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WCK 5222 (Cefepime-Zidebactam) Antimicrobial Activity Tested against Gram-negative Organisms Producing Clinically Relevant β-Lactamases

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Abstract

Background: Zidebactam (ZID) is a β-lactam enhancer with a dual mechanism of action involving binding to Gram-negative (GN) PBP2 and β-lactamase (BL) inhibition. Cefepime (FEP) combined with ZID is under clinical development.

Methods: 193 clinical GN strains producing the most clinically relevant BL types plus 71 wild type (WT) strains were tested for susceptibility (S) by a reference broth microdilution method against FEP-ZID (1:1 and 2:1 ratios tested at 0.06-128 µg/mL), FEP and ZID. BL encoding genes were evaluated by a microarray-based assay.

Results: FEP-ZID (1:1) was very active against Enterobacteriaceae (ENT) producing CTX-M-15 (21; $MIC_{50/90}$, 0.25/1 µg/mL), SHV (20; $MIC_{50/90}$, 0.12/0.25 µg/mL), other extended-spectrum BLs (ESBLs; 20, including GES-18; OXA-1/30, OXY-, PER-, TEM- and VEB-like; $MIC_{50/90}$, 0.25/1 µg/mL), plasmidic AmpC (10; $MIC_{50/90}$, ≤0.06/≤0.06 µg/mL), derepressed AmpC (23; $MIC_{50/90}$, 0.12/0.5 µg/mL), KPC (35; $MIC_{50/90}$, 0.25/1 µg/mL), metallo-BL (MBL; 20 including VIM, IMP and NDM; $MIC_{50/90}$, 0.5/8 µg/mL; **Table**). WT ENT had $MIC_{50/90}$ values of ≤0.06/≤0.06, ≤0.06/0.12 and 0.25/>128 µg/mL for FED-ZID (1:1), FEP and ZID, respectively. FEP-ZID (1:1) was also active against *P. aeruginosa* (PSA) producing derepressed AmpC (21; $MIC_{50/90}$, 4/8 µg/mL) and MBL (12 [VIM and IMP]; $MIC_{50/90}$, 4/8 µg/mL). FEP-ZID 1:1 ratio was slightly (2-fold) more active than FEP-ZID 2:1 ratio when tested against BL-producing ENT and PSA, and ZID alone exhibited potent *in vitro* activity against some ENT and PSA, including BL-producing strains. FEP-ZID 1:1 ratio ($MIC_{50/90}$, 32/32 µg/mL) showed only moderate activity against OXA-23/24-producing *Acinetobacter baumannii* (ASP), but it was ≥4-fold more active than FEP or ZID tested alone.

Conclusion: FEP-ZID (1:1 and 2:1 ratios) showed potent in vitro activities against ENT and PSA producing various clinically relevant BLs, including ESBLs, KPCs, AmpC and MBLs, for which limited treatment options are currently available. These *in vitro* results support further clinical development of FEP-ZID (WCK 5222).

β-lactamase (organism; no. tested)	No. of isolates (cumulative %) inhibited at FEP-ZID (1:1 ratio) MIC (µg/mL) of:								
	≤0.12	0.25	0.5	1	2	4	8	16	32
CTX-M-15 (ENT; 21)	6 (28.6)	8 (66.7)	4 (85.7)	1 (90.5)	1 (95.2)	1 (100.0)	--	--	--
SHV (ENT; 20)	14 (70.0)	5 (95.0)	0 (95.0)	1 (100.0)	--	--	--	--	--
Other ESBLs (ENT; 20)	9 (45.0)	6 (75.0)	2 (85.0)	3 (100.0)	--	--	--	--	--
Plasmidic AmpC (ENT; 10)	10 (100.0)	--	--	--	--	--	--	--	--
Derepressed AmpC (ENT; 23)	15 (65.2)	4 (82.6)	2 (91.3)	2 (100.0)	--	--	--	--	--
KPC (ENT; 35)	7 (20.0)	12 (54.3)	11 (85.7)	4 (97.1)	1 (100.0)	--	--	--	--
MBL (ENT; 20)	1 (5.0)	6 (35.0)	3 (50.0)	1 (55.0)	4 (75.0)	1 (80.0)	2 (90.0)	1 (95.0)	1 (100.0)
Derepressed AmpC (PSA; 21)	--	--	1 (4.8)	1 (9.5)	4 (28.6)	7 (61.9)	6 (90.5)	2 (100.0)	--
MBL (PSA; 12)	--	--	1 (8.3)	0 (8.3)	2 (25.0)	6 (75.0)	2 (91.7)	1 (100.0)	--
OXA-23/24 (ASP; 11)	--	--	--	--	--	--	1 (9.1)	3 (36.4)	6 (90.9)

