P1261
Paper Poster Session
Cefepime-tazobactam

In vitro activity of WCK 4282 (high-dose cefepime-tazobactam) against resistant subsets of Enterobacteriaceae collected worldwide (2014)

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Background: WCK 4282 (cefepime-tazobactam) is being developed for treatment of serious Gram-negative infections at dosages of 2g/2g q8 and q12 hours. Cefepime-tazobactam was tested against clinical isolates of Enterobacteriaceae with extended-spectrum β-lactamase (ESBL) phenotype and those with chromosomal AmpC collected in medical centers worldwide as part of the SENTRY Antimicrobial Surveillance Program.

Material/methods: A total of 1,151 Enterobacteriaceae isolates with an ESBL-phenotype (*E. coli* [EC], *Klebsiella* spp. [KSP] and *P. mirabilis* [PM]), and 264 isolates from Enterobacteriaceae species with inducible cephalosporinases (AmpC-ENT; includes *Citrobacter* spp., *Enterobacter* spp., indole-positive Proteae and *Serratia* spp.) that exhibited decreased susceptibility to ceftazidime (ceftazidime-non-susceptible, CAZ-NS; MIC ≥8 mg/L) were tested for susceptibility by a reference broth microdilution method against cefepime-tazobactam (tazobactam at fixed 8 mg/L) and comparator agents.

Results: Overall ESBL rates were 21.3, 31.0 and 8.3% for EC, KSP and PM, respectively. ESBL-EC isolates were very susceptible to cefepime-tazobactam (98.7% inhibited at ≤8 mg/L [cefepime high-dose, CLSI]) and meropenem (99.4% susceptible), but showed decreased susceptibility to piperacillin-tazobactam (82.1%) and other agents (see Table). ESBL-PM isolates were very susceptible to cefepime-tazobactam, piperacillin-tazobactam and meropenem (100.0% susceptible); whereas ESBL-KSP showed higher resistance rates to most agents tested. Among ESBL-KSP, 73.7% of strains were inhibited at ≤8 mg/L of cefepime-tazobactam and 71.9% were susceptible to meropenem; whereas only 36.8% were susceptible to piperacillin-tazobactam. The most active β-lactams tested against CAZ-NS AmpC-ENT were meropenem (96.6% susceptible) and cefepime-tazobactam (96.2% inhibited at ≤8 mg/L), and only 37.5% of isolates were susceptible to piperacillin-tazobactam. Among Enterobacteriaceae isolates non-susceptible to CAZ, ceftriaxone, gentamicin and levofloxacin (n=178), 96.1% were inhibited at ≤8 mg/L of cefepime-tazobactam and 97.2% were susceptible to meropenem.

Conclusions: WCK 4282 (cefepime-tazobactam) demonstrated potent *in vitro* activity against a large collection of antimicrobial-resistant Enterobacteriaceae strains, and exhibited a spectrum of activity comparable to meropenem and significantly superior to piperacillin-tazobactam and cefepime. These *in vitro* results support further clinical development of WCK 4282 (cefepime-tazobactam) for treatment of Gram-negative infections, including those caused by multidrug-resistant Enterobacteriaceae.

	MIC_{50} / MIC_{90} /% susceptible [CLSI] (no. tested)			
Antimicrobial	**ESBL *E. coli* (471)**	**ESBL *Klebsiella* spp. (661)**	**ESBL *P. mirabilis* (19)**	**CAZ-NS AmpC-ENT[a] (264)**
Cefepime-tazobactam	0.12/0.5/[96.2/98.7][b]	0.5/64/[65.5/73.7][b]	0.12/0.25/[100.0/100.0][b]	0.25/2/[92.8/96.2][b]
Cefepime	16/>64/23.4	32/>64/18.5	1/>64/57.9	0.5/16/74.6

Piperacillin-tazobactam	8/64/82.1	>64/>64/36.8	1/8/100.0	32/>64/37.5
Meropenem	≤0.06/≤0.06/99.4	≤0.06/>8/71.9	≤0.06/0.12/100.0	≤0.06/0.12/96.6
Levofloxacin	>4/>4/23.4	>4/>4/41.1	>4/>4/15.8	0.25/>4/77.7
Gentamicin	2/>8/51.8	>8/>8/46.3	4/>8/57.9	≤1/>8/79.2
a. Includes *Citrobacter* spp., *Enterobacter* spp., indole-positive Proteae and *Serratia* spp. with CAZ MIC ≥8 mg/L. b. % inhibited at ≤2/≤8 mg/L (CLSI; cefepime low/high dose).				