Dynamic simulation of oral fosfomycin for enterococcal UTI treatment **is effective** following a **single dose** with high urinary concentrations, or **two doses** given daily with low urinary concentrations.

Oral Fosfomycin Treatment for Enterococcal Urinary Tract Infections in a Dynamic *In Vitro* Model

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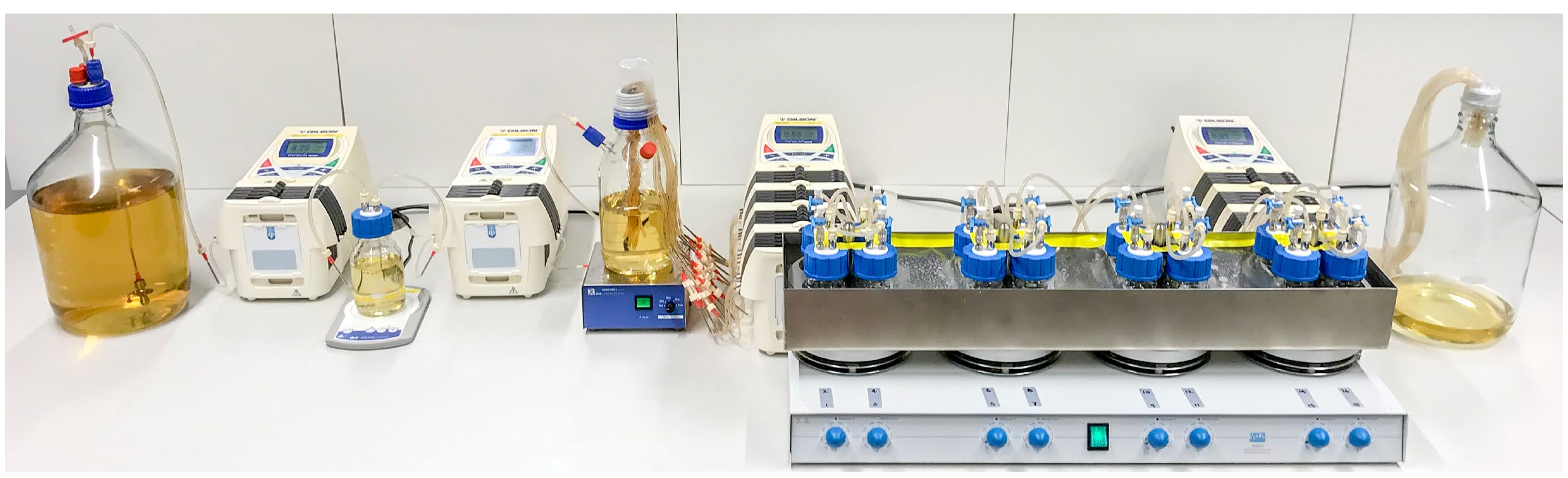


Introduction

- *Enterococcus* spp. are responsible for 5% of community-acquired infections, the third leading cause of hospital-acquired UTIs and implicated in 30% of catheter-associated UTIs.
- Limited oral treatment options available, especially for vancomycin-resistant *Enterococcus* (VRE).
- Oral fosfomycin is a potential therapeutic option, although limited data are available to guide dosing and susceptibility.

Methods

- Eighty-four isolates underwent fosfomycin agar dilution susceptibility testing.
- Sixteen isolates (inc. *E. faecalis* and *E. faecium* ATCC strains), chosen to reflect the MIC range, were tested in a dynamic bladder infection model with synthetic human urine (SHU).
- Isolates were exposed to high and low fosfomycin exposures after a single dose, and two-daily-doses with low exposure.

