Antimicrobial Activity of the Novel β-Lactam Enhancer Combination Cefepime-Zidebactam (WCK 5222) Tested against Gram-Negative Bacteria Isolated in United States Medical Centers from Patients with Bloodstream Infections

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Introduction

- Zidebactam, a bicyclo-acyl hydrazide ($C_{13}H_{21}N_5O_7S$), 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 non-fermentative Gram-negative bacilli (NF-GNB)
- Clinical indications currently approved by the United States (US) Food and Drug Administration for treatment with cefepime 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
- *In vivo* lung and thigh infection studies employing cefepime-zidebactam human-simulated regimens in neutropenic mice have demonstrated 2-3 log kill of multidrug-resistant (MDR) and extensively drug-resistant (XDR) *A. baumannii* and *P. aeruginosa* with cefepime-zidebactam MICs up to 64 mg/L and 32 mg/L, respectively
- We evaluated the activity of cefepime combined with zidebactam against contemporary clinical isolates of GNB causing bloodstream infections (BSIs) in US hospitals

Materials and Methods

- A total of 1,348 clinical isolates of GNB were consecutively collected from patients with BSIs (1/patient) in 34 US medical centers in 2018 by the SENTRY Antimicrobial Surveillance Program
- The isolates were susceptibility tested against cefepime-zidebactam (1:1 ratio), ceftazidime-avibactam (avibactam at fixed 4 mg/L), ceftolozane-tazobactam (tazobactam at fixed 4 mg/L), and other comparator agents by the reference broth microdilution method
- The cefepime susceptible (S) breakpoint of ≤8 mg/L (Clinical and Laboratory Standards Institute [CLSI], high dose) was applied for cefepime-zidebactam for comparison purposes only, and also a cefepime-zidebactam susceptible breakpoint of ≤64 mg/L proposed on the basis of pharmacokinetic/pharmacodynamic target attainment, and *in vivo* efficacy employing human-simulated regimen was applied
- 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)
- MDR and XDR *Enterobacterales* strains were classified according to recommended guidelines (Magiorakos et al., 2012) as follows
  - MDR: Not susceptible to 3 or more drug classes (CLSI)
  - XDR: Susceptible to only 2 or fewer classes (CLSI)
- All CRE isolates were evaluated by next-generation sequencing

Results

- Cefepime-zidebactam was the most active agent against *Enterobacterales* ($MIC_{50/90}$, 0.03/0.12 mg/L; highest MIC, 4 mg/L; Table 1 and Figure 1), including MDR ($MIC_{50/90}$, 0.12/0.25 mg/L; Table 1) and CRE isolates (n=7; MIC_{50}, 0.5 mg/L; data not shown)
- The most active comparators tested against MDR *Enterobacterales* were ceftazidime-avibactam ($MIC_{50/90}$, 0.25/1 mg/L; 98.0%S), meropenem ($MIC_{50/90}$, 0.03/0.12 mg/L; 92.1%S), and amikacin ($MIC_{50/90}$, 4/16 mg/L; 92.1%S), whereas ceftolozane-tazobactam ($MIC_{50/90}$, 0.5/>16 mg/L) was active against 81.8% of isolates (Table 1)
- The most common ESBLs produced by *Enterobacterales* were CTX-M-15 (88 isolates; 65.7% of ESBL producers), followed by OXA-1/30 (59 isolates; 44.0%) and CTX-M-27 (19 isolates; 14.2%); 53 isolates (38.8%) produced CTX-M-15 and OXA-1/30 (data not shown)
- The most active agents against ESBL-producing *Enterobacterales* (n=134) were cefepime-zidebactam ($MIC_{50/90}$, 0.12/0.25 mg/L; highest MIC, 1 mg/L), ceftazidime-avibactam ($MIC_{50/90}$, 0.12/0.5 mg/L; 98.5%S), and meropenem ($MIC_{50/90}$, 0.03/0.06 mg/L; 96.3%S; Figure 2)
- The highest cefepime-zidebactam MIC values among *E. coli*, *K. pneumoniae*, and *E. cloacae* were 1, 2, and 0.25 mg/L, respectively (data not shown)
- The most active agents tested against *P. aeruginosa* were cefepime-zidebactam ($MIC_{50/90}$, 1/4 mg/L; highest MIC, 8 mg/L), colistin ($MIC_{50/90}$, 0.5/1 mg/L; 100.0%S), and amikacin ($MIC_{50/90}$, 4/8 mg/L; 99.2%S), whereas ceftazidime-avibactam and ceftolozane-tazobactam were active against 96.5%-96.7% of isolates (Table 1 and Figures 1 and 2)
- Against *P. aeruginosa* isolates not susceptible to meropenem (n=18), cefepime-zidebactam MIC values ranged from 1 to 8 mg/L ($MIC_{50/90}$, 4/8 mg/L), whereas ceftazidime-avibactam ($MIC_{50/90}$, 4/32 mg/L) and ceftolozane-tazobactam ($MIC_{50/90}$, 2/8 mg/L) were active against 77.8% and 81.2% of isolates, respectively
- Cefepime-zidebactam exhibited good activity against *Acinetobacter* spp. (n=22; $MIC_{50/90}$, 2/8 mg/L; 95.5% and 100.0% inhibited at ≤8 and ≤16 mg/L, respectively) and *S. maltophilia* (n=20; $MIC_{50/90}$, 4/32 mg/L; 80.0% and 100.0% inhibited at ≤8 and ≤32 mg/L, respectively; Figure 2)