Introduction

Zidebactam (ZID; molecular formula, $C_{13}H_{21}N_5O_7S$ [see **Figure 1** of poster 446]) is a non-β-lactam agent with a dual mechanism of action involving selective and high-affinity Gram-negative PBP2 binding and β-lactamase inhibition. Owing to its PBP2 binding feature, ZID demonstrates antibacterial activity against various Enterobacteriaceae and *Pseudomonas*. Therefore, ZID combined with cefepime (FEP-ZID or WCK 5222) is under clinical development for treatment of Gram-negative infections (NCT02707107 and NCT02674347; www.clinicaltrials.gov).

We evaluated the antimicrobial interaction between FEP and ZID and assessed the feasibility of undertaking MICs with FEP-ZID in two different ratios (1:1 and 2:1) by employing a reference broth microdilution susceptibility testing method.

Methods

Susceptibility testing: MIC values were determined using Clinical and Laboratory Standards Institute (CLSI) broth microdilution methodology as described in CLSI document M07-A10 (2015). The combination of FEP-ZID (WCK 5222; two ratio concentrations, 1:1 and 2:1) and both compounds alone were tested in 96-well, frozen-form panels produced by JMI Laboratories (North Liberty, Iowa, USA). Quality control (QC) isolates were tested in each test batch and the inoculum density was monitored by colony counts. QC ranges and interpretive criteria for the comparator compounds were as published in CLSI M100-S26 (2016). The sponsor provided available target MIC information for FEP-ZID and ZID alone tested against the listed QC organisms. The tested QC strains included the following: *Escherichia coli* ATCC 25922, ATCC 35218 and NCTC 13353, *Klebsiella pneumoniae* ATCC 700603 and ATCC BAA-1705, and *Pseudomonas aeruginosa* ATCC 27853.

Organism collection: A total of 264 contemporary clinical isolates producing the most clinically relevant β-lactamases were tested, including:

- Enterobacteriaceae (200 isolates)
  - Wild type (cefepime-susceptible) isolates (51 total)
    - *E. coli* (10 isolates)
    - *Klebsiella* spp. (11 isolates)
    - *Enterobacter* spp. (10 isolates)
    - Indole-positive Proteeae (10 isolates)
    - *Serratia marcescens* (10 isolates)
  - ESBL-producing isolates (61)
    - CTX-M-15-producing (21 isolates; nine *E. coli* and 12 *K. pneumoniae*)
    - SHV-producing (20 isolates; one *E. coli* and 19 *K. pneumoniae*)
    - Other less common ESBL types or combinations (20 isolates, including *Citrobacter freundii* [2], *E. coli* [5], *E. cloacae* [1], *Klebsiella oxytoca* [4], *K. pneumoniae* [3], *Proteus mirabilis* [3], and *Providencia* spp. [2]). The ESBLs produced by these isolates included GES-18 (1 isolate), OXA-1/30 (3), OXY-like (4), PER-like (4), TEM-like (6) and VEB-like (2).
  - AmpC-producing isolates (33)
    - Plasmidic AmpC (10 isolates; seven *E. coli* and three *K. pneumoniae*)
    - Derepressed AmpC (23 isolates; including *C. freundii* [5], *Citrobacter koseri* [1], *E. aerogenes* [4], *E. cloacae* [7], *and S. marcescens* [6]).
  - KPC-producing isolates (35), including: *K. pneumoniae* (24 isolates), *C. freundii* (2), *E. coli* (3), *E. aerogenes* (2), *E. cloacae* (1), *P. mirabilis* (1), and *S. marcescens* (2)
  - Metallo-β-lactamase producing isolates (20)
    - IMP-producing (four isolates; *E. cloacae* [1], *K. oxytoca* [1], *K. pneumoniae* [1], and *S. marcescens* [1])
    - NDM-producing (eight isolates; *E. coli* [3], *E. cloacae* [1], *K. pneumoniae* [2], and *P. mirabilis* [1], and *S. marcescens* [1])
    - VIM-producing (eight isolates; *C. freundii* [1], *E. cloacae* [4], *K. pneumoniae* [2], and *P. mirabilis* [1])
- *P. aeruginosa* (43 isolates)
  - Cefepime-susceptible (MIC, ≤8 µg/mL; 10 isolates)
  - Isolates with overexpression of AmpC and/or efflux pump(s) (21 isolates)
  - Metallo-β-lactamase producing (12 isolates, including IMP-13 [1 isolate], IMP-15 [1], VIM-1 [1], VIM-2 [6], VIM-4 [2] and VIM-7 [1])
- *Acinetobacter baumannii* (21 isolates)
  - Imipenem-susceptible (10 isolates)
  - OXA-producing isolates (11 isolates)

