Cefepime-Zidebactam (WCK 5222) Activity when Tested against *Enterobacterales* Isolated from Patients Hospitalized in the United States and Latin America in 2018

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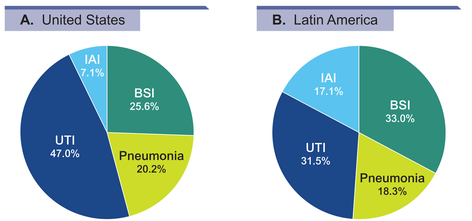
Introduction

- Zidebactam, a bicyclo-acyl hydrazide ($C_{13}H_{13}N_5O_7S$), is a non-β-lactam agent with a dual mechanism of action involving selective and high-affinity gram-negative penicillin-binding-protein (PBP) 2 binding and β-lactamase inhibition
- Due to PBP2 binding, zidebactam demonstrates antibacterial activity against various *Enterobacterales* isolates and nonfermentative gram-negative bacilli (NF-GNB)
- Cefepime was initially approved by the United States Food and Drug Administration (US FDA) in 1997
- Cefepime indications currently approved by the US FDA include moderate to severe pneumonia, complicated and uncomplicated 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 *Enterobacterales* isolates from the United States (USA) and Latin America (LATAM)

Materials and Methods

- A total of 7,323 *Enterobacterales* isolates (1/patient) were consecutively collected in 2018
  - 6,663 from 69 US medical centers
  - 660 from 8 medical centers located in 5 LATAM nations
- Susceptibility testing was performed in a central laboratory by a reference broth microdilution method against cefepime-zidebactam (1:1 ratio) and comparators
- The cefepime susceptible (S) breakpoint of ≤8 mg/L (Clinical Laboratory Standards Institute [CLSI], high dose) was applied for cefepime-zidebactam for comparison purposes
- CLSI breakpoints were applied for comparators, when available
- Carbapenem-resistant *Enterobacterales* (CRE) was defined as resistant per CLSI criteria to meropenem, imipenem, or doripenem (imipenem was not applied to *Proteus mirabilis* or indole-positive Proteeae)
- Multidrug-resistant (MDR) and extensively drug-resistant (XDR) *Enterobacterales* strains were classified according to recommended guidelines (Magiorakos et al., 2012) as follows
  - MDR: 3 or more drug classes have a nonsusceptible drug
  - XDR: all but 2 or fewer classes have a nonsusceptible drug
- All CRE isolates were evaluated by next-generation sequencing
- Isolates were from (USA/LATAM) bloodstream (25.6%/33.0%), pneumonia (20.2%/18.3%), urinary tract (47.0%/31.5%), and intra-abdominal infections (7.1%/17.1%; Figure 1)

Figure 1 Isolate distribution by infection type



BSI, bloodstream infection; UTI, urinary tract infection; IAI, intra-abdominal infection

Results

- Cefepime-zidebactam exhibited potent *in vitro* activity ($MIC_{50/90}$, 0.03/0.12 mg/L) against *Enterobacterales* (Table 1 and Figure 2) with only 1 isolate with an MIC >4 mg/L, *Klebsiella pneumoniae* with an MIC of 16 mg/L (cefepime-zidebactam proposed pharmacokinetic/pharmacodynamic breakpoint ≤64 mg/L) isolated from a urinary tract infection in New York City, that displayed 2 carbapenemase genes (bla_{NDM-1} and bla_{OXA-48}-like), reduced expression of OmpK35, disruption of OmpK36, and overexpression of efflux pump AcrAB-TolC
- Cefepime-zidebactam retained good activity against ceftriaxone-nonsusceptible isolates from the USA/LATAM with 99.9%/100.0% of isolates inhibited at ≤8 mg/L; susceptibility rates for ceftazidime-avibactam and meropenem were 99.2%/95.3% and 93.4%/78.1%, respectively (Figure 3A)
- CRE and MDR rates were higher in LATAM (8.9% and 34.2%, respectively) than in the USA (0.9% and 9.3%, respectively; data not shown)
- The most active agents against CRE from the USA/LATAM (n= 59/59) were cefepime-zidebactam (98.3%/100.0% inhibited at ≤8 mg/L), ceftazidime-avibactam (88.1%/78.0%S), colistin (82.8%/72.9%S), and amikacin (78.0%/57.6%S; Figure 3B)
- A carbapenemase gene was observed in 105 of 118 CRE isolates (89.0%), and the most common genes were bla_{KPC-2} (n=58; 49.2% of CREs), bla_{KPC-3} (n=25; 21.2%), and bla_{NDM-1} (n=17; 14.4%; Table 2)
- Twenty-one isolates were ceftazidime-avibactam resistant, 8 from the USA, 12 from Mexico, and 1 from Argentina; all produced a metallo-β-lactamase (17 NDM-1, 2 VIM-1, 1 IMP-4, and 1 IMP-8), and 20 (95.2%) had cefepime-zidebactam MIC values of ≤8 mg/L (data not shown)
- Cefepime-zidebactam (99.8%/100.0% inhibited at ≤8 mg/L) and ceftazidime-avibactam (98.7%/94.2%S) were the most active compounds tested against MDR *Enterobacterales* from the USA/LATAM; meropenem was active against 88.8%/73.0% of isolates and ceftolozane-tazobactam and piperacillin-tazobactam exhibited limited activity against these organisms (Figure 3C)
- Cefepime-zidebactam remained highly active against XDR *Enterobacterales* (MIC_{50}/MIC_{90}, 0.5/2 mg/L; 98.9%/100.0% [USA/LATAM] inhibited at ≤8 mg/L) and ceftazidime-avibactam (MIC_{50}/MIC_{90}, 1/>32 mg/L) was active against 90.8%/85.3% of isolates (USA/LATAM), but all other compounds exhibited limited activity (Figure 3D)

