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Antimicrobial Activity of High-Dose Extended-Infusion Cefepime-Tazobactam (WCK 4282) Tested against Gram-Negative Organisms Collected from Medical Centers in the United States and Latin America (2018)

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Introduction

- Cefepime-tazobactam is under clinical development at 2g/2g q8 hours dosage as a 90-minute infusion
- Cefepime was initially approved by the United States Food and Drug Administration (US FDA) in 1997, and the clinical indications in the current US FDA product package insert include the treatment for 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 dosages vary from 1g q12 hours to 2g q8 hours administered as a 30-minute infusion
- The cefepime-tazobactam combination demonstrated activity against several isolates producing extended-spectrum β-lactamases (ESBLs) and AmpC β-lactamases
- We evaluated the potency and spectrum of activity of cefepime-tazobactam against contemporary gram-negative isolates collected by the SENTRY Antimicrobial Surveillance Program in 2018

Materials and Methods

- A total of 7,295 *Enterobacterales* and 1,471 *Pseudomonas aeruginosa* isolates (1/patient) were consecutively collected in 2018
  - 6,637 *Enterobacterales* and 1,310 *P. aeruginosa* from the United States (USA; 69 centers)
  - 658 *Enterobacterales* and 161 *P. aeruginosa* from Latin America (LATAM; 8 centers in 5 nations)
- Susceptibility testing against cefepime-tazobactam (tazobactam at fixed 8 mg/L) and comparators was performed by reference broth microdilution methods
- The percentages of isolates inhibited at cefepime ≤8 mg/L (Clinical and Laboratory Standards Institute [CLSI], cefepime high-dose breakpoint) and at ≤16 mg/L (pharmacokinetic/pharmacodynamic [PK/PD]-susceptible (S) breakpoint based on high-dose extended infusion) in presence of tazobactam were evaluated
- CLSI breakpoints were applied for comparators and for categorizing multidrug-resistant (MDR) subsets

Results

- Isolates were from bloodstream (23.2%/30.0% in USA/LATAM), pneumonia (30.2%/29.8%), urinary tract (39.9%/24.9%), and intra-abdominal infections (6.7%/15.2%: Figure 1)
- Against *Enterobacterales* from USA/LATAM (n=6,637/658), cefepime-tazobactam inhibited 99.6%/92.9% of isolates at ≤16 mg/L (99.3%/91.8% at ≤8 mg/L) with spectrum similar to meropenem (99.0%/90.7%S) and greater than ceftolozane-tazobactam (95.3%/83.3%S) and piperacillin-tazobactam (92.8%/80.4%S; Table 1 and Figures 2–4)
- Among MDR *Enterobacterales* (n=615/226 in USA/LATAM), 88.8%/73.0% were meropenem-susceptible and cefepime-tazobactam inhibited 95.3%/79.2% at ≤16 mg/L (Figure 5)
- ESBL-phenotype rates were 15.1%/34.7% in the USA/LATAM among *Escherichia coli* and 15.6%/64.1% among *Klebsiella pneumoniae*
- Among ESBL-producing isolates from the USA (n=585), 98.5% and 99.0% of isolates were inhibited at ≤8 mg/L and ≤16 mg/L, respectively, of cefepime-tazobactam, whereas susceptibility rates for meropenem and ceftolozane-tazobactam were 98.5% and 90.1%, respectively (Figure 6)
- Cefepime-tazobactam exhibited greater *in vitro* activity against *P. aeruginosa* ($MIC_{50/90}$, 2/16 mg/L; 92.9%/91.3% inhibited at ≤16 mg/L in USA/LATAM) when compared to piperacillin-tazobactam ($MIC_{50/90}$, 4/128 mg/L; 78.2%/75.8%S for USA/LATAM) and meropenem ($MIC_{50/90}$, 0.5/8-16 mg/L; 78.0%/79.5%S for USA/LATAM; Table 1 and Figures 7 and 8)

Conclusions

- Cefepime-tazobactam showed potent activity against clinical isolates from United States and Latin American medical centers, including MDR and ESBL-producing isolates
- Cefepime-tazobactam was highly active against *P. aeruginosa*, with spectrum of activity similar to those of ceftazidime-avibactam and ceftolozane-tazobactam and greater than those of meropenem and piperacillin-tazobactam
- Cefepime-tazobactam may represent a valuable option for treating serious infections caused by gram-negative bacilli, including MDR and ESBL-producing isolates

