidime-avibactam was active *in vitro* against CRE, with the exception of isolates that carried genes encoding MBL enzymes.
- Ceftazidime-avibactam was active against CRE mediated by KPC- or OXA-48.
- Ceftazidime-avibactam was active against CRE where carbapenem resistance was not mediated by known carbapenemases.
- Ceftazidime-avibactam is a potentially valuable therapeutic option for the treatment of infections of infections caused by non-MBL-carrying CRE.

## References and Acknowledgments

1. Clinical Laboratory Standards Institute. 2012. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standards – Ninth Edition. CLSI document M07-A9 Wayne, PA.
2. The European Committee on Antimicrobial Susceptibility Testing – EUCAST Clinical Breakpoints 2014; http://www.eucast.org/clinical_breakpoints/

This study at IHMA was supported by AstraZeneca Pharmaceuticals LP, which also included compensation fees for services in relation to preparing the abstract/poster. B. deJonge and W.W. Nichols are employees of AstraZeneca.