Figure 1 Cefepime-zidebactam activity against Gram-negative bacilli isolated from patients with bloodstream infections in US medical centers (2018)

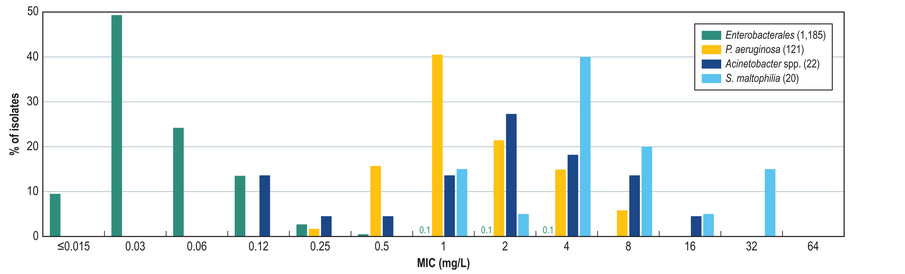
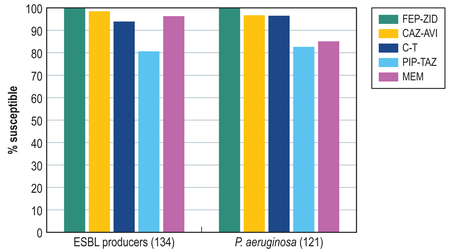


Table 1 Antimicrobial susceptibility of *Enterobacterales* and *P. aeruginosa* isolates from patients with bloodstream infections from US medical centers in 2018

Organism/organism group (no. of isolates)			CLSI[a]	
Antimicrobial agent	MIC_{50}	MIC_{90}	%S	%R
Enterobacterales (1,185)				
Cefepime-zidebactam	0.03	0.12	[100.0][b]	
Ceftazidime-avibactam	0.12	0.25	99.8	0.2
Ceftolozane-tazobactam	0.25	1	97.1	2.3
Piperacillin-tazobactam	2	8	94.0	3.0
Ceftriaxone	≤0.06	>8	83.9	15.4
Meropenem	0.03	0.06	99.3	0.6
Levofloxacin	0.06	16	75.1	22.8
Amikacin	2	4	99.3	0.3
MDR *Enterobacterales* (101)				
Cefepime-zidebactam	0.12	0.25	[100.0][b]	0.0
Ceftazidime-avibactam	0.25	1	98.0	2.0
Ceftolozane-tazobactam	0.5	>16	81.8	13.6
Piperacillin-tazobactam	8	>128	64.4	15.8
Ceftriaxone	>8	>8	12.9	84.2
Meropenem	0.03	0.12	92.1	6.9
Levofloxacin	8	>32	13.0	80.0
Amikacin	4	16	92.1	4.0
P. aeruginosa (121)				
Cefepime-zidebactam	1	4	[100.0][b]	0.0
Ceftazidime-avibactam	2	4	96.7	3.3
Ceftolozane-tazobactam	0.5	2	96.5	1.8
Piperacillin-tazobactam	4	64	82.6	8.3
Ceftazidime	2	32	85.1	12.4
Meropenem	0.5	4	85.1	9.9
Levofloxacin	0.5	8	70.2	19.0
Tobramycin	0.5	1	98.3	0.8
Amikacin	4	8	99.2	0.0
Colistin	0.5	1	100.0	0.0

MDR, multidrug-resistant
[a] Criteria as published by CLSI (2019).
[b] Percentage inhibited at ≤8 mg/L are shown in brackets for comparison.

Figure 2 Antimicrobial susceptibility of ESBL-producing *Enterobacterales* and *P. aeruginosa* isolated from patients with bloodstream infections in US medical centers (2018)



Abbreviations: ESBL producers, *Enterobacterales* producing extended-spectrum β-lactamase; FEP-ZID, cefepime-zidebactam (% inhibited at ≤8 mg/L); CAZ-AVI, ceftazidime-avibactam; C-T, ceftolozane-tazobactam; PIP-TAZ, piperacillin-tazobactam; MEM, meropenem.

Conclusions

- Cefepime-zidebactam showed complete activity against *Enterobacterales* and *P. aeruginosa* with 100.0% of isolates inhibited at ≤8 mg/L
- Cefepime-zidebactam was slightly more active than ceftazidime-avibactam and ceftolozane-tazobactam against *P. aeruginosa* overall and retained 100.0% susceptibility against isolates not susceptible to meropenem and other anti-pseudomonal drugs currently used to treat bloodstream infections
- Cefepime-zidebactam demonstrated potent *in vitro* activity and complete activity against *Enterobacterales*, including MDR, ESBL producers, and CRE isolates
- Cefepime-zidebactam activity against *Enterobacterales* was comparable to that of ceftazidime-avibactam and superior to the activities of ceftolozane-tazobactam and meropenem
- Cefepime-zidebactam demonstrated good *in vitro* activity against *S. maltophilia* and *Acinetobacter* spp.
- The *in vitro* results of this investigation support the clinical development of cefepime-zidebactam as a therapeutic option for the treatment of serious infections caused by GNB, including MDR phenotypes

Acknowledgements

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