Acknowledgements

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References

- 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.
- Castanheira M, Duncan LR, Rhomberg PR, et al. (2017). Enhanced activity of cefepime-tazobactam (WCK 4282) against KPC-producing *Enterobacteriaceae* when tested in media supplemented with human serum or sodium chloride. *Diagn Microbiol Infect Dis* 89: 305-309.
- Clinical and Laboratory Standards Institute (2019). *M100Ed29E. Performance standards for antimicrobial susceptibility testing: 29th informational supplement*. Wayne, PA: CLSI.
- Maxepime Package Insert (2012). Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/050679s036lbl.pdf. Accessed February 18, 2016.
- Sader HS, Castanheira M, Mendes RE, et al. (2017). Antimicrobial activity of high-proportion cefepime-tazobactam (WCK 4282) against a large number of Gram-negative isolates collected worldwide in (2014). *Antimicrob Agents Chemother* 61: e02409.

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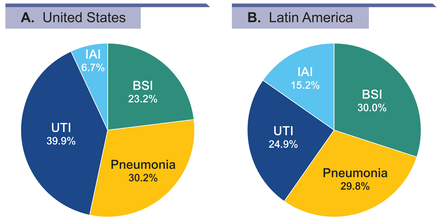
Table 1 Summary of cefepime-tazobactam activity against the main species and resistant subsets

Organism (no. of isolates from USA/LATAM)	Cefepime-tazobactam MIC_{50}/MIC_{90} (% inhibited at ≤8 mg/L [CLSI high dose] / ≤16 mg/L [proposed PK/PD breakpoint])	
	USA	LATAM
Enterobacterales (6,637 / 658)	0.03 / 0.12 (99.3 / 99.6)	0.06 / 4 (91.8 / 92.9)
Escherichia coli (3,116 / 251)	0.03 / 0.06 (99.8 / 99.9)	0.03 / 0.12 (99.2 / 99.2)
Klebsiella pneumoniae (1,371 / 206)	0.06 / 0.25 (98.2 / 98.8)	0.06 / 64 (79.1 / 82.0)
Enterobacter spp. (668 / 70)	0.06 / 0.5 (99.1 / 99.4)	0.06 / 4 (92.9 / 94.3)
Proteus mirabilis (367 / 36)	0.06 / 0.06 (100.0 / 100.0)	0.06 / 0.12 (100.0 / 100.0)
S. marcescens (294 / 45)	0.06 / 0.25 (98.6 / 99.0)	0.12 / 8 (91.1 / 91.1)
P. aeruginosa (1,310 / 161)	2 / 16 (84.3 / 93.7)	2 / 16 (82.6 / 91.3)

USA, United States; LATAM, Latin America; PK/PD, pharmacokinetic/pharmacodynamic.

Figure 1 Distribution of isolates from the United States (1A) and Latin America (1B) according to the infection type



Abbreviations: BSI, bloodstream infection; UTI, urinary tract infection; and IAI, intraabdominal infection.

Figure 2 MIC distributions for cefepime-tazobactam and ceftolozane-tazobactam when tested against *Enterobacterales* isolates from the United States

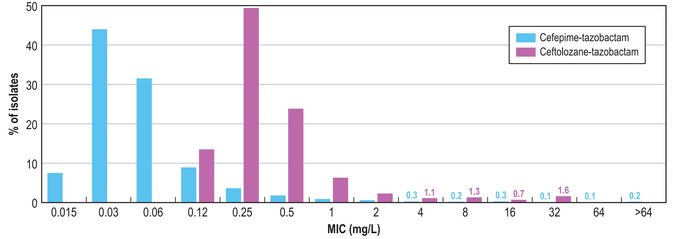
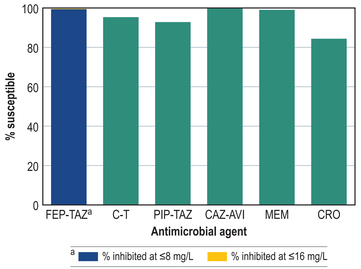
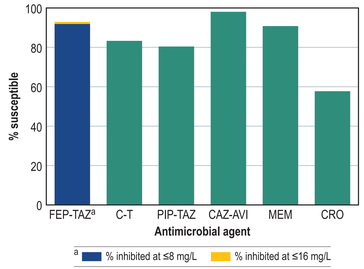


