

P0806

Paper Poster Session

Antimicrobial susceptibility testing of Gram-negative bacteria

WCK 4282 (cefepime-tazobactam) MIC quality control ranges using a multi-laboratory study design

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Background: We conducted a study to establish MIC quality control (QC) ranges for WCK 4282 (cefepime-tazobactam) with tazobactam at a fixed concentration of 8 mg/L, using the reference broth microdilution (BMD) method. Cefepime-tazobactam is under clinical development for the treatment of serious Gram-negative infections.

Material/methods: An eight laboratory study design followed CLSI M23-A3 guidelines. Seven QC strains were tested (*Escherichia coli* ATCC 25922 [EC25922], *E. coli* NCTC 13353 [EC13353], *Klebsiella pneumoniae* ATCC 700603 [KPN700603], *Pseudomonas aeruginosa* ATCC 27853 [PSA27853], *Haemophilus influenzae* ATCC 49247 [HI49247], *Streptococcus pneumoniae* ATCC 49619 [SPN49619] and *Staphylococcus aureus* ATCC 29213 [SA29213]), using three media lots (three manufacturers) of cation-adjusted Mueller-Hinton broth (CA-MHB), Haemophilus Test Medium (HTM) and CA-MHB supplemented with 2.5-5% lysed horse blood. Ten replicate tests were performed for each QC organism generating 240 BMD values/QC strain (1,680 total results). Cefepime and meropenem were used as control agents.

Results: A cefepime-tazobactam MIC QC range of 0.03/8 – 0.12/8 mg/L was proposed for EC25922 (see Table), which included all reported results and a mode at 0.06/8 mg/L (203 of 240 results; 84.6%). EC13353 is a CTX-M-15 producer and was included to properly evaluate tazobactam inhibition effect. The proposed MIC QC range of 0.06/8 – 0.25/8 mg/L for EC13353 included 95.8% of results. The KPN700603 strain, a SHV-18 producer, provided a three doubling dilution QC range of 0.12/8 – 0.5/8 mg/L with 99.2% of the results included. A four doubling dilution range was proposed for PSA27853 (0.5/8 – 4/8 mg/L) due to a bimodal MIC distribution. A three doubling dilution QC range was proposed for both HI49247 and SPN49619, which included 100.0 and 95.8% of MIC results, respectively. A three doubling dilution range of 1/8 – 4/8 mg/L included all MIC results for SA29213, with >89% of the results at the modal MIC (2/8 mg/L). No significant differences were noted among media lots. Only two of 1,120 MIC values (0.2%) generated for the control agents were outside the CLSI published QC ranges. The CLSI Subcommittee on Antimicrobial Susceptibility Testing approved these WCK 4282 (cefepime-tazobactam) QC ranges in January 2015.

Conclusions: The recently approved MIC QC ranges for WCK 4282 (cefepime-tazobactam) should accurately guide clinical or reference laboratories participating in the testing of clinical trial isolates, and facilitate the regulatory review process for this investigational antimicrobial combination.

QC organism (ATCC no.)	WCK 4282^a MIC (mg/L) QC ranges (% of results in range):
<i>E. coli</i> (ATCC 25922)	0.03/8 – 0.12/8 (100.0)
<i>E. coli</i> (NCTC 13353)	0.06/8 – 0.25/8 (95.8)

<i>K. pneumoniae</i> (ATCC 700603)	0.12/8 – 0.5/8 (99.2)
<i>P. aeruginosa</i> (ATCC 27853)	0.5/8 – 4/8 (100.0)
<i>H. influenzae</i> (ATCC 49247)	0.5/8 – 2/8 (100.0)
<i>S. pneumoniae</i> (ATCC 49619)	0.03/8 – 0.12/8 (100.0)
<i>S. aureus</i> (ATCC 29213)	1/8 – 4/8 (100.0)

a. Cefepime-tazobactam with tazobactam at fixed concentration of 8 mg/L