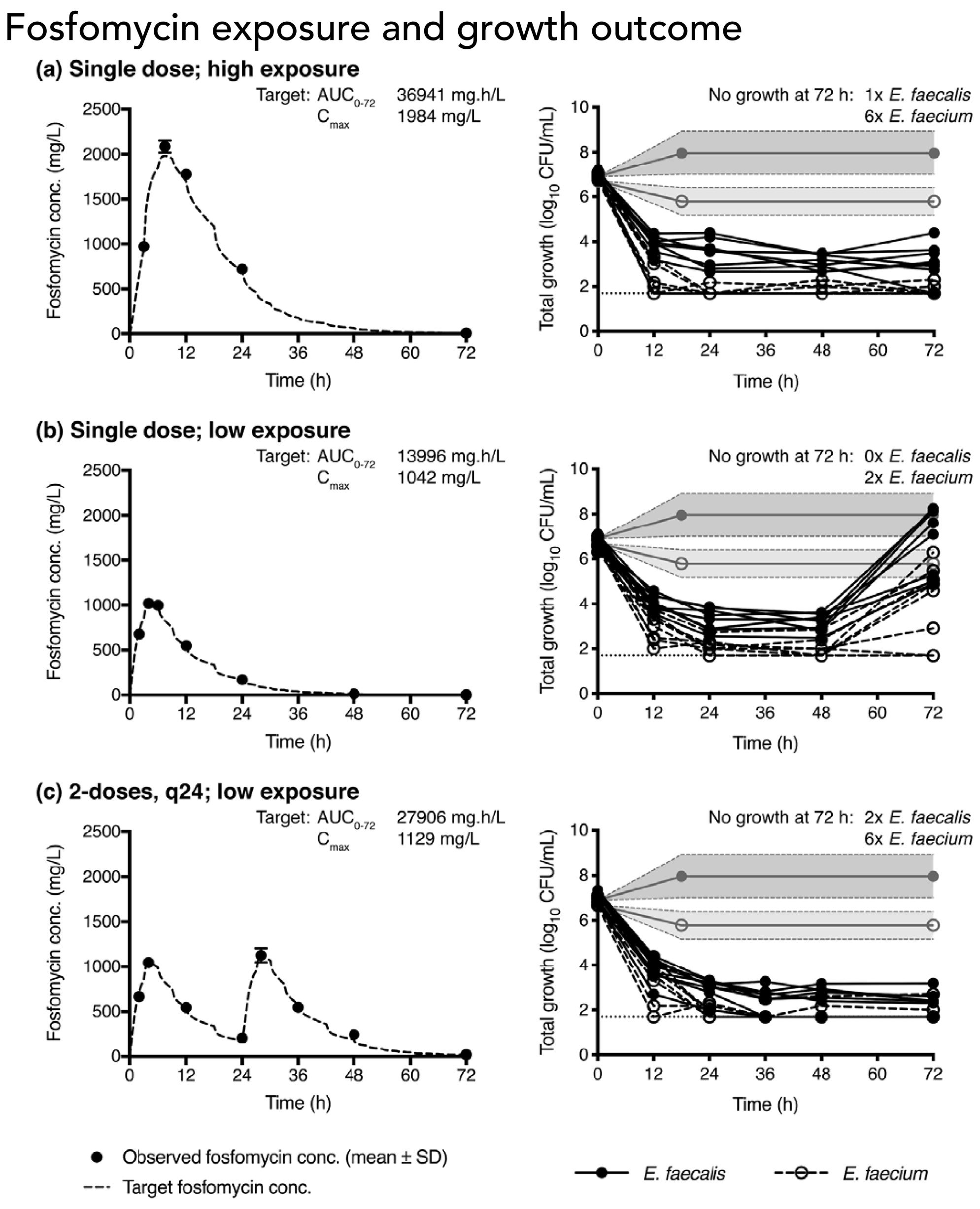
Discussion

- A dynamic *in vitro* model that simulates a range of urinary antimicrobial exposures in the urinary environment, while mimicking human urodynamics.
- Highlights the impact of the laboratory medium on bacterial growth kinetics and antimicrobial activity; important factors when translating *in vitro* results to humans.
- Support the use of oral fosfomycin as a bacteriostatic treatment option for enterococcal UTIs.

Results

- Simulated fosfomycin concentrations closely matched target.
- *E. faecalis* required greater fosfomycin exposure for 3 $\log_{10}$ kill c/w *E. faecium* (*f*AUC/MIC and *f*%T>MIC: 672 and 70% vs. 216 and 51%, respectively).
- Low-level re-growth related to isolate persistence, rather than emergence of resistance (no rise in MIC post-exposure).
- Growth restriction of *E. faecium* in drug-free SHU under dynamic incubation (1 $\log_{10}$ kill) provided additional kill.

Fosfomycin exposure and growth outcome



Limit of detection 50 CFU/mL. Grey lines and shading correspond to ave. (± SD) growth in the bladder infection model in drug-free SHU.

