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Antimicrobial Activity of Novel β-Lactamase Inhibitor Combinations Tested against Organisms Causing Complicated Urinary Tract Infections in United States Medical Centers

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Introduction

- Cefepime-tazobactam (WCK 4282) 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
  - The clinical indications in the current US FDA product package insert include treatment for moderate to severe pneumonia, uncomplicated and complicated urinary tract infections (cUTIs), 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, but in WCK 4282 a cefepime dose of 2g is combined with a high tazobactam dose of 2g to be infused for a longer duration (90 minutes)
- The cefepime-tazobactam combination demonstrated activity against several isolates producing extended-spectrum β-lactamases (ESBLs) and AmpC β-lactamases, including those resistant to piperacillin-tazobactam, cefoperazone-sulbactam, and ceftolozane-tazobactam
- We evaluated the potency and spectrum of activity of cefepime-tazobactam, ceftolozane-tazobactam, ceftazidime-avibactam, and comparators against Gram-negative bacilli causing cUTIs in US hospitals

Materials and Methods

- A total of 3,023 Gram-negative organisms, including 2,841 *Enterobacterales*, 165 *Pseudomonas aeruginosa*, and 17 other non-fermentative Gram-negative bacilli (1/patient) were consecutively collected in 2018 as part of a worldwide surveillance program
- Susceptibility testing against cefepime-tazobactam (tazobactam at fixed 8 mg/L), ceftolozane-tazobactam (tazobactam at fixed 4 mg/L), ceftazidime-avibactam (avibactam at fixed 4 mg/L), and comparators was performed by reference broth microdilution method
- 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 breakpoint based on high-dose extended infusion) in presence of tazobactam were evaluated
- CLSI breakpoints were applied for comparators and for categorizing the resistant subsets