Results

Wild type (cefepime-susceptible) Enterobacteriaceae (**Table 1**)

- The highest FEP MIC value among wild type (cefepime-susceptible) Enterobacteriaceae was 1 µg/mL ($MIC_{50/90}$, ≤0.06/0.12 µg/mL), and MIC values for FEP-ZID at 2:1 ($MIC_{50/90}$, ≤0.06/0.12 µg/mL) and 1:1 ($MIC_{50/90}$, ≤0.06/≤0.06 µg/mL) ratios were similar to those of FEP. A significant decrease in the FEP MIC value was observed for only one isolate, an *E. coli* with FEP MIC of 1 µg/mL and MIC values for FEP-ZID at 2:1 and 1:1 ratios of 0.12 and ≤0.06 µg/mL, respectively.
- ZID alone exhibited variable activity ($MIC_{50/90}$, 0.25/>128 µg/mL) when tested against wild type Enterobacteriaceae. Overall, *E. coli* ($MIC_{50/90}$, 0.12/0.12 µg/mL) and *Enterobacter* spp. ($MIC_{50/90}$, 0.12/0.25 µg/mL) isolates exhibited low ZID MIC values, whereas indole-positive Proteeae ($MIC_{50/90}$, >128/>128 µg/mL) and *S. marcescens* ($MIC_{50/90}$, >128/>128 µg/mL) showed much higher ZID MIC results. Among wild type *Klebsiella* spp. isolates, ZID MIC values ranged from 0.12 to >128 µg/mL ($MIC_{50/90}$, 0.25/>128 µg/mL).

β-lactamase producing Enterobacteriaceae (**Table 2**)

- The MIC values for the FEP-ZID combinations (2:1 and 1:1 ratios) were substantially lower than those for FEP alone among ESBL-phenotype Enterobacteriaceae.
- Among CTX-M-producing isolates, important reduction of FEP MIC values were noticeable with *E. coli* (MIC_{50} values of >128, 0.5 and 0.25 µg/mL for FEP, FEP-ZID 2:1 and 1:1 ratios, respectively) and *K. pneumoniae* (MIC_{50} values of 64, 0.5 and 0.5 µg/mL for FEP, FEP-ZID 2:1 and 1:1 ratios, respectively). Overall, 85.7% of isolates were inhibited at ≤2 µg/mL of ZID alone. Furthermore, MIC values for FEP-ZID 1:1 ratio were generally two-fold lower than those of FEP-ZID 2:1 ratio.
- When tested against SHV-producing isolates, MIC values for the FEP-ZID combinations ($MIC_{50/90}$, 0.12-0.25/0.25 µg/mL) were 8- to 32-fold lower than those for FEP alone ($MIC_{50/90}$, 2/8 µg/mL). MIC values for FEP-ZID 1:1 ratio ($MIC_{50/90}$, 0.12/0.25 µg/mL) were generally two-fold lower than those of FEP-ZID 2:1 ratio ($MIC_{50/90}$, 0.25/0.25 µg/mL).
- ZID alone exhibited potent in vitro activity against CTX-M-producing *E. coli* (MIC_{50}, 0.25 µg/mL and highest MIC, 0.5 µg/mL; nine isolates tested) and variable activity against CTX-M-producing *Klebsiella* spp. ($MIC_{50/90}$, 0.5/>128 µg/mL), SHV-producing isolates (most *K. pneumoniae*; $MIC_{50/90}$, 1/128 µg/mL) and Enterobacteriaceae isolates producing other β-lactamases ($MIC_{50/90}$, 64/>128 µg/mL).
- FEP ($MIC_{50/90}$, 0.25/0.5 µg/mL), FEP-ZID 2:1 ratio ($MIC_{50/90}$, ≤0.06/0.12 µg/mL) and FEP-ZID 1:1 ratio ($MIC_{50/90}$, ≤0.06/≤0.06 µg/mL) were very active against plasmidic AmpC-producing isolates. MIC values for the FEP-ZID combinations were at least four-fold lower than those for FEP alone.
- When tested against derepressed AmpC-producing isolates, MIC values for the FEP-ZID combinations ($MIC_{50/90}$, 0.12-0.25/0.5-1 µg/mL), were four- to 32-fold lower than those for FEP alone ($MIC_{50/90}$, 1/16 µg/mL), and MIC values for FEP-ZID 1:1 ratio were usually two-fold lower than those of FEP-ZID 2:1 ratio.
- ZID alone was active against some plasmidic AmpC- ($MIC_{50/90}$, 0.25/16 µg/mL) as well as some derepressed AmpC ($MIC_{50/90}$, 2/>128 µg/mL) producing isolates.
- FEP-ZID 2:1 ($MIC_{50/90}$, 0.5/2 µg/mL) and FEP-ZID 1:1 ($MIC_{50/90}$, 0.25/1 µg/mL) were very active against KPC-producing isolates. MIC values for the FEP-ZID combinations were 64- to 128-fold lower than those for FEP alone. Overall, 51.4% of isolates were inhibited at a ZID concentration of 4 µg/mL or less ($MIC_{50/90}$, 4/>128 µg/mL.
- FEP-ZID 1:1 ($MIC_{50/90}$, 0.5/8 µg/mL) inhibited 75.0 and 90.0% of MBL-producing Enterobacteriaceae isolates at ≤2 and ≤8 µg/mL, respectively. Of note, ZID alone ($MIC_{50/90}$, 0.5/>128 µg/mL) inhibited 55.0 and 60.0% (12/20) of MBL-producing isolates at 4 µg/mL, whereas the remaining 40.0% (8/20) had ZID MIC values of >128 µg/mL.
- When tested against NDM-1- and VIM-producing Enterobacteriaceae, MIC values for FEP-ZID 1:1 ratio (MIC_{50}, 0.25 and 0.5 µg/mL, respectively) were two- to four-fold lower than those of FEP-ZID 2:1 ratio (MIC_{50}, 1 µg/mL) for both subsets.

