**P1259**
**Paper Poster Session**
**Cefepime-tazobactam**

# WCK 4282 (high-dose cefepime-tazobactam) – assessment of synergy through time-kill curve and MIC determination against Pseudomonas aeruginosa producing OXA and VEB beta-lactamases

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**Background:** *Pseudomanas aeruginosa* (PS) deploy multiple resistance mechanisms and therefore pose significant therapeutic challenge. In addition to AmpC and ESBL, clinical PS isolates also harbour OXA and VEB resistance determinants. Typically, these genotypes impose high degree of cephalosporin and piperacillin (PIP)-tazobactam (TAZ) resistance, but generally retain carabapenem susceptibility. However, concurrent over-expression of efflux and/or porin down-regulation might impart even carbapenbem resistance. Development of novel combination therapy based on clinically established agents is an attractive strategy of providing safe and effective treatment. WCK 4282 [Cefepime (FEP)-Tazobactam (TAZ)] is currently under development for treating MDR Gram-negative infections and has been recently evaluated in Phase-I studies in Europe. In this study, we evaluate the synergy between FEP and TAZ employing time-kill and MIC studies against PS harbouring OXA and VEB.

**Material/methods:** FEP-TAZ and comparator MICs were determined by CLSI agar dilution method against 31 PS strains collected from Indian tertiary-care hospitals. Briefly, for time-kill studies, the exponentially growing culture was diluted appropriately in fresh CAMHB to attain 1-5 $\times 10^6$ CFU/mL. Antibacterial agents were added to the culture medium and incubated under shaking conditions. The viable counts were enumerated periodically up to 8h by plating aliquots of serially diluted culture.

**Results:** For 75% of PS strains TAZ reduced the MIC of FEP by 4-8 times. Overall FEP-TAZ MICs were comparable to ceftazidime (CAZ)-avibactam (AVI) and 2-4 times lower than ceftolozane (TOL)-TAZ. Interestingly, FEP-TAZ at its proposed PK-PD breakpoint (≤ 16/8 µg/mL) provided 1.5-1.7 $\log_{10}$ CFU/mL kill for 2 strains (PS Q124 and PS S533) showing FEP-TAZ MIC of 32 µg/mL. For the other two strains with MIC of 16 µg/mL, FEP (16 µg/mL)- TAZ (8 µg/mL) provided 2.44–2.73 $\log_{10}$ CFU/mL kill. Comparable extent of cidality was not observed with comparators when tested at their respective CLSI denoted susceptible (CAZ-AVI and PIP-TAZ), intermediate (TOL-TAZ) breakpoints or even higher concentrations [imipenem (IPM) and meropenem (MEM)]. For all the above strains stand-alone FEP did not show bactericidal effect up to 32 µg/mL.

| Antibacterial agent | MIC (µg/mL) | | |
|---|---|---|---|
| | Range | $MIC_{50}$ | $MIC_{75}$ |
| FEP | 4 – >256 | 32 | 128 |
| FEP + TAZ (8 µg/mL) | ≤0.25 – 32 | 8 | 16 |
| TOL + TAZ (4µg/mL) | ≤0.5 – 128 | 16 | 64 |
| PIP + TAZ (4 µg/mL) | 2 – >128 | 16 | 64 |
| CAZ + AVI (4 µg/mL) | ≤0.25 – 64 | 4 | 16 |
| MEM | ≤0.5 – 128 | 2 | 4 |

| | | | |
|---|---|---|---|
| IPM | ≤0.5 – 16 | 1 | 4 |

**Conclusions:** Cumulatively, based on overall MIC and cidality assessment against high FEP-TAZ MIC strain, WCK 4282 demonstrates therapeutically relevant activity against OXA and VEB harbouring PS strains and warrants further investigations.