Comparison of cefepime-zidebactam (WCK 5222), ceftazidime-avibactam, and ceftolozane-tazobactam tested against Gram-negative organisms causing pneumonia in United States hospitals in 2018

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Introduction

- Zidebactam, a bicyclo-acyl hydrazide ($C_{13}H_{21}N_4O_7S$), 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)
- *In vivo* lung and thigh eradication studies employing cefepime-zidebactam human-simulated regimens in neutropenic animals have demonstrated 2-3 log kill of multidrug (MDR)- and extensively drug-resistant (XDR) *Acinetobacter baumannii* and *Pseudomonas aeruginosa* with cefepime-zidebactam MIC values up to 64 mg/L and 32 mg/L, respectively
- Clinical indications currently approved by the 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
- We evaluated the frequency and antimicrobial susceptibility of Gram-negative bacilli isolated from patients with pneumonia in United States (US) hospitals

Materials and Methods

- A total of 3,086 clinical isolates were consecutively collected from patients hospitalized with pneumonia (1/patient) in 29 US medical centers in 2018 by the SENTRY Antimicrobial Surveillance Program
- The GNB (n=2,171) 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 comparators by reference broth microdilution method
- The cefepime susceptible (S) breakpoint of ≤8 mg/L (CLSI, high dose) was applied for cefepime-zidebactam for comparison purposes only, and a cefepime-zidebactam susceptible breakpoint of ≤64 mg/L proposed on the basis of pharmacokinetic/pharmacodynamic (PK/PD) 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

- GNB represented 70.3% and the Gram-positives represented 29.7% of the organisms isolated from patients with pneumonia; the most common species were *Staphylococcus aureus* (27.0%), *P. aeruginosa* (24.6%), *Klebsiella pneumoniae* (7.6%), *Escherichia coli* (6.8%), *Serratia marcescens* (5.4%), and *Stenotrophomonas maltophilia* (4.5%; Figure 1)
- Cefepime-zidebactam was highly active against *P. aeruginosa* ($MIC_{50/90}$, 2/8 mg/L; 98.8% and 99.9% inhibited at ≤8 and ≤16 mg/L, respectively; highest MIC, 32 mg/L), including resistant subsets (Table 1 and Figure 2)
- Among comparators, colistin (99.6%S [data not shown]), ceftazidime-avibactam (95.2%S), and ceftolozane-tazobactam (94.5%S) were the most active compounds against *P. aeruginosa* (Table 1 and Figure 2)
- Against MDR and XDR *P. aeruginosa*, cefepime-zidebactam showed significantly superior activity (99%S at 16 mg/L) compared to ceftazidime-avibactam (81.2%S) and ceftolozane-tazobactam (79.7%S; Figure 2)
- Cefepime-zidebactam retained good activity against *P. aeruginosa* isolates not susceptible to ceftazidime-avibactam and/or ceftolozane-tazobactam, inhibiting 70.8% and 95.8% of isolates not susceptible to both compounds at ≤8 mg/L and ≤16 mg/L, respectively (Table 1)
- Cefepime-zidebactam inhibited all *Enterobacterales* at ≤4 mg/L, including extended-spectrum β-lactamase (ESBL) producers (MIC_{90}, 0.25 mg/L) and CRE (MIC_{90}, 4 mg/L; Table 1 and Figure 3)
- The most active comparators against *Enterobacterales* were ceftazidime-avibactam (99.9%S), amikacin (98.5%S), and meropenem (98.3%S; Table 1 and Figure 3)
- The most common carbapenemases produced by CRE isolates were KPC-3 (9 isolates; 52.9%) and KPC-2 (4 isolates; 23.5%); 1 isolate (5.9%) produced an NDM-1 and no carbapenemase was found in 3 CRE isolates (17.6% [data not shown])
- Cefepime-zidebactam inhibited 75.0% and 97.9% of *S. maltophilia* isolates at ≤8 mg/L and ≤16 mg/L, respectively (highest MIC, 64 mg/L; Table 1); the only other compounds active against *S. maltophilia* were trimethoprim-sulfamethoxazole ($MIC_{50/90}$, ≤0.12/2 mg/L; 95.7%S) and levofloxacin ($MIC_{50/90}$, 1/8 mg/L; 70.7%S; data not shown)
- Cefepime-zidebactam inhibited 72.1% and 99.0% of *Acinetobacter* spp. isolates at ≤8 mg/L and at the proposed PK/PD breakpoint of ≤64 mg/L, respectively (Table 1)