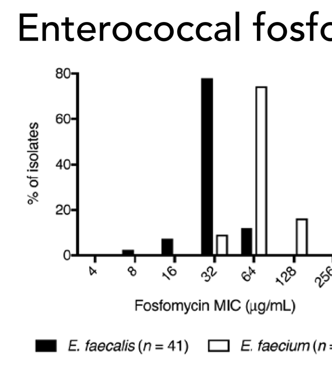
Additional Information

Baseline fosfomycin susceptibility and growth outcomes

Strain	Source	*van* gene	Baseline fosfomycin susceptibility testing					Change in bacterial counts ($\Delta \log_{10}$ CFU/mL)[a]			
			AD MIC (µg/mL)	BMD MIC (µg/mL)			DD (mm)	Drug free control	High exposure	Low exposure	
				MHB	MHB + G6P	SHU			Single dose	Single dose	2-doses, q24
E. faecalis											
42601	Urine	-[b]	8	4	8	8	23	-1.2	-[c]	-1.7	-
36361	Blood	-	16	8	8	8	23	0.9	-4.3	-2.1	-4.7
47130	Urine	-	32	64	64	16	23	1.7	-3.7	1.4	-4.9
16313	Urine	-	32	64	32	16	18	1.1	-4.1	0.1	-
29212	ATCC	-	32	32	32	16	17	1.2	-3.7	1.6	-4.9
46182	Blood	-	64	32	64	32	19	1.6	-2.7	0.7	-4.8
46639	Blood	-	64	64	64	16	15	1.6	-4.2	-1.8	-4.7
46222	Blood	-	64	64	64	32	12	1.6	-3.2	2.0	-3.6
E. faecium											
44131	Aspirate	A	32	16	16	16	17	-0.6	-	-	-
20143	Blood	A	32	32	32	32	18	-1.0	-	-3.9	-
12818	Urine	A	32	64	128	32	19	-0.9	-	-1.9	-
35667	ATCC	-	64	64	64	32	14	0.2	-5.0	-0.7	-
01976	Urine	A	64	32	32	16	19	-1.6	-	-1.7	-
20292	Urine	B	64	64	64	64	13	-0.7	-	-1.8	-4.7
08582	Urine	A	64	128	64	32	14	-1.2	-4.7	-1.1	-4.1
14242	Blood	A	128	64	64	32	15	-1.5	-	-	-

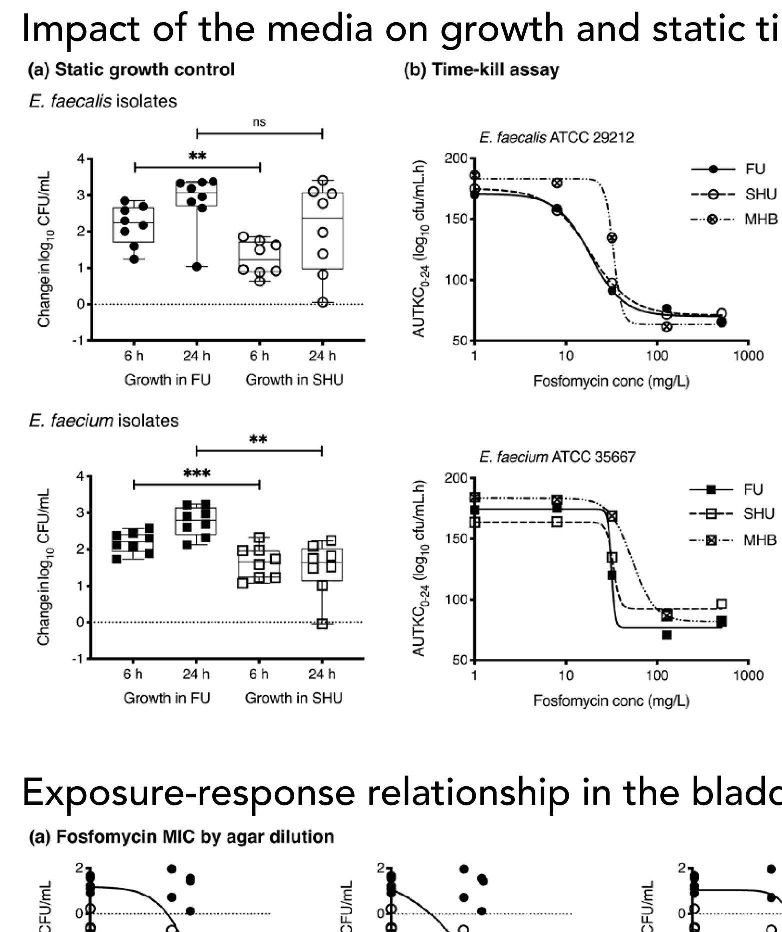
[a] Starting inoculum approx. 7.0 $\log_{10}$ CFU/mL.
[b] *vanA* and *vanB* gene not detected.
[c] No growth detected after 72 h incubation.
AD, agar dilution. BMD, broth microdilution. MHB, Mueller-Hinton broth. G6P, glucose-6-phosphate. SHU, synthetic human urine. DD, disk diffusion.

