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Activity of ceftazidime-avibactam against carbapenem non-susceptible Enterobacteriaceae isolated from respiratory infections as part of the INFORM global surveillance programme, 2014-2015

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Background: Carbapenem-resistant *Enterobacteriaceae* (CRE) pose a growing health threat worldwide. Carbapenem resistance can be mediated through production of Class A or D serine carbapenemases (KPC, GES, OXA-48-like), Class B metallo-β-lactamases (MBLs), or Class A or C β-lactamases combined with impaired compound permeability. Ceftazidime-avibactam is a β-lactam/β-lactamase inhibitor combination with activity against Class A, C, and some D β-lactamases developed to treat infections caused by CRE. We evaluated the *in vitro* activity of ceftazidime-avibactam against carbapenem non-susceptible respiratory isolates collected in 2014–2015 through the INFORM surveillance program.

Material/methods: 5686 non-duplicate respiratory *Enterobacteriaceae* isolates were collected from 147 sites in 37 countries. Susceptibility testing was performed by CLSI broth microdilution and interpreted using EUCAST breakpoints (ceftazidime-avibactam; ≤8 mg/L, susceptible; ≥16 mg/L, resistant). Ceftazidime-avibactam was tested at a fixed concentration of 4 mg/L avibactam. CRE were defined as isolates with meropenem MIC >1 mg/L and were screened for the presence of β-lactamase genes by PCR and sequencing.

Results: 251 CRE isolates were identified (218 isolates of *Klebsiella pneumoniae* and 33 isolates of 8 other species) of which 86% carried carbapenemases (KPC, n=116; OXA-48-like, n=49; MBL, n=49; GES, n=1). Ceftazidime-avibactam showed potent activity against carbapenemase-positive MBL-negative isolates (100% susceptible) and carbapenemase-negative isolates (87.5–100% susceptible). Ceftazidime-avibactam was not active against MBL-positive isolates (<5% susceptible), as expected. As a result, ceftazidime-avibactam showed diminished activity in regions where MBLs were more frequently encountered in CRE (Asia/Pacific and Middle East/Africa). No regional differences in activity

against CRE subgroups were observed, with the exception of slightly diminished activity against carbapenemase-negative isolates collected in the Asia/Pacific region.

Percentage of respiratory isolates susceptible to ceftazidime-avibactam according to enzyme type					
Phenotype/Enzyme content[b] (n)	CAZ-AVI %S (n)[a]				
	Global[c]	EUR	LA	AP	MEA
All RTI (5686)	99.0 (5686)	99.3 (3350)	99.0 (761)	98.4 (1092)	98.6 (483)
All CRE (251)	80.1 (251)	85.8 (148)	89.1 (64)	46.4 (28)	36.4 (11)
CRE, Carbapenemase- (36)	94.4 (36)	92.3 (13)	100 (14)	87.5 (8)	100(1)
CRE, KPC+, MBL- (116)	100 (116)	100 (69)	100 (42)	100 (5)	NA[d] (0)
CRE, GES+, MBL- (1)	100 (1)	NA (0)	NA (0)	100 (1)	NA (0)
CRE, OXA-48-like+, MBL- (49)	100 (49)	100 (45)	100 (1)	NA (0)	100 (3)
CRE, MBL+ (49)	2.0 (49)	4.8 (21)	0.0 (7)	0.0 (14)	0.0 (7)

[a] CAZ-AVI, ceftazidime-avibactam; %S, percent susceptible (MIC ≤8 mg/L); n, number of isolates.
[b] Includes isolates that co-carry Class A original spectrum β-lactamases and extended-spectrum β-lactamases and Class C AmpC β-lactamases.
[c] Global, all; EUR, Europe; LA, Latin America; AP, Asia/Pacific; MEA, Middle East/Africa.
[d] NA, not applicable (no isolates collected).

Conclusions: Ceftazidime-avibactam provides a new treatment option against CRE from respiratory infections that possess serine carbapenemases or non-carbapenemase-mediated mechanisms. Regional differences in the incidence of MBL-mediated resistance are important to consider when assessing the value of ceftazidime-avibactam.