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P1174 Antimicrobial activity of high-dose extended infusion cefepime-tazobactam (WCK 4282) tested against Gram-negative organisms collected from medical centres located in Europe and the Asia-Pacific region in 2018

Helio S. Sader*[1], Mariana Castanheira[1], Jennifer Streit[1], Leonard Duncan[1], Robert Flamm[1]

[1] JMI Laboratories, North Liberty, United States

Background: High-dose extended-infusion cefepime-tazobactam is in clinical development at 2g/2g q8 hours to be administered over 90 minutes. We evaluated the potency and spectrum of activity of cefepime-tazobactam tested against contemporary gram-negative isolates collected by the SENTRY Antimicrobial Surveillance Program.

Materials/methods: A total of 4,437 Enterobacteriaceae and *Pseudomonas aeruginosa* isolates (1/patient) were collected in 2018, including 3,718 from Europe (EUR; 29 centers in 14 nations) and 719 from Asia-Pacific (APAC; 9 centers in 5 nations) and susceptibility tested against cefepime-tazobactam (tazobactam at fixed 8 mg/L) and comparators by reference broth microdilution method. Percentage of isolates inhibited at ≤8mg/L (CLSI, cefepime high dose) and at ≤16 mg/L (pharmacokinetic/pharmacodynamic [PK/PD] susceptible breakpoint based on extended infusion and high dosage) were evaluated. EUCAST breakpoints were applied for comparators.

Results: Isolates were from bloodstream (34.0%), pneumonia (29.3%), urinary tract (25.7%), and intra-abdominal infections (11.0%). Against Enterobacteriaceae (n=3,607), cefepime-tazobactam inhibited 98.2% of isolates at ≤16 mg/L (96.5% at ≤2 mg/L; CLSI low dose), with spectrum of activity similar to meropenem (97.6% susceptible [S]) and greater than ceftolozane-tazobactam (89.2%S) and piperacillin-tazobactam (82.8%S). Among multidrug-resistant Enterobacteriaceae (n=552), 84.1% were meropenem-S [EUCAST; 81.3% per CLSI] and cefepime-tazobactam inhibited 88.4% at ≤16 mg/L. Extended-spectrum β-lactamase (ESBL)-phenotype rates were 17.2/24.6% in EUR/APAC among *Escherichia coli* and 39.9/19.8% among *Klebsiella pneumoniae*. Among ESBL-phenotype *E. coli* and *K. pneumoniae* from EUR, 99.6% and 81.1% of isolates were inhibited at a cefepime-tazobactam MIC of ≤16 mg/L (Table), 86.1% and 35.5% were ceftolozane-tazobactam-S, and 63.7% and 23.5% were piperacillin-tazobactam-S, respectively. Cefepime-tazobactam inhibited 99.3/95.5% of *Enterobacter* spp. from EUR/APAC at ≤16 mg/L and exhibited good activity against ceftazidime-nonsusceptible isolates (n=140; $MIC_{50/90}$, 0.25/4 mg/L; 96.4% inhibited at ≤16 mg/L). When tested against *P. aeruginosa*, cefepime-tazobactam activity ($MIC_{50/90}$, 2-4/16 mg/L; 94.0/92.0% inhibited at ≤16 mg/L for EUR/APAC) was greater than that of piperacillin-tazobactam ($MIC_{50/90}$, 4-8/64-128 mg/L; 70.7/81.3%S for EUR/APAC) and meropenem ($MIC_{50/90}$, 0.5/8-16 mg/L; 71.8/81.3%S for EUR/APAC).

Conclusions: Cefepime-tazobactam demonstrated potent activity against Enterobacteriaceae, including multidrug-resistant, ESBL-phenotype, and ceftazidime-nonsusceptible isolates, and *P. aeruginosa* isolated in hospitals from EUR and APAC. Cefepime-tazobactam may represent a valuable option for treating serious infections caused by gram-negative bacilli, including multidrug-resistant isolates.

Organism (no. of isolates from EUR/APAC)	Cefepime-tazobactam MIC_{50}/MIC_{90} (% inhibited at ≤8 mg/L [CLSI high dose] / ≤16 mg/L [proposed PK/PD breakpoint]) EUR	APAC
Enterobacteriaceae (3,038/569)	0.06/0.25 (97.8/98.3)	0.03/0.25 (97.4/97.9)
Escherichia coli (1,590/276)	0.03/0.12 (99.9/99.9)	0.03/0.12 (99.3/99.3)
ESBL-phenotype *E. coli* (273/68)	0.06/0.5 (99.3/99.6)	0.06/0.25 (97.1/97.1)
Klebsiella pneumoniae (596/116)	0.06/8 (90.4/92.4)	0.03/0.25 (95.7/95.7)
ESBL-phenotype *K. pneumoniae* (238/23)	0.25/128 (76.1/81.1)	0.12/64 (78.3/78.3)
Enterobacter spp. (280/67)	0.06/1 (98.9/99.3)	0.06/8 (91.0/95.5)
Proteus mirabilis (158/21)	0.06/0.12 (100.0/100.0)	0.06/0.12 (100.0/100.0)
S. marcescens (114/31)	0.06/0.25 (99.1/99.1)	0.12/0.25 (100.0/100.0)
P. aeruginosa (680/150)	4/16 (81.0/94.0)	2/16 (89.3/92.0)