Table 1 Activity of cefepime-zidebactam and comparators tested against *Enterobacterales* collected from medical centers in the United States (USA) and Latin America (LATAM)

Organism Antimicrobial agent	MIC_{50}	MIC_{90}	% susceptible[a] USA	% susceptible[a] LATAM
Enterobacterales (no. tested)			(6,663)	(660)
Cefepime-zidebactam	0.03	0.12	[>99.9][b]	[100.0][b]
Ceftazidime-avibactam	0.12	0.25	99.9	98.0
Ceftolozane-tazobactam	0.25	1	95.3	83.3
Piperacillin-tazobactam	2	16	92.8	80.4
Cefepime	0.06	16	89.7	61.1
Ceftazidime	0.25	32	87.6	64.1
Ceftriaxone	≤0.06	>8	84.3	57.7
Meropenem	0.03	0.06	99.0	90.8
Ertapenem	0.008	0.06	97.9	88.3
Amikacin	2	4	99.4	94.2
Gentamicin	0.5	8	91.6	70.2
Tobramycin	0.5	8	91.4	68.3
Levofloxacin	0.06	16	79.2	62.6
Ciprofloxacin	≤0.03	>16	77.0	54.2
Colistin[c]	0.12	>8	85.6	81.6
CRE (no. tested)			(59)	(59)
Cefepime-zidebactam	**0.5**	**4**	**[98.3][b]**	**[100.0][b]**
Ceftazidime-avibactam	**1**	**>32**	**88.1**	**78.0**
Ceftolozane-tazobactam	**>16**	**>16**	**1.8**	**0.0**
Piperacillin-tazobactam	>128	>128	0.0	1.7
Amikacin	4	>32	78.0	57.6
Gentamicin	16	>16	52.5	28.8
Tobramycin	>16	>16	27.1	16.9
Levofloxacin	16	>32	18.6	18.6
Ciprofloxacin	>16	>16	15.3	5.1
Colistin[c]	0.12	>8	82.8	72.9

[a] Criteria as published by CLSI 2019.
[b] % inhibited at ≤8 mg/L for comparison; 1 CRE isolate from the USA with a cefepime-zidebactam MIC of 16 mg/L.
[c] Based on breakpoints published by EUCAST since CLSI does not currently have published breakpoints.

