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P2118 Evaluation of activity and emergence of resistance of fosfomycin and tigecycline against NDM- and KPC-producing *Enterobacter cloacae* in a hollow fibre infection model

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Background: Globally, fosfomycin had increasingly been used to treat extensively drug-resistant (XDR) Gram-negative infections. We previously found that fosfomycin plus tigecycline was bactericidal against XDREC in time-kill studies. We aim to validate this finding in a HFIM.

Materials/methods: A HFIM simulating fosfomycin (8g every 8h over a 4-h infusion) and tigecycline (100mg every 12h) alone and in combination against 2 non-clonal XDREC isolates (EC1268 and EC276) at 5$\log_{10}$CFU/mL were conducted over 80h. Fosfomycin and tigecycline MICs of EC1268 and EC276 were 16mg/L and 1mg/L; and 0.5mg/L and 1mg/L, respectively. EC1268 harboured KPC-2, NDM-1 and *fos*A, while EC276 harboured NDM-7, CTX-M-15 and RmtF. Emergence of resistance against fosfomycin and/or tigecycline in the HFIM was quantified using drug-free and -selective (fosfomycin and/or tigecycline at 3x MIC) media. Serial passages on drug-free and -selective media were carried out over 20 days on resistant isolates obtained at end of HFIM. Antibiotic levels (measured by liquid-chromatography tandem mass-spectrometry) and *in vitro* growth rates to measure biofitness deficit of any resistant subpopulations were analysed via ADAPT 5.

Results: Against both isolates, tigecycline alone exhibited bacteriostatic activity followed by regrowth similar to controls by 24h. EC1268 and EC276 at 48h had increased tigecycline MICs of 4mg/L. Fosfomycin alone exhibited bactericidal activity against EC276 until 72h with no emergence of resistance, but not against EC1268 with regrowth similar to controls by 32h. EC1268 at 48h had increased fosfomycin MICs of ≥2048mg/L. Fosfomycin plus tigecycline were bactericidal against EC1268 for 24h followed by regrowth by 48h. EC1268 had increased fosfomycin and tigecycline MICs of ≥2048mg/L and 4mg/L, respectively. All resistant isolates exhibited slower growth compared to the parent isolate. No reversal of increased fosfomycin and tigecycline MICs was observed in all resistant isolates, suggesting that the selected resistance phenotypes were stable. All pharmacokinetic profiles of the simulated dosing regimens were satisfactory.

Conclusions: Fosfomycin plus tigecycline had rapid, sustained bactericidal activity for 24h against KPC- and NDM-producing XDREC before regrowth sets in with emergence of resistance. Further evaluation of novel dosing strategies such as altering fosfomycin infusion duration is warranted to optimise therapy.