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P1171 Antimicrobial activity of cefepime-zidebactam (WCK-5222) against clinical isolates of carbapenem-resistant *Enterobacteriaceae* collected worldwide in 2018

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Background: Zidebactam is a bicyclo-acyl hydrazide with a dual mechanism of action: selective gram-negative penicillin-binding protein (PBP) 2 binding and β-lactamase inhibition. Cefepime-zidebactam is in clinical development at 2g/1g q8 hours dosage. We evaluated the *in vitro* activity of cefepime-zidebactam against contemporary clinical isolates of carbapenem-resistant Enterobacteriaceae (CRE).

Materials/methods: A total of 14,500 Enterobacteriaceae isolates were collected by the SENTRY Antimicrobial Surveillance Program worldwide in 2018 and 200 (1.4%) were categorized as CRE (resistant to meropenem, imipenem, or meropenem per EUCAST criteria). CRE isolates were from 54 medical centres in 14 countries located in Europe (n=81), the United States (n=63), Latin America (n=40), and Asia-Pacific region (APAC; n=16). Susceptibility testing was performed in a central laboratory by a reference broth microdilution method against cefepime-zidebactam (1:1 ratio) and comparators. All CRE isolates were characterized by whole genome sequencing.

Results: The most common CRE species were *Klebsiella pneumoniae* (74.0%), *Enterobacter cloacae* (11.5%), and *Serratia marcescens* (5.0%). Isolates were mainly from bloodstream infections (30.5%), pneumonia (25.0%), and urinary tract infections (18.5%). Cefepime-zidebactam was the most active agent, with $MIC_{50/90}$ of 0.5/2 mg/L and highest MIC value of 8 mg/L (Table). Tigecycline was the most active comparator ($MIC_{50/90}$, 1/2 mg/L; 77.0% susceptible [S]), followed by ceftazidime-avibactam ($MIC_{50/90}$, 1/>32 mg/L; 76.5%S), colistin ($MIC_{50/90}$, 0.25/>8 mg/L; 74.9%S), and amikacin ($MIC_{50/90}$, 8/>32 mg/L; 56.5%S). Cefepime-zidebactam was active against CRE isolates from all regions, and isolates from APAC exhibited slightly lower cefepime-zidebactam MIC values ($MIC_{50/90}$, 0.25/1 mg/L) compared to other regions ($MIC_{50/90}$, 0.5-1/2 mg/L). Susceptibility to ceftazidime-avibactam ranged from 0.0% in APAC, 72.5% in Latin America, 82.7% in Europe, and 90.5% in the United States.

Conclusions: Cefepime-zidebactam demonstrated potent *in vitro* activity against contemporary (2018) CRE isolates collected worldwide. Antimicrobial agents currently available for clinical use exhibited limited activity against CRE, emphasizing the urgent need for novel agents to treat infections caused by these multidrug-resistant organisms.

	Cumulative % inhibited at MIC (mg/L) of:								
Antimicrobial agent	**≤0.25**	**0.5**	**1**	**2**	**4**	**8**	**16**	**32**	**%S[a]**
Cefepime-zidebactam	36.5	56.0	78.0	93.0	99.5	100.0			
Ceftazidime-avibactam	5.5	21.0	51.5	72.0	76.0	76.5	76.5	77.5[b]	**76.5**
Amikacin	0.0	1.5	13.0	30.0	47.0	56.5	71.0	83.0[b]	**56.5**
Tigecycline	6.0	42.0	77.0	92.0	99.5	100.0			**77.0**
Colistin	69.8	71.4	74.4	74.9	77.4	80.4[b]			**74.9**

[a] Per EUCAST (2018) criteria. [b] Highest dilution tested.