Figure 3 Antimicrobial susceptibility of 6,637 *Enterobacterales* isolates from United States medical centers (2018)



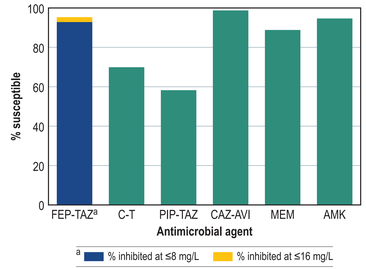
Abbreviations: FEP-TAZ, cefepime-tazobactam; C-T, ceftolozane-tazobactam; PIP-TAZ, piperacillin-tazobactam; CAZ-AVI, ceftazidime-avibactam; MEM, meropenem; CRO, ceftriaxone.

Figure 4 Antimicrobial susceptibility of 658 *Enterobacterales* isolates from Latin American medical centers (2018)



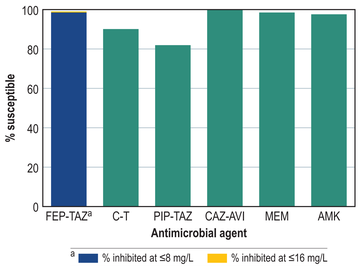
Abbreviations: FEP-TAZ, cefepime-tazobactam; C-T, ceftolozane-tazobactam; PIP-TAZ, piperacillin-tazobactam; CAZ-AVI, ceftazidime-avibactam; MEM, meropenem; CRO, ceftriaxone.

Figure 5 Antimicrobial susceptibility of 615 MDR *Enterobacterales* isolates from United States medical centers (2018)



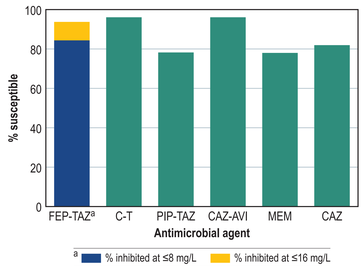
Abbreviations: FEP-TAZ, cefepime-tazobactam; C-T, ceftolozane-tazobactam; PIP-TAZ, piperacillin-tazobactam; CAZ-AVI, ceftazidime-avibactam; MEM, meropenem; AMK, amikacin.

Figure 6 Antimicrobial susceptibility of 585 ESBL-producing *Enterobacterales* from United States medical centers (2018)



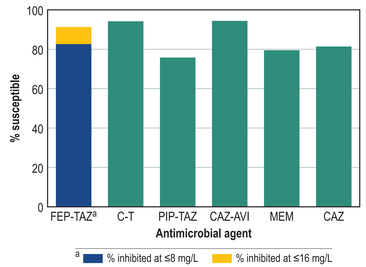
Abbreviations: ESBL, extended-spectrum β-lactamase; FEP-TAZ, cefepime-tazobactam; C-T, ceftolozane-tazobactam; PIP-TAZ, piperacillin-tazobactam; CAZ-AVI, ceftazidime-avibactam; MEM, meropenem; AMK, amikacin.

Figure 7 Antimicrobial susceptibility of 1,310 *P. aeruginosa* isolates from United States medical centers (2018)



Abbreviations: FEP-TAZ, cefepime-tazobactam; C-T, ceftolozane-tazobactam; PIP-TAZ, piperacillin-tazobactam; CAZ-AVI, ceftazidime-avibactam; MEM, meropenem; CAZ, ceftazidime.

Figure 8 Antimicrobial susceptibility of 161 *P. aeruginosa* isolates from Latin American medical centers (2018)



Abbreviations: FEP-TAZ, cefepime-tazobactam; C-T, ceftolozane-tazobactam; PIP-TAZ, piperacillin-tazobactam; CAZ-AVI, ceftazidime-avibactam; MEM, meropenem; CAZ, ceftazidime.