Table 1 *In vitro* activities of β-lactamase inhibitor combinations and meropenem tested against Gram-negative bacilli isolates from patients with pneumonia hospitalized in US medical centers in 2018

	MIC_{50} (mg/L) / % susceptible (CLSI)				
Organism (no. tested)	**FEP-ZID[a]**	**CAZ-AVI**	**C-T**	**PIP-TAZ**	**MEM**
P. aeruginosa (757)	2 / (98.8/99.9)[a]	2 / 95.2	1 / 94.5	8 / 75.2	0.5 / 74.4
MEM-NS (194)	4 / (95.4/99.5)[a]	4 / 84.5	2 / 82.9	32 / 41.2	8 / 0.0
CAZ-AVI-NS (36)	8 / (77.8/97.2)[a]	32 / 0.0	16 / 33.3	>128 / 5.6	16 / 16.7
C-T-NS (40)	8 / (82.5/97.5)[a]	16 / 40.0	>16 / 0.0	>128 / 7.5	16 / 17.5
CAZ-AVI- & C-T-NS (24)	8 / (70.8/95.8)[a]	32 / 0.0	>16 / 0.0	>128 / 8.3	16 / 12.5
MDR (186)	4 / (95.2/99.5)[a]	4 / 81.2	2 / 79.7	64 / 23.1	8 / 25.8
XDR (119)	8 / (92.4/99.2)[a]	8 / 74.8	2 / 70.1	128 / 8.4	16 / 10.9
Enterobacterales (1,012)	0.06 / (100.0)[b]	0.12 / 99.9	0.5 / 90.9	2 / 87.9	0.03 / 98.3
K. pneumoniae (236)	0.03 / (100.0)[b]	0.12 / 100.0	0.5 / 93.3	4 / 89.8	0.03 / 95.8
E. coli (210)	0.03 / (100.0)[b]	0.12 / 100.0	0.25 / 97.2	2 / 94.3	≤0.015 / 99.5
S. marcescens (166)	0.06 / (100.0)[b]	0.25 / 99.4	0.5 / 94.0	2 / 91.6	0.06 / 98.2
S. maltophilia (140)	4 / (75.0/97.9)[a]	32 / (31.4)[c]	>16 / (12.9)[c]	>128 / (0.0)[c]	>32 / (2.1)[c]
Acinetobacter spp. (104)	4 / (72.1/98.9)[c]	8 / (62.5)[c]	1 / (67.1)[c]	2 / 58.7	0.5 / 66.3

[a] % inhibited at ≤8/≤16 mg/L; all isolates (100.0%) inhibited at the PK/PD proposed breakpoint of ≤64 mg/L.
[b] % inhibited at ≤8 mg/L.
[c] % inhibited at ≤8/≤64 mg/L (PK/PD breakpoint).
[d] % inhibited at the *P. aeruginosa*-susceptible breakpoint (CLSI); for comparison purpose.
FEP-ZID, cefepime-zidebactam; CAZ-AVI, ceftazidime-avibactam; C-T, ceftolozane-tazobactam; MEM, meropenem; NS, nonsusceptible; MDR, multidrug-resistant; XDR, extensively drug-resistant

Figure 1 Frequency of organisms isolated from patients hospitalized with pneumonia in US medical centers (SENTRY Program, 2018)

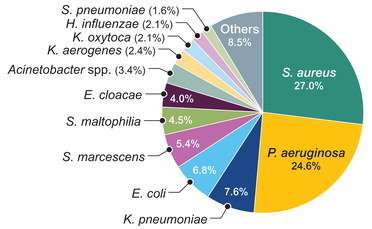
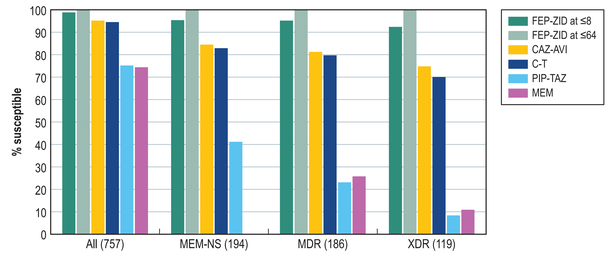
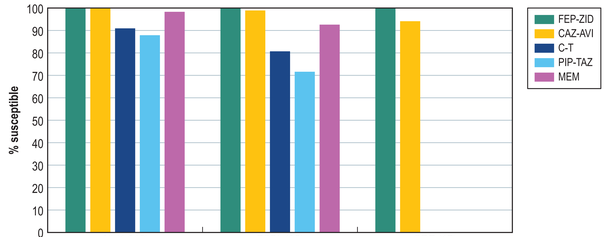