Results

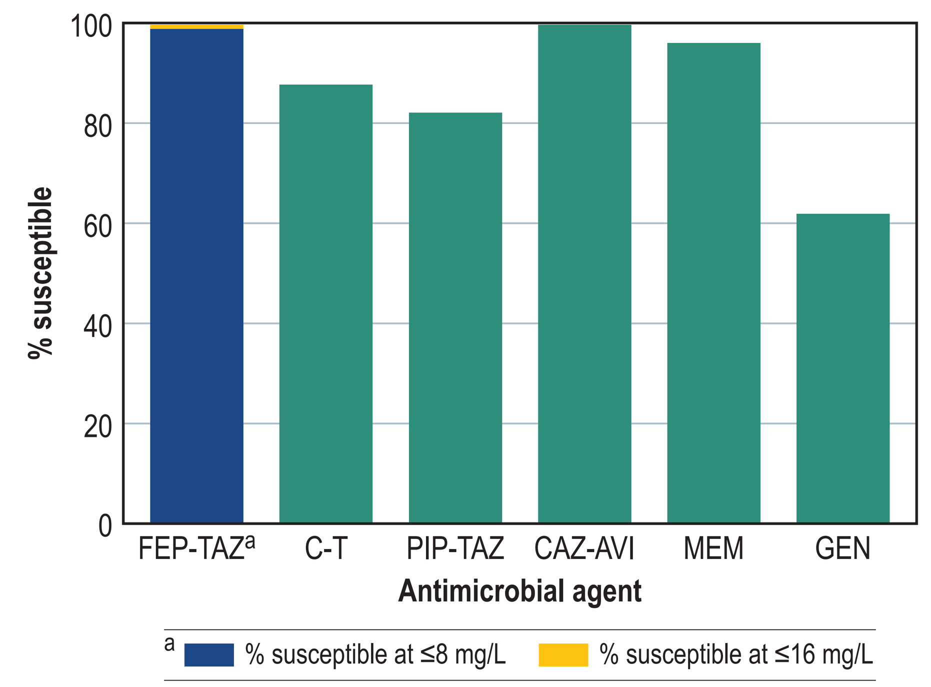
- Cefepime-tazobactam (MIC$_{50/90}$, 0.03/0.06 mg/L) and ceftazidime-avibactam (MIC$_{50/90}$, 0.12/0.25 mg/L) exhibited potent activity against *Escherichia coli* with 100% susceptibility (Table 1)
- The most active agents against *Klebsiella pneumoniae* were cefepime-tazobactam (99.2% and 99.6% inhibited at ≤8 mg/L and ≤16 mg/L, respectively), ceftazidime-avibactam (100.0% susceptible [S]), and amikacin (99.4%S)
  - MIC$_{90}$ values of cefepime-tazobactam against *K. pneumoniae* were 8 times lower than those of ceftolozane-tazobactam (Table 1)
- All *Proteus mirabilis* isolates were susceptible to cefepime-tazobactam (highest MIC, 0.12 mg/L), ceftolozane-tazobactam, ceftazidime-avibactam, meropenem, piperacillin-tazobactam, and amikacin (data not shown)
- Cefepime-tazobactam was highly active against *Enterobacter cloacae* (n=94; MIC$_{90}$, 0.5 mg/L; 98.9% inhibited at ≤16 mg/L) and *Citrobacter* spp. (n=91; MIC$_{90}$, 0.12 mg/L; highest MIC, 0.5 mg/L; data not shown)
- Cefepime-tazobactam activity against *Enterobacterales* was greater than cefepime alone
  - Overall, cefepime-tazobactam (99.8% and 99.9% inhibited at ≤8 mg/L and ≤16 mg/L, respectively), ceftazidime-avibactam (99.9%S) and meropenem (99.5%S) were the most active agents against *Enterobacterales* (data not shown)
- When tested against ESBL-producing *Enterobacterales*, cefepime-tazobactam inhibited 98.8% and 99.6% of isolates at ≤8 mg/L and 16 mg/L, respectively
  - Ceftazidime-avibactam and ceftolozane-tazobactam were active against 99.6% and 87.7% of isolates, respectively (Table 1 and Figure 1)
- Against *P. aeruginosa*, cefepime-tazobactam inhibited 90.9% and 97.6% of isolates at ≤8 mg/L and ≤16 mg/L, respectively (Table 1 and Figure 2)
- The cefepime-tazobactam spectrum of activity (MIC $_{50/90}$, 1/8 mg/L; 90.9% and 97.6% of isolates inhibited at ≤8 mg/L and ≤16 mg/L, respectively) was similar to ceftazidime-avibactam (MIC$_{50/90}$, 2/4 mg/L; 96.4%S), ceftolozane-tazobactam (MIC$_{50/90}$, 1/2 mg/L; 99.4%S), and tobramycin (MIC$_{50/90}$, 0.5/2 mg/L; 93.3%S; Table 1 and Figure 2)
- Cefepime-tazobactam (90.9% and 97.6% of isolates inhibited at ≤8 mg/L and ≤16 mg/L, respectively) exhibited greater anti-pseudomonal spectrum than meropenem (MIC$_{50/90}$, 0.5/8 mg/L; 85.5%S) and piperacillin-tazobactam (MIC$_{50/90}$, 4/32 mg/L; 87.3%S; Table 1 and Figure 2)

Table 1. Activity of cefepime-tazobactam and comparator antimicrobial agents when tested against *Enterobacterales* and *P. aeruginosa* collected from medical centers in the United States during 2018