Figure 2 MIC distributions for cefepime-zidebactam, ceftazidime-avibactam, and ceftolozane-tazobactam when tested against *Enterobacterales* from the United States

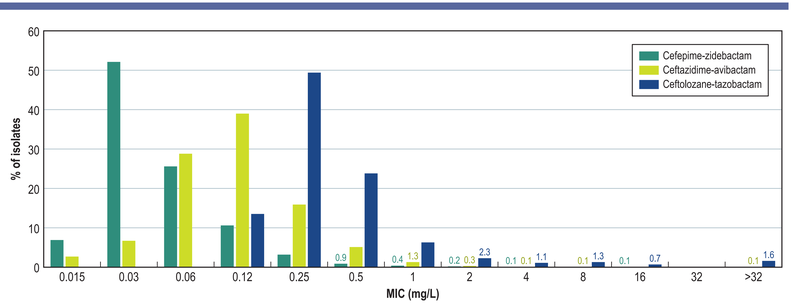
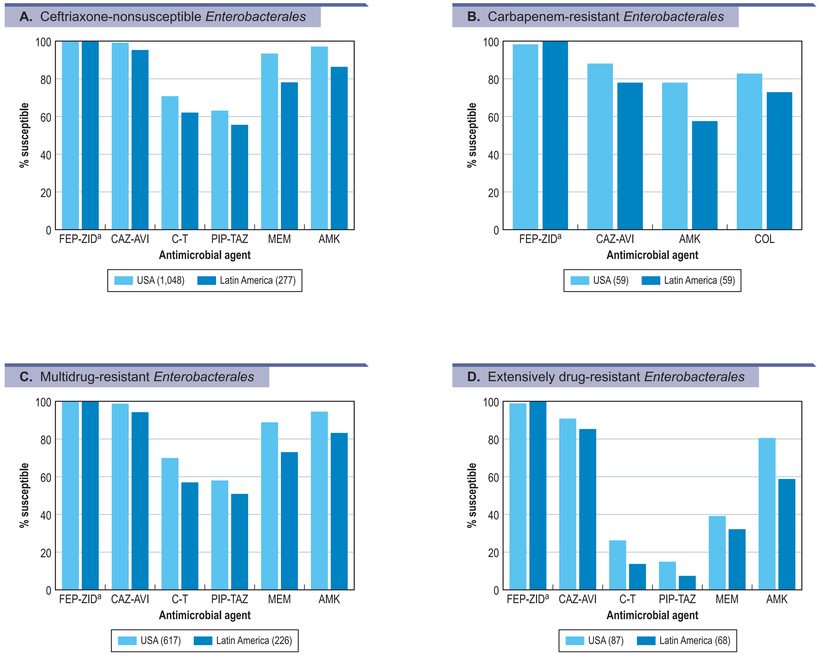


Figure 3 Antimicrobial susceptibility of pathogens from United States and Latin American medical centers (2018)



[a] % inhibited at ≤8/8 mg/L. USA, United States of America; LATAM, Latin America; FEP-ZID, cefepime-zidebactam; CAZ-AVI, ceftazidime-avibactam; C-T, ceftolozane-tazobactam; PIP-TAZ, piperacillin-tazobactam; MEM, meropenem; AMK, amikacin; COL, colistin.

Table 2 Carbapenemases identified in *Enterobacterales* isolates stratified by geography and organism species

Organism/β-lactamase	No. of Isolates
USA	
Citrobacter freundii	3
KPC-3	3
Enterobacter cloacae	8
KPC-2	1
KPC-3	4
NDM-1	2
VIM-1	1
Escherichia coli	3
KPC-2	1
KPC-3	1
NDM-1	1
Klebsiella oxytoca	1
KPC-2	1
Klebsiella pneumoniae	29
KPC-2	13
KPC-3	14
NDM-1 plus OXA-48-like	1
OXA-48	1
Serratia marcescens	4
KPC-3	2
NDM-1	1
VIM-1	1
Raoultella spp.	1
KPC-2	1
USA total	49

Organism/β-lactamase	No. of Isolates
Latin America	
Enterobacter cloacae	6
KPC-2	1
NDM-1	5
Escherichia coli	1
NDM-1	1
Klebsiella pneumoniae	46
KPC-2	37
KPC-3	1
NDM-1	6
IMP-8	1
OXA-163	1
Serratia marcescens	3
KPC-2	3
Latin America total	56
Grand total	**105**

Conclusions

- Cefepime-zidebactam demonstrated potent *in vitro* activity against *Enterobacterales* isolated in US and LATAM hospitals, including CRE, MDR, XDR, and isolates resistant to antimicrobial agents currently used to treat serious *Enterobacterales* infections such as meropenem and ceftazidime-avibactam
- Cefepime-zidebactam retained activity against metallo-β-lactamase-producing isolates, including NDM-1, VIM-2, IMP-4, and IMP-8
- Resistance rates for comparator agents were much higher in LATAM compared to the USA

Acknowledgements

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