P. aeruginosa and *A. baumannii* (**Table 3**)

- MIC values for the FEP-ZID combinations ($MIC_{50/90}$, 1/2 µg/mL for both combinations) were generally two-fold lower than those for FEP and ZID alone ($MIC_{50/90}$, 2/4 µg/mL) when tested against FEP-susceptible *P. aeruginosa* isolates.
- When tested against *P. aeruginosa* with overexpression of AmpC and/or efflux pump(s), MIC values for the FEP-ZID combinations ($MIC_{50/90}$, 4-8/8-16 µg/mL) were generally two- to four-fold lower than those for FEP alone ($MIC_{50/90}$, 16/64 µg/mL). Furthermore, MIC values for the FEP-ZID 1:1 ratio were usually two-fold lower than those of the FEP-ZID 2:1 ratio.
- FEP alone showed limited activity against MBL-producing *P. aeruginosa* isolates ($MIC_{50/90}$, 32/128 µg/mL). In contrast, FEP-ZID 2:1 ($MIC_{50/90}$, 8/16 µg/mL) and FEP-ZID 1:1 ($MIC_{50/90}$, 4/8 µg/mL) inhibited 75.0 (9/12) and 91.7% (11/12) of isolates at ≤8 µg/mL, respectively. Furthermore, the in vitro activity of ZID alone ($MIC_{50/90}$, 4/16 µg/mL) was similar to those of the FEP-ZID combinations ($MIC_{50/90}$, 4-8/8-16 µg/mL) when tested against MBL-producing *P. aeruginosa*.
- MIC values for the FEP-ZID combinations ($MIC_{50/90}$, 4/8 µg/mL for both combinations) were similar or slightly lower (two-fold) than those for FEP alone ($MIC_{50/90}$, 8/16 µg/mL) when tested against imipenem-susceptible *Acinetobacter baumannii* isolates.
- FEP ($MIC_{50/90}$, 128/>128 µg/mL) and ZID alone ($MIC_{50/90}$, >128/>128 µg/mL) showed very limited activity against OXA-producing (OXA-23/24/58) *A. baumannii* isolates. The FEP-ZID combinations were at least two-fold more active ($MIC_{50/90}$, 32/32-64 µg/mL) than either of the agents tested alone. For this collection of MDR *Acinetobacter,* the imipenem and meropenem MIC_{50} values were >8 µg/mL (data not shown).