Antimicrobial agent	mg/L		%S[a]	%R[a]
	MIC$_{50}$	MIC$_{90}$		
E. coli (1,814)				
Cefepime-tazobactam	0.03	0.06	[100.0/100.0][b]	
Ceftolozane-tazobactam	0.25	0.5	99.0	0.7
Piperacillin-tazobactam	2	4	97.6	0.6
Ceftazidime-avibactam	0.12	0.25	100.0	0.0
Ampicillin-sulbactam	8	64	55.8	28.3
Cefepime	0.06	2	90.2	7.8
Ceftriaxone	≤0.06	>8	88.6	11.2
Ceftazidime	0.25	4	91.2	7.3
Meropenem	≤0.015	0.03	99.8	0.1
Ertapenem	0.008	0.015	99.5	0.2
Gentamicin	0.5	2	90.5	9.3
Amikacin	2	4	99.8	0.1
Levofloxacin	0.03	16	74.0	25.1
K. pneumoniae (473)				
Cefepime-tazobactam	0.03	0.12	[99.2/99.6][b]	
Ceftolozane-tazobactam	0.25	1	97.6	1.8
Piperacillin-tazobactam	2	16	93.9	3.2
Ceftazidime-avibactam	0.12	0.25	100.0	0.0
Ampicillin-sulbactam	8	64	71.9	18.8
Cefepime	0.06	4	89.9	9.1
Ceftriaxone	≤0.06	>8	88.4	11.0
Ceftazidime	0.25	16	88.6	10.8
Meropenem	0.03	0.03	98.3	1.1
Ertapenem	0.008	0.03	98.3	1.7
Gentamicin	0.25	0.5	93.2	5.7
Amikacin	1	2	99.4	0.2
Levofloxacin	0.06	1	87.7	7.4
Other *Enterobacterales* (554)[c]				
Cefepime-tazobactam	0.06	0.12	[99.5/99.6][b]	
Ceftolozane-tazobactam	0.5	1	93.1	4.8
Piperacillin-tazobactam	2	16	91.7	4.9
Ceftazidime-avibactam	0.12	0.25	99.6	0.4
Ampicillin-sulbactam	16	64	49.9	34.9
Cefepime	0.06	0.5	95.9	2.2
Ceftriaxone	0.12	>8	84.8	13.5
Ceftazidime	0.12	8	89.4	9.7
Meropenem	0.03	0.06	99.6	0.4
Ertapenem	0.015	0.12	97.5	0.7
Gentamicin	0.5	1	95.3	3.4
Amikacin	2	4	99.8	0.2
Levofloxacin	0.06	1	87.5	10.0
ESBL-producing *Enterobacterales* (252)[d]				
Cefepime-tazobactam	0.06	0.5	[98.8/99.6][b]	
Ceftolozane-tazobactam	0.5	4	87.7	7.9
Piperacillin-tazobactam	4	64	82.1	7.9
Ceftazidime-avibactam	0.12	0.5	99.6	0.4
Ampicillin-sulbactam	32	>64	15.9	69.4
Cefepime	64	>256	9.5	74.6
Ceftriaxone	>8	>8	3.2	96.0
Ceftazidime	16	>32	21.0	69.0
Meropenem	0.03	0.06	96.0	2.4
Ertapenem	0.03	0.5	94.0	4.0
Gentamicin	1	>16	61.9	35.7
Amikacin	4	8	98.8	0.4
Levofloxacin	8	32	19.9	75.3
P. aeruginosa (165)				
Cefepime-tazobactam	2	8	[90.9/97.6][b]	
Ceftolozane-tazobactam	1	2	99.4	0.6
Piperacillin-tazobactam	4	32	87.3	5.5
Ceftazidime-avibactam	2	4	96.4	3.6
Cefepime	2	8	90.3	3.0
Ceftazidime	2	8	90.9	5.5
Meropenem	0.5	8	85.5	10.9
Amikacin	4	8	97.6	0.6
Tobramycin	0.5	2	93.3	6.7
Levofloxacin	0.5	32	68.3	22.0

