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Antimicrobial Activity of Cefepime-Zidebactam (WCK 5222) against Clinical Isolates of Carbapenem-Resistant *Enterobacterales* Collected Worldwide in 2018

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Introduction

- Zidebactam is a bicyclo-acyl hydrazide ($C_{14}H_{20}N_6O_7S$), a non-β-lactam agent with a dual mechanism of action: selective gram-negative penicillin-binding protein (PBP) 2 binding and β-lactamase inhibition
- Due to PBP2 binding, zidebactam demonstrates antibacterial activity against many *Enterobacterales* species
- Cefepime is a parenteral fourth-generation oxyimino-cephalosporin with broad-spectrum activity against aerobic gram-positive and gram-negative bacteria, including *Pseudomonas aeruginosa*, that was initially approved by the United States Food and Drug Administration (US FDA) in 1997
- Clinical indications currently approved by the US FDA for treatment with cefepime include moderate to severe pneumonia, complicated urinary tract infections, complicated intra-abdominal infections, and uncomplicated skin and skin structure infections, as well as empiric therapy for febrile neutropenic patients
- Cefepime-zidebactam is in clinical development at 2g/1g q8 hours as a 60-minute infusion dosage
- We evaluated the *in vitro* activity of cefepime-zidebactam against contemporary clinical isolates of carbapenem-resistant *Enterobacterales* (CRE)

Materials and Methods

- A total of 14,500 *Enterobacterales* isolates were collected by the SENTRY Antimicrobial Surveillance Program worldwide from January 2018 to October 2018 and 200 (1.4%) were categorized as CRE
  - CRE was defined as resistant per EUCAST criteria to meropenem, imipenem, or doripenem (imipenem was not applied to *Proteus mirabilis* or indole-positive Proteeae)
- 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 the Asia-Pacific region (APAC; n=16; Figure 1)
- Susceptibility testing was performed in a central laboratory by a reference broth microdilution method against cefepime-zidebactam (1:1 ratio) and comparators
- Cefepime susceptible breakpoint of ≤8mg/L (CLSI, high dose) was applied for cefepime-zidebactam for comparison purposes only
- EUCAST breakpoints were applied for comparators, when available
- β-lactamase screening was performed by whole genome sequencing

Results

- The most common CRE species were *Klebsiella pneumoniae* (74.0%), *Enterobacter cloacae* (11.5%), and *Serratia marcescens* (5.0%; Figure 2).
- Isolates were from bloodstream infections (30.5%), pneumonia (25.0%), urinary tract infections (18.5%), intra-abdominal infections (12.5%), skin and skin structure infections (10.5%), and other infection types (3.0%; Figure 3)
- Cefepime-zidebactam was the most active agent with $MIC_{50/90}$ values of 0.5/2 mg/L and the highest MIC value of 8 mg/L in all geographic regions (Table 1)
- The most active comparator agents were ceftazidime-avibactam ($MIC_{50/90}$, 1/>32 mg/L; 76.5%S), colistin ($MIC_{50/90}$, 0.25/>8 mg/L; 74.5%S), and amikacin ($MIC_{50/90}$, 8/>32 mg/L; 56.5%S; Table 1)
- 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 (Table 1)
- A serine carbapenemase was identified in 136 (68.0%) isolates, and 86.0% of these isolates produced KPC-2 or KPC-3 (Figure 1)
- A metallo-β-lactamase (MBL) was observed in 47 (23.5%) isolates, and NDM-type represented 85.1% of the MBLs (Figure 1)
- Cefepime-zidebactam was highly active *in vitro* against MBL- ($MIC_{50/90}$, 0.25/1 mg/L) and serine carbapenemase-producing ($MIC_{50/90}$, 0.5/2 mg/L) isolates, inhibiting all isolates at ≤8 mg/L (Figure 4)

Table 1 Activity of cefepime-zidebactam and comparator agents tested against carbapenem-resistant *Enterobacterales* (CRE) collected in 2018 and stratified by geographic region

Antimicrobial agent	MIC_{50}	MIC_{90}	% susceptible per EUCAST (no. of isolates)				
			Europe (81)	USA (63)	LATAM (40)	APAC (16)	All (200)
Cefepime-zidebactam	0.5	2	[100.0][a]	[100.0][a]	[100.0][a]	[100.0][a]	[100.0][a]
Ceftazidime-avibactam	1	>32	82.7	90.5	72.5	0.0	76.5
Ceftolozane-tazobactam	>16	>16	0.0	1.6	0.0	0.0	0.5
Cefoperazone-sulbactam	>32	>32	0.0[b]	4.8[b]	0.0[b]	0.0[b]	1.5[b]
Amikacin	8	>32	50.6	65.1	47.5	75.0	56.5
Gentamicin	8	>16	43.2	44.4	32.5	43.8	41.5
Levofloxacin	32	>32	9.9	19.0	22.5	18.8	16.0
Tigecycline	1	2	29.6[c]	49.5[c]	52.5[c]	50.0[c]	42.0[c]
Colistin	0.25	>8	69.1	74.6	77.5	93.8	74.5

USA, United States; LATAM, Latin America; APAC, Asia-Pacific region
[a] Percentage inhibited at ≤8 mg/L in brackets for comparison purpose.
[b] Criteria as published in the Sulperazone Package Insert.
[c] EUCAST susceptible breakpoint of ≤0.5 mg/L has been established for *E. coli* and *C. koseri* only but has been applied for all CRE isolates.