Conclusions

- **FEP-ZID combinations (2:1 and 1:1 ratios) demonstrated potent *in vitro* activities against Enterobacteriaceae producing various clinically relevant β-lactamases, including MBLs, KPC, ESBLs and AmpC.**
- **FEP-ZID combinations (2:1 and 1:1 ratios) were also very active against *P. aeruginosa*, including MBL- and AmpC-producing isolates.**
- **FEP-ZID 1:1 ratio was slightly (two-fold) more active than FEP-ZID 2:1 ratio when tested against β-lactamase producing Enterobacteriaceae and *P. aeruginosa*.**
- **ZID tested alone exhibited potent *in vitro* antimicrobial activity against some Enterobacteriaceae as well as *P. aeruginosa* isolates, including β-lactamase producing isolates.**
- **FEP and ZID alone showed limited activity against OXA-producing (OXA-23/24/58) *Acinetobacter baumannii* isolates ($MIC_{50/90}$, 128->128/>128 µg/mL). However, the FEP-ZID 1:1 ratio ($MIC_{50/90}$, 32/32 µg/mL) was at least four-fold more active than FEP or ZID tested alone.**

Acknowledgements

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Table 1. Cumulative frequency distribution of cefepime (FEP), FEP + zidebactam at 2:1 and 1:1 ratios, and zidebactam MIC results when tested against wild type (cefepime-susceptible) Enterobacteriaceae strains.

Organism group/ Antimicrobial agent	Count	No. of isolates (cumulative %) inhibited at cefepime MIC (µg/mL) of:													MIC_{50}	MIC_{90}
		≤0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	>128		
All strains																
FEP	51	42 (82.4)	5 (92.2)	3 (98.0)	0 (98.0)	1 (100.0)	--	--	--	--	--	--	--	--	≤0.06	0.12
FEP-Zidebactam (2:1)	51	43 (84.3)	8 (100.0)	--	--	--	--	--	--	--	--	--	--	--	≤0.06	0.12
FEP-Zidebactam (1:1)	51	48 (94.1)	3 (100.0)	--	--	--	--	--	--	--	--	--	--	--	≤0.06	≤0.06
Zidebactam	51	1 (2.0)	20 (41.2)	5 (51.0)	1 (52.9)	1 (54.9)	1 (56.9)	0 (56.9)	0 (56.9)	0 (56.9)	0 (56.9)	0 (56.9)	0 (56.9)	22 (100.0)	0.25	>128
E. coli																
FEP	10	7 (70.0)	1 (80.0)	1 (90.0)	0 (90.0)	1 (100.0)	--	--	--	--	--	--	--	--	≤0.06	0.25
FEP-Zidebactam (2:1)	10	8 (80.0)	2 (100.0)	--	--	--	--	--	--	--	--	--	--	--	≤0.06	0.12
FEP-Zidebactam (1:1)	10	10 (100.0)	--	--	--	--	--	--	--	--	--	--	--	--	≤0.06	≤0.06
Zidebactam	10	1 (10.0)	9 (100.0)	--	--	--	--	--	--	--	--	--	--	--	0.12	0.12
***Klebsiella* spp.**																
FEP	11	11 (100.0)	--	--	--	--	--	--	--	--	--	--	--	--	≤0.06	≤0.06
FEP-Zidebactam (2:1)	11	11 (100.0)	--	--	--	--	--	--	--	--	--	--	--	--	≤0.06	≤0.06
FEP-Zidebactam (1:1)	11	11 (100.0)	--	--	--	--	--	--	--	--	--	--	--	--	≤0.06	≤0.06
Zidebactam	11	--	3 (27.3)	3 (54.5)	1 (63.6)	1 (72.7)	1 (81.8)	0 (81.8)	0 (81.8)	0 (81.8)	0 (81.8)	0 (81.8)	0 (81.8)	2 (100.0)	0.25	>128
***Enterobacter* spp.**																
FEP	10	10 (100.0)	--	--	--	--	--	--	--	--	--	--	--	--	≤0.06	≤0.06
FEP-Zidebactam (2:1)	10	8 (80.0)	2 (100.0)	--	--	--	--	--	--	--	--	--	--	--	≤0.06	0.12
FEP-Zidebactam (1:1)	10	10 (100.0)	--	--	--	--	--	--	--	--	--	--	--	--	≤0.06	≤0.06
Zidebactam	10	--	8 (80.0)	2 (100.0)	--	--	--	--	--	--	--	--	--	--	0.12	0.25
Indole positive Proteeae																
FEP	10	10 (100.0)	--	--	--	--	--	--	--	--	--	--	--	--	≤0.06	≤0.06
FEP-Zidebactam (2:1)	10	10 (100.0)	--	--	--	--	--	--	--	--	--	--	--	--	≤0.06	≤0.06
FEP-Zidebactam (1:1)	10	10 (100.0)	--	--	--	--	--	--	--	--	--	--	--	--	≤0.06	≤0.06
Zidebactam	10	--	--	--	--	--	--	--	--	--	--	--	--	10 (100.0)	>128	>128
S. marcescens																
FEP	10	4 (40.0)	4 (80.0)	2 (100.0)	--	--	--	--	--	--	--	--	--	--	0.12	0.25
FEP-Zidebactam (2:1)	10	6 (60.0)	4 (100.0)	--	--	--	--	--	--	--	--	--	--	--	≤0.06	0.12
FEP-Zidebactam (1:1)	10	7 (70.0)	3 (100.0)	--	--	--	--	--	--	--	--	--	--	--	≤0.06	0.12
Zidebactam	10	--	--	--	--	--	--	--	--	--	--	--	--	10 (100.0)	>128	>128

