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O0729 Impact of urine on fosfomycin PK/PD activity in a dynamic bladder infection in vitro model

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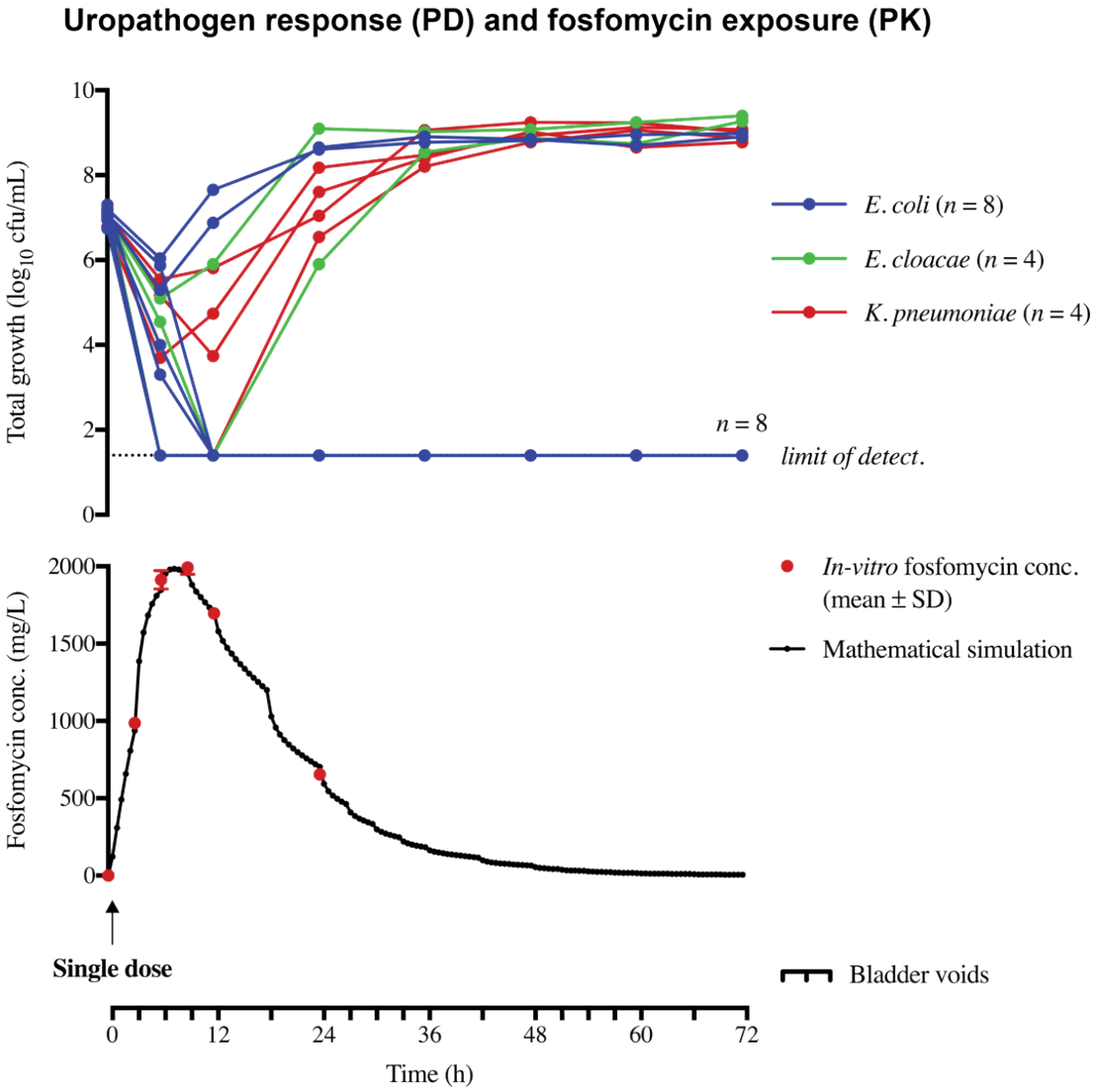
Background: Oral fosfomycin is a first-line antibiotic for uncomplicated urinary tract infections, with good activity against MDR-uropathogens. Little is known of the impact of urine on fosfomycin activity. We simulate urinary fosfomycin pharmacokinetics, using drug-free urine, within a dynamic bladder-infection *in-vitro* model to assess the antibacterial effects.

