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P2128 The pharmacodynamic target of cefepime and its reduction at higher MICs

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Background: Cefepime is a cephalosporin belonging to the β-lactam class of antibiotics with activity against a wide range of Gram-negative bacteria, including Enterobacterales and *P. aeruginosa*. Despite its long term use, surprisingly few preclinical pharmacodynamic data are available. We evaluated the exposure response relationship of cefepime in the neutropenic lung and thigh model.

Materials/methods: A standard neutropenic thigh and lung model was used in CD-1 mice. A total of 29 Enterobacterales (*E. coli*, *K. pneumoniae* and *E. cloacae;* n=17 in the lung- and n=14 in the thigh model) and 10 *P. aeruginosa* strains (8 lung, 2 thigh) were used, including *E.coli* ATCC25922 and *P. aeruginosa* ATCC27853. Strains harboured a variety of beta-lactamase genes :TEM(-1, -84), SHV(-1, -11, -18), OXA-1, CTX-M(-1,-9,-14,-15,-25,-39), VIM, KPC-2, CMY-2, OprD^{-}, Class A^{-}, Class B^{-}, AmpC^{con}, derepressed AmpC, or chromosomal AmpC. MICs of the strains varied from 0.031-256mg/L. Treatment with cefepime started 2 hours after infection with q2h dosing regimens that continued for 24 hours. Pharmacokinetics of cefepime in mice were determined earlier (AAC2017 61:1). Exposure response curves were constructed for each strain and the static, 1log – and 2log kill %*f*T>MIC determined.

Results: In both the thigh and lung model all exposure-response curves followed a sigmoid pattern, reaching at least stasis. A 1logkill was reached for all except six strains. For Enterobacterales, the mean (range) %*f*T>MIC required for stasis was 7.7 (0-44.6) and 7.4 (0-34.4) in the lung and thigh, respectively. For Pseudomonas this was 10.1 (1.6-26.2) and 20.2 (0-40.4) The low numbers prompted further analysis, and showed that strains with higher MICs required less %*f*T>MIC for stasis and 1logkill and were 0 in some cases. A reasonable correlation was therefore found when 0.25x MIC was plotted against %*f*T>0.25xMIC for all strains (see figure) rather than 1xMIC.

Conclusions: The %*f*T>MIC stasis and 1logkill target of cefepime concurs with that of other cephalosporins for wild type strains. However, much less %*f*T>MIC is required at higher MICs. These findings implicate that strains with elevated MICs due to beta-lactamases could be well treated if higher dosing regimens are used and should be explored for cefepime and other cephalosporins.