Table 2. Cumulative frequency distribution of cefepime (FEP), FEP + zidebactam at 2:1 and 1:1 ratios, and zidebactam MIC results when tested against β-lactamase-producing Enterobacteriaceae strains.

Organism group/ Antimicrobial agent	Count	No. of isolates (cumulative %) inhibited at MIC (µg/mL) of:													MIC_{50}	MIC_{90}
		≤0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	>128		
CTX-M-15-producing strain[a]																
FEP	21	--	--	--	--	--	--	--	--	--	2 (9.5)	4 (28.6)	2 (38.1)	13 (100.0)	>128	>128
FEP-Zidebactam (2:1)	21	--	--	3 (14.3)	12 (71.4)	3 (85.7)	1 (90.5)	1 (95.2)	1 (100.0)	--	--	--	--	--	0.5	2
FEP-Zidebactam (1:1)	21	--	6 (28.6)	8 (66.7)	4 (85.7)	1 (90.5)	1 (95.2)	1 (100.0)	--	--	--	--	--	--	0.25	1
Zidebactam	21	--	2 (9.5)	9 (52.4)	4 (71.4)	2 (81.0)	1 (85.7)	0 (85.7)	0 (85.7)	0 (85.7)	0 (85.7)	1 (90.5)	0 (90.5)	2 (100.0)	0.25	64
SHV-producing strains[b]																
FEP	20	--	1 (5.0)	2 (15.0)	1 (20.0)	2 (30.0)	4 (50.0)	5 (75.0)	3 (90.0)	2 (100.0)	--	--	--	--	2	8
FEP-Zidebactam (2:1)	20	2 (10.0)	6 (40.0)	10 (90.0)	1 (95.0)	0 (95.0)	1 (100.0)	--	--	--	--	--	--	--	0.25	0.25
FEP-Zidebactam (1:1)	20	4 (20.0)	10 (70.0)	5 (95.0)	0 (95.0)	1 (100.0)	--	--	--	--	--	--	--	--	0.12	0.25
Zidebactam	20	--	8 (40.0)	2 (50.0)	0 (50.0)	0 (50.0)	0 (50.0)	0 (50.0)	0 (50.0)	0 (50.0)	1 (55.0)	0 (55.0)	0 (55.0)	9 (100.0)	0.25	>128
Other ESBLs[c]																
FEP	20	--	--	1 (5.0)	2 (15.0)	2 (25.0)	4 (45.0)	2 (55.0)	3 (70.0)	2 (80.0)	1 (85.0)	1 (90.0)	2 (100.0)	--	4	64
FEP-Zidebactam (2:1)	20	--	3 (15.0)	9 (60.0)	3 (75.0)	4 (95.0)	1 (100.0)	--	--	--	--	--	--	--	0.25	1
FEP-Zidebactam (1:1)	20	1 (5.0)	8 (45.0)	6 (75.0)	2 (85.0)	3 (100.0)	--	--	--	--	--	--	--	--	0.25	1
Zidebactam	20	--	3 (15.0)	1 (20.0)	2 (30.0)	2 (40.0)	0 (40.0)	1 (45.0)	0 (45.0)	0 (45.0)	0 (45.0)	1 (50.0)	1 (55.0)	9 (100.0)	64	>128
Plasmidic AmpC-producing strains[d]																
FEP	10	--	1 (10.0)	5 (60.0)	4 (100.0)	--	--	--	--	--	--	--	--	--	0.25	0.5
FEP-Zidebactam (2:1)	10	6 (60.0)	3 (90.0)	1 (100.0)	--	--	--	--	--	--	--	--	--	--	≤0.06	0.12
FEP-Zidebactam (1:1)	10	9 (90.0)	1 (100.0)	--	--	--	--	--	--	--	--	--	--	--	≤0.06	≤0.06
Zidebactam	10	1 (10.0)	2 (30.0)	5 (80.0)	0 (80.0)	0 (80.0)	0 (80.0)	0 (80.0)	0 (80.0)	1 (90.0)	1 (100.0)	--	--	--	0.25	16
Derepressed AmpC-producing strains[e]																
FEP	23	1 (4.3)	2 (13.0)	0 (13.0)	5 (34.8)	4 (52.2)	0 (52.2)	3 (65.2)	5 (87.0)	1 (91.3)	2 (100.0)	--	--	--	1	16
FEP-Zidebactam (2:1)	23	3 (13.0)	5 (34.8)	6 (60.9)	6 (87.0)	2 (95.7)	1 (100.0)	--	--	--	--	--	--	--	0.25	1
FEP-Zidebactam (1:1)	23	6 (26.1)	9 (65.2)	4 (82.6)	2 (91.3)	2 (100.0)	--	--	--	--	--	--	--	--	0.12	0.5
Zidebactam	23	--	5 (21.7)	3 (34.8)	3 (47.8)	0 (47.8)	2 (56.5)	0 (56.5)	0 (56.5)	1 (60.9)	0 (60.9)	0 (60.9)	0 (60.9)	9 (100.0)	2	>128
KPC-producing strains[f]																
FEP	35	--	--	--	--	--	2 (5.7)	5 (20.0)	2 (25.7)	5 (40.0)	5 (54.3)	3 (62.9)	3 (71.4)	10 (100.0)	32	>128
FEP-Zidebactam (2:1)	35	--	--	8 (22.9)	14 (62.9)	7 (82.9)	5 (97.1)	1 (100.0)	--	--	--	--	--	--	0.5	2
FEP-Zidebactam (1:1)	35	--	7 (20.0)	12 (54.3)	11 (85.7)	4 (97.1)	1 (100.0)	--	--	--	--	--	--	--	0.25	1
Zidebactam	35	--	1 (2.9)	7 (22.9)	3 (31.4)	5 (45.7)	1 (48.6)	1 (51.4)	0 (51.4)	3 (60.0)	1 (62.9)	1 (65.7)	1 (68.6)	11 (100.0)	4	>128
MBL-producing strains[g]																
FEP	20	--	--	--	--	--	--	--	1 (5.0)	0 (5.0)	2 (15.0)	2 (25.0)	1 (30.0)	14 (100.0)	>128	>128
FEP-Zidebactam (2:1)	20	--	--	2 (10.0)	5 (35.0)	6 (65.0)	2 (75.0)	0 (75.0)	2 (85.0)	1 (90.0)	2 (100.0)	--	--	--	1	16
FEP-Zidebactam (1:1)	20	--	1 (5.0)	6 (35.0)	3 (50.0)	1 (55.0)	4 (75.0)	1 (80.0)	2 (90.0)	1 (95.0)	1 (100.0)	--	--	--	0.5	8
Zidebactam	20	--	1 (5.0)	4 (25.0)	5 (50.0)	1 (55.0)	0 (55.0)	1 (60.0)	0 (60.0)	0 (60.0)	0 (60.0)	0 (60.0)	0 (60.0)	8 (100.0)	0.5	>128

