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P2135 PK/PD assessment of fosfomycin in synthetic human urine compared to pooled human urine in a dynamic *in vitro* bladder infection model

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Background: Little is known of the impact of the bladder environment on fosfomycin activity, nor how to best simulate this *in-vitro*. In a dynamic bladder infection *in-vitro* model, we compare laboratory media to pooled human urine and synthetic alternatives to test which best resembles *in-vivo*.

Materials/methods: Urinary fosfomycin concentrations after absorption of a 3g oral dose were simulated with different media: Mueller-Hinton-broth(MHB); MHB with glucose-6-phosphate(MHB+G6P, 25mg/L); female midstream urine(MSU, randomly pooled); female 24h-collected urine(24U, pooled equal volume); artificial urine medium(AUM, Brooks *et al.*1997); synthetic human urine(SHU, Ipe *et al.*2016). Target fosfomycin exposure (C_{max}:1984mg/L, T_{max}:7.5h, AUC_{0-24}:30938mg.h/L) was validated by LC-MS/MS. Pharmacodynamic response of 16-Enterobacteriaceae were examined (8-*E. coli*, 4-*E. cloacae*, 4-*K. pneumoniae*; agar dilution MIC ≤0.25–64mg/L). Broth microdilution(BMD) MIC was performed in MHB, MHB+G6P, 24U and SHU. Pathogen kill/resistance was assessed over 72h by quantitative cultures on drug-free and fosfomycin-containing Mueller-Hinton agar (64mg/L, 512mg/L).

Results: MSU was more dilute than 24U (pH 7.0, osmolality 260mOsm, glucose <0.1mmol/L; compared to pH 6.5, osmolality 468mOsm, glucose 0.2mmol/L). Neither had detectable G6P (<2nmoles). Synthetic urine alternatives differed slightly in chemical composition and pH (AUM pH 6.5; SHU pH 5.6), however, AUM precipitation limited its used. BMD in MHB+G6P demonstrated ≥1-dilution higher MIC compared to agar dilution. Without G6P, MICs were ≥4-fold higher, except two *E. coli* (MIC 32 & 64mg/L) where MIC was unchanged, and were killed in the model in all media. Overall, the same 8-isolates (2 *E. coli*, 2 *E. cloacae*, 4 *K. pneumoniae*) re-grew and 4-isolates (4 *E. coli*) killed in all media. Remaining 4-isolates (2 *E. coli*, 2 *E. cloacae*) re-grew variably in urine and synthetic media. Emergence high-level resistance (proportion >0.01%) depended on media (7/8 MHB+G6P; 6/8 MHB, 4/8 MSU; 5/8 24U; 0/8 AUM; 1/8 SHU). Dynamic *in-vitro* fosfomycin concentrations matched simulation (accuracy: 4.7% ±2.7%), with minimal variation (relative: SD 4.4% ±3.0%).

Conclusions: The media in which fosfomycin susceptibility testing and PK/PD experiments are performed impacts upon results obtained. By using SHU, a more accurate representation of the *in-vivo* PK/PD activity of fosfomycin can be reproduced, although emergence of resistance appears to be restricted.