Conclusions

- Cefepime-zidebactam demonstrated potent *in vitro* activity against contemporary (2018) CRE isolates collected worldwide.
- Cefepime-zidebactam demonstrated consistent activity against CRE strains resistant to ceftazidime-avibactam, colistin, and amikacin.
- The most common carbapenemases found among CRE isolates worldwide were KPC-2/3 (58.5% of CREs) and NDM-type (20.0% of CREs)
- 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

Acknowledgements

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Figure 1 Distribution of carbapenem-resistant *Enterobacterales* and occurrence of serine carbapenemases and metallo-β-lactamases stratified by geographic region

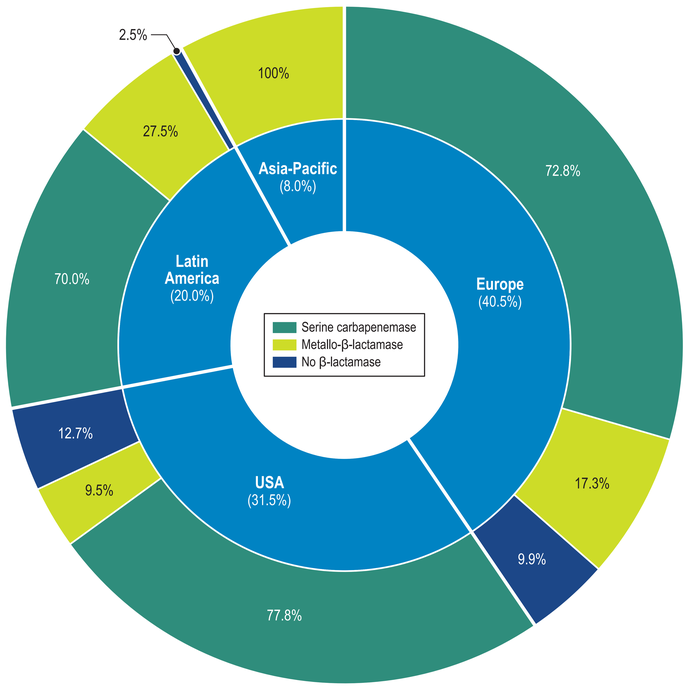


Figure 2 Distribution of carbapenem-resistant *Enterobacterales* isolates by species

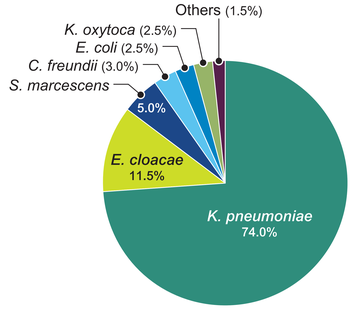
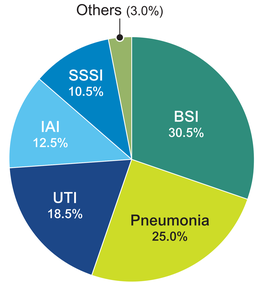
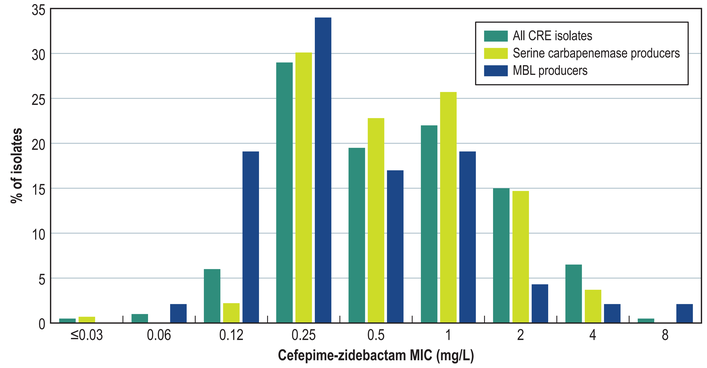


Figure 3 Distribution of carbapenem-resistant *Enterobacterales* isolates by infection type



BSI, bloodstream infection; UTI, urinary tract infection; IAI, intra-abdominal infection; SSSI, skin and skin structure infection

Figure 4 Antimicrobial activity of cefepime-zidebactam against serine carbapenemase- and metallo-β-lactamase-producing isolates



CRE, carbapenem-resistant *Enterobacterales*; MBL, metallo-β-lactamase

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