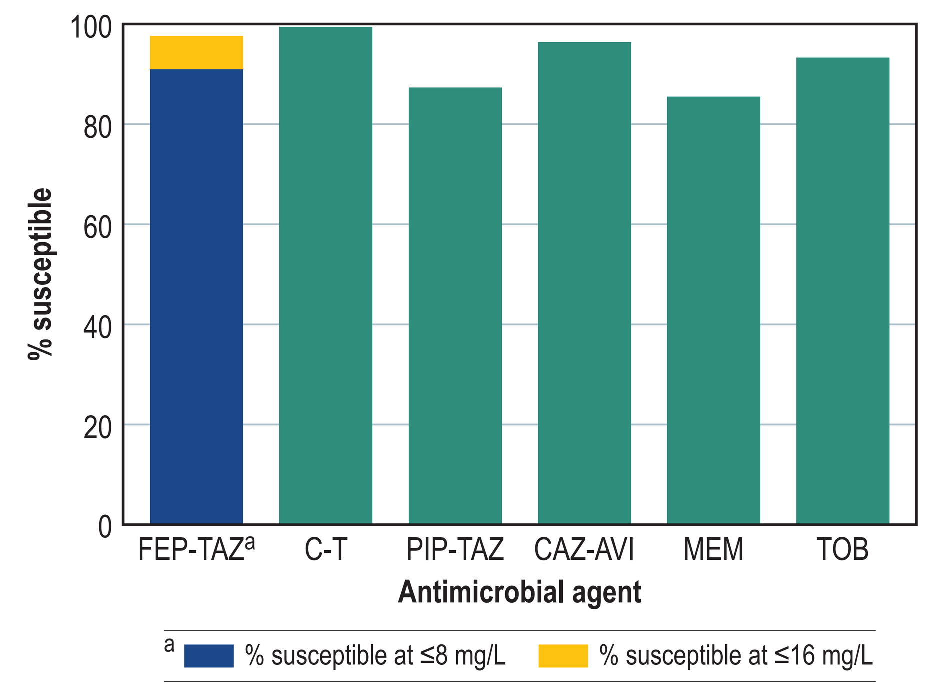
ESBL, extended-spectrum β-lactamase
[a] Criteria as published by CLSI (2019).
[b] Percentage of isolates inhibited at cefepime-tazobactam of ≤8/16 mg/L in brackets for comparison purpose only.
[c] Organisms include: *Citrobacter amalonaticus/farmeri* (3), *C. freundii* species complex (52), *C. koseri* (36), *Enterobacter cloacae* species complex (94), *Hafnia alvei* (4), *Klebsiella aerogenes* (43), *K. oxytoca* (66), *K. variicola* (2), *Morganella morganii* (26), *Proteus hauseri* (1), *P. mirabilis* (165), *P. penneri* (1), *P. vulgaris* group (6), *Providencia alcalifaciens* (1), *P. rettgeri* (13), *P. stuartii* (9), *Raoultella ornithinolytica* (1), *Serratia marcescens* (23), unspeciated *Pantoea* (1), unspeciated *Providencia* (2), unspeciated *Raoultella* (5).
[d] Organisms include: *Citrobacter freundii* species complex (2), *Enterobacter cloacae* species complex (7), *Escherichia coli* (184), *Klebsiella oxytoca* (5), *K. pneumoniae* (53), *Proteus mirabilis* (1).

Figure 1. Antimicrobial susceptibility of 252 ESBL-producing *Enterobacterales* isolates from complicated urinary tract infections collected worldwide in 2018



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

Figure 2. Antimicrobial susceptibility of 165 *P. aeruginosa* isolates from complicated urinary tract infections collected worldwide in 2018



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

Conclusions

- Cefepime-tazobactam showed potent activity against *Enterobacterales* and *P. aeruginosa* isolated from patients with cUTIs in US hospitals in 2018
- Cefepime-tazobactam's overall spectrum (*Enterobacterales* + *P. aeruginosa*) was similar to ceftazidime-avibactam and greater than ceftolozane-tazobactam, piperacillin-tazobactam, and meropenem when the cefepime-tazobactam proposed PK/PD susceptible breakpoint of ≤16 mg/L was applied
- High-dose extended infusion cefepime-tazobactam may represent a carbapenem- and ceftazidime-avibactam-sparing valuable empiric therapy option, superior to piperacillin-tazobactam and ceftolozane-tazobactam for the treatment of infections caused by *Enterobacterales* and *P. aeruginosa*
- The cefepime-tazobactam combination also provides coverage of certain carbapenem-nonsusceptible organisms

Acknowledgements

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