Materials/methods: A bladder-infection *in-vitro* model simulating urinary fosfomycin concentrations after gastrointestinal absorption of a 3g dose was used using pooled, drug-free urine, pH 7.0, from healthy female volunteers, filtered prior to use. Fosfomycin exposure (PK simulation: C_{max} 1984mg/L, T_{max} 7.5h, $AUC_{0\text{-}24}$ 30938mg.h/L) was validated by LC-MS/MS measurements from bladder compartments during voiding time-points. Pharmacodynamic response of 16-Enterobacteriaceae strains were examined (8 *E. coli*, 4 *E. cloacae*, 4 *K. pneumoniae*; agar dilution MIC 0.25–64mg/L). Pathogen kill and resistance was assessed over 72h by quantitative cultures on drug-free and fosfomycin-containing Mueller-Hinton agar (64mg/L, 512mg/L).

Results: Observed *in-vitro* fosfomycin concentrations closely matched the simulation (see figure). Eight-isolates were killed. Isolates that re-grew had significant rise in total population fosfomycin MIC (MIC_{50} 12mg/L, MIC_{90} 16mg/L; to MIC_{50} 128mg/L, MIC_{90} >1024mg/L, p=0.0078). All *K. pneumoniae* isolates re-grew regardless of MIC. For *E. coli* and *E. cloacae* isolates, PK/PD EI_{50} for effective kill (72h $\log_{10}$cfu/mL) were: *f*$AUC_{0\text{-}24}$/MIC 6777, *f*C_{max}/MIC 435 (Hill-slope -7.2, R^2 0.997 for both), *f*Time >4xMIC 52h (Hill-slope -44.9, R^2 0.997). Area-under-time-kill-curve demonstrated similar results: *f*$AUC_{0\text{-}24}$/MIC 5744, *f*C_{max}/MIC 368 (Hill-slope -3.1, R^2 0.996 for both), *f*Time >4xMIC 51h (Hill-slope -17.9, R^2 0.995). The exposure-response curves were steep. The proportion of resistant sub-population at baseline was also related to effective kill (EC_{50} 0.0001%, Hill-slope 2.1, R^2 0.998) and area-under-time-kill-curve (EC_{50} 0.0001%, Hill-slope 1.3, R^2 0.991). Two-*E. coli* isolates identified as outliers in non-linear regression analysis, were killed despite baseline fosfomycin MIC 32 and 64mg/L, but lacked a detectable sub-population.

Conclusions: Compared to Mueller-Hinton broth with glucose-6-phosphate, human urine impedes fosfomycin activity, despite concurrent limitations on uropathogen growth. Of clinical significance, *E. coli* and *E. cloacae* isolates with MIC >4mg/L are not reliably killed in urine, together with all *K. pneumoniae* isolates. Emergence of resistance was significant. These results challenge oral fosfomycin dosing and clinical breakpoints for UTIs.


Uropathogen response (PD) and fosfomycin exposure (PK)
Total growth (log10 cfu/mL)
10
8
6
4
2
0
E. coli (n = 8)
E. cloacae (n = 4)
K. pneumoniae (n = 4)
n = 8
limit of detect.
Fosfomycin conc. (mg/L)
2000
1500
1000
500
0
In-vitro fosfomycin conc. (mean ± SD)
Mathematical simulation
Single dose
Bladder voids
0
12
24
36
48
60
72
Time (h)