Figure 2 Antimicrobial susceptibility of *P. aeruginosa* isolated from patients hospitalized with pneumonia in US medical centers in 2018



Abbreviations: FEP-ZID, cefepime-zidebactam (% at ≤8 mg/L and at ≤64 mg/L); CAZ-AVI, ceftazidime-avibactam; C-T, ceftolozane-tazobactam; PIP-TAZ, piperacillin-tazobactam; MEM, meropenem; NS, nonsusceptible; MDR, multidrug-resistant; XDR, extensively drug-resistant

Figure 3 Antimicrobial susceptibility of *Enterobacterales* isolated from patients hospitalized with pneumonia in US medical centers in 2018



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

Conclusions

- GNB were responsible for the majority (70%) of bacterial pneumonia cases in US hospitals in 2018
- Cefepime-zidebactam showed complete activity against *P. aeruginosa* with 98.8% and 99.9% of isolates inhibited at ≤8 mg/L and ≤16 mg/L, respectively
- Cefepime-zidebactam was more active than ceftazidime-avibactam and ceftolozane-tazobactam against MDR and XDR *P. aeruginosa* and retained activity against most isolates resistant to these recently approved β-lactamase inhibitor combinations
- Cefepime-zidebactam demonstrated potent *in vitro* activity and 100.0% susceptibility rates against *Enterobacterales*, including CRE, MDR, XDR isolates
- Cefepime-zidebactam activity against *Enterobacterales* was similar 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., considering the ≤64 mg/L proposed PK/PD breakpoint
- In summary, cefepime-zidebactam exhibited potent *in vitro* activity against GNB causing pneumonia in US hospitals and may represent a valuable therapeutic option for these difficult-to-treat infections

Acknowledgements

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References

Almarzoky Abuhussain SS, Avery LM, Abdelraouf K, et al. (2019). *In vivo* efficacy of humanized WCK 5222 (cefepime-zidebactam) exposures against carbapenem-resistant *Acinetobacter baumannii* in the neutropenic thigh model. *Antimicrob Agents Chemother* 63: e01931.

Avery LM, Abdelraouf K, Nicolau DP (2018). Assessment of the *in vivo* efficacy of WCK 5222 (cefepime-zidebactam) against carbapenem-resistant *Acinetobacter baumannii* in the neutropenic murine lung infection model. *Antimicrob Agents Chemother* 62: e00948.

Burgess SV, Mabasa VH, Chow I, et al. (2015). Evaluating outcomes of alternative dosing strategies for cefepime: a qualitative systematic review. *Ann Pharmacother* 49: 311–322.

Clinical and Laboratory Standards Institute (2019). *M100Ed29. Performance standards for antimicrobial susceptibility testing: 29th informational supplement*. Wayne, PA: CLSI.

Maxepime (2012). Maxepime Package Insert. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/050679s036lbl.pdf. Accessed February 18, 2016.

Monogue ML, Tabor-Rennie J, Abdelraouf K, et al. (2019). *In vivo* efficacy of WCK 5222 (cefepime-zidebactam) against multidrug-resistant *Pseudomonas aeruginosa* in the neutropenic murine thigh infection model. *Antimicrob Agents Chemother* 63: e00233.

Sader HS, Castanheira M, Huband M, et al. (2017). WCK 5222 (cefepime-zidebactam) antimicrobial activity against clinical isolates of Gram-negative bacteria collected worldwide in 2015. *Antimicrob Agents Chemother* 61: e00072.

Sader HS, Rhomberg PR, Flamm RK, et al. (2017). WCK 5222 (cefepime/zidebactam) antimicrobial activity tested against Gram-negative organisms producing clinically relevant beta-lactamases. *J Antimicrob Chemother* 72: 1696–1703.

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