a. Includes *E. coli* (9) and *K. pneumoniae* (12).
b. Includes *E. coli* (1) and *K. pneumoniae* (19). It does not exclude the production of other β-lactamases.
c. Includes GES-18, OXA-1/30, OXY-like, PER-like, ESBL TEM-like and VEB-like (see M&M section). The organisms are *C. freundii* (2), *E. coli* (5), *E. cloacae* (1), *K. oxytoca* (4), *K. pneumoniae* (3), *P. mirabilis* (3), and *Providencia* spp. (2). It does not exclude the production of other β-lactamase.
d. Includes *E. coli* (7) and *K. pneumoniae* (3). It does not exclude the production of other β-lactamases.
e. Includes *C. freundii* (5), *C. koseri* (1), *E. aerogenes* (4), *E. cloacae* (7) and *S. marcescens* (6). It does not exclude the production of other β-lactamases.
f. Includes *Klebsiella* spp. (24), *C. freundii* (2), *E. coli* (3), *E. aerogenes* (2), *E. cloacae* (1), *P. mirabilis* (1), and *S. marcescens* (2).
g. Includes IMP-producers (4; *E. cloacae* [1], *K. oxytoca* [1], *K. pneumoniae* [1], and *S. marcescens* [1]), NDM-producers (8; *E. coli* [3], *E. cloacae* [1], *K. pneumoniae* [2], and *P. mirabilis* [1], and *S. marcescens* [1]) and VIM-producers (8; *C. freundii* [1], *E. cloacae* [4], *K. pneumoniae* [2], and *P. mirabilis* [1]).