Enterococcal fosfomycin MIC distribution



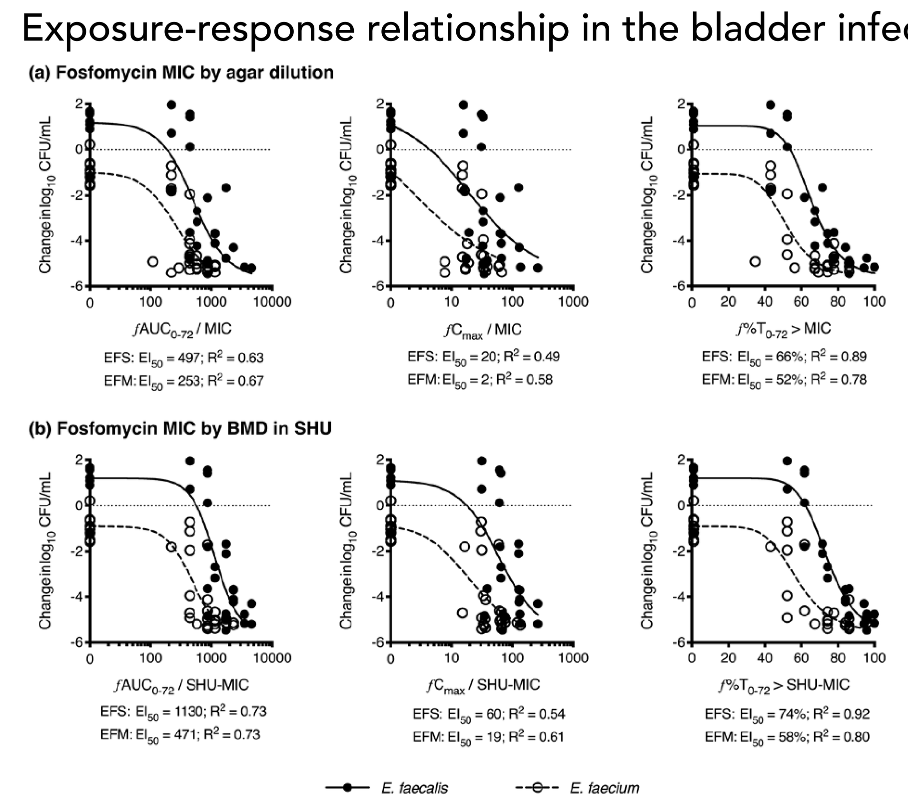
41 *E. faecalis* and 43 *E. faecium* isolates screened for susceptibility by agar dilution. *E. faecalis* MIC_{50}/MIC_{90}=32/64 µg/mL, *E. faecium* MIC_{50}/MIC_{90}=64/128 µg/mL.

Impact of the media on growth and static time-kill assay



(a) Growth capacity of 8 *E. faecalis* and 8 *E. faecium* in pooled female urine (FU) and synthetic human urine (SHU). Average starting inoculum 4.9 ± 0.2 $\log_{10}$ CFU/mL. ns, not significant. ** $p \leq 0.01$. *** $p \leq 0.001$. (b) Comparison of exposure-response curves of *E. faecalis* and *E. faecium* ATCC strains from static time-kill assays performed in FU, modified-SHU and Mueller-Hinton broth (MHB). $R^2 > 0.99$ for all E_{max} non-linear regression lines.

Exposure-response relationship in the bladder infection model



MIC values determined by (a) agar dilution and (b) broth microdilution (BMD) in synthetic human urine (SHU). Variable slope E_{max} non-linear regression lines for *E. faecalis* (EFS) and *E. faecium* (EFM).

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