Table 3. Cumulative frequency distribution of cefepime (FEP), FEP + zidebactam at 2:1 and 1:1 ratios, and zidebactam MIC results when tested against *P. aeruginosa* and *A. baumannii* strains.

Organism group/ Antimicrobial agent	Count	No. of isolates (cumulative %) inhibited at MIC (µg/mL) of:											MIC_{50}	MIC_{90}
		0.25	0.5	1	2	4	8	16	32	64	128	>128		
P. aeruginosa														
FEP-susceptible														
FEP	10	--	--	3 (30.0)	3 (60.0)	3 (90.0)	1 (100.0)	--	--	--	--	--	2	4
FEP-Zidebactam (2:1)	10	--	1 (10.0)	7 (80.0)	2 (100.0)	--	--	--	--	--	--	--	1	2
FEP-Zidebactam (1:1)	10	--	1 (10.0)	7 (80.0)	2 (100.0)	--	--	--	--	--	--	--	1	2
Zidebactam	10	--	--	1 (10.0)	6 (70.0)	3 (100.0)	--	--	--	--	--	--	2	4
AmpC-producing strains														
FEP	21	--	--	--	--	1 (4.8)	4 (23.8)	6 (52.4)	7 (85.7)	3 (100.0)	--	--	16	64
FEP-Zidebactam (2:1)	21	--	--	1 (4.8)	2 (14.3)	6 (42.9)	6 (71.4)	5 (95.2)	1 (100.0)	--	--	--	8	16
FEP-Zidebactam (1:1)	21	--	1 (4.8)	1 (9.5)	4 (28.6)	7 (61.9)	6 (90.5)	2 (100.0)	--	--	--	--	4	8
Zidebactam	21	--	--	--	2 (9.5)	7 (42.9)	2 (52.4)	7 (85.7)	1 (90.5)	0 (90.5)	1 (95.2)	1 (100.0)	8	32
MβL-producing strains														
FEP	12	--	--	--	--	--	1 (8.3)	0 (8.3)	5 (50.0)	4 (83.3)	1 (91.7)	1 (100.0)	32	128
FEP-Zidebactam (2:1)	12	--	--	1 (8.3)	0 (8.3)	2 (25.0)	6 (75.0)	2 (91.7)	1 (100.0)	--	--	--	8	16
FEP-Zidebactam (1:1)	12	--	1 (8.3)	0 (8.3)	2 (25.0)	6 (75.0)	2 (91.7)	1 (100.0)	--	--	--	--	4	8
Zidebactam	12	--	1 (8.3)	0 (8.3)	0 (8.3)	6 (58.3)	3 (83.3)	2 (100.0)	--	--	--	--	4	16
Acinetobacter baumannii														
Imipenem-susceptible strains														
FEP	10	--	--	1 (10.0)	2 (30.0)	1 (40.0)	4 (80.0)	2 (100.0)	--	--	--	--	8	16
FEP-Zidebactam (2:1)	10	--	--	1 (10.0)	0 (10.0)	5 (60.0)	4 (100.0)	--	--	--	--	--	4	8
FEP-Zidebactam (1:1)	10	--	--	1 (10.0)	1 (20.0)	6 (80.0)	2 (100.0)	--	--	--	--	--	4	8
Zidebactam	10	--	--	--	--	--	--	--	--	--	--	10 (100.0)	>128	>128
OXA-23-/OXA-24-producing strains[a]														
FEP	11	--	--	--	--	--	--	1 (9.1)	2 (27.3)	2 (45.5)	2 (63.6)	4 (100.0)	128	>128
FEP-Zidebactam (2:1)	11	--	--	--	--	--	--	3 (27.3)	6 (81.8)	2 (100.0)	--	--	32	64
FEP-Zidebactam (1:1)	11	--	--	--	--	--	1 (9.1)	3 (36.4)	6 (90.9)	1 (100.0)	--	--	32	32
Zidebactam	11	--	--	--	--	--	--	--	--	--	--	11 (100.0)	>128	>128

a. OXA-23- (6), OXA-24- (3), OXA-58 (1) and OXA-23 and OXA-58-producing (1) strains.