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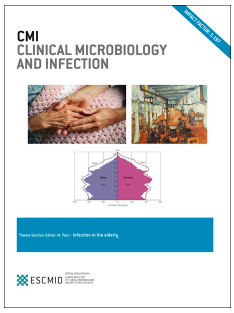

Population pharmacokinetics and pharmacodynamics of fosfomycin in non-critically ill patients with bacteremic urinary infection caused by multidrug-resistant *Escherichia coli*

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Population pharmacokinetics and pharmacodynamics of fosfomycin in non-critically ill patients with bacteremic urinary infection caused by multidrug-resistant *Escherichia coli*

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Keywords. Fosfomycin, pharmacokinetics, pharmacodynamics, mathematical model, PTA, susceptibility breakpoints.

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ABSTRACT

Objective

The aim of the present study was to describe the population pharmacokinetics of fosfomycin for patients with bacteraemic urinary tract infection (B-UTI). The analysis identified optimal regimens, based on pharmacodynamic targets and assessed the adequacy of CLSI and EUCAST susceptibility breakpoints for *Escherchia coli*.

Methods

Sixteen patients with B-UTI caused by multidrug-resistant *E. coli,* (FOREST clinical trial) received intravenous fosfomycin (4g/Q6h) were analysed. A population pharmacokinetic analysis was performed, and Monte Carlo simulations were undertaken using 4g/Q6h or 8g/Q8h. The probability of pharmacodynamic target attainment (PTA) was assessed using pharmacodynamic targets for *E. coli* for static effect, 1-log drop in bacterial burden (murine thigh infection model, Lepak *et al.* AAC 2017), and for resistance suppression (hollow fiber infection model, Docobo-Perez *et al.* AAC 2015).

Results

Sixty-four plasma samples were collected over a single dosing interval (day 2 or 3 after starting fosfomycin treatment). Fosfomycin concentrations were highly variable. PTA analysis showed mild improvement by increasing fosfomycin dosing (4g/Q6h vs 8g/Q8h). These dosages showed success for decreasing 1-log bacterial burden in 89-96% (EUCAST breakpoints) and 33-54% (CLSI breakpoints) of patients, but unable to reach bacterial resistance suppression targets.

Conclusions

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Fosfomycin concentrations are highly variable, partially explained by renal impairment. The present work supports the use of 4g/Q6h as an effective regimen for the treatment of non-critically ill patients with B-UTI caused by multidrug-resistant *E. coli* as higher dosages might increase toxicity but may not significantly increase efficacy. The current information may suggest the reappraisal of fosfomycin susceptibility breakpoints.

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INTRODUCTION

Fosfomycin is a cell wall synthesis inhibitor with broad spectrum antimicrobial activity [1]. Studies from multiple countries have consistently demonstrated high rates of susceptibility of ESBL- and carbapenemase-producing Enterobacteriaceae [2–4] to fosfomycin. Due to the paucity of active compounds, fosfomycin has been suggested as a potential treatment for severe infections caused by multidrug-resistant Enterobacteriaceae [5]. The oral formulation of fosfomycin has been widely used for the treatment of acute uncomplicated urinary tract infection [6]. In contrast, there is less experience and a relative absence of quality data that supports the use of the intravenous formulation for treatment of invasive infections caused by multidrug-resistant bacteria [7].

Several fosfomycin pharmacokinetic studies have been performed [8,9]. However, to our knowledge only the recent study conducted by Parker *et al.* in critically-ill patients has used a population pharmacokinetic methodology [10]. Moreover, several pharmacodynamic studies have been recently performed just to better understand dose-exposure-response relationships of fosfomycin [5,11]. For example, Lepak AJ *et al.* have recently evaluated the activity fosfomycin was evaluated in the neutropenic murine thigh infection model against *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* strains, including a subset with ESBL and carbapenem resistance phenotype. The study showed that *f*AUC/MIC is the relevant pharmacodynamic index against these multidrug-resistant gram-negative bacteria [12]. Optimized dosing of fosfomycin has not yet been explored using these *in vivo* pharmacodynamic targets.

Thus, the aim of the present study was to better understand the variability of fosfomycin pharmacokinetics in patients with bacteraemic urinary tract infection (B-

UTI) and to identify optimal regimens that are based on the recently described pharmacodynamic targets for orders of logarithmic killing and resistance suppression. Such as approach also provides an opportunity to reflect on the adequacy of currently recommended *in vitro* susceptibility breakpoints established by CLSI and EUCAST committees for *E. coli* clinical isolates.

MATERIAL AND METHODS

Study design and patient's population

Patients with B-UTI due to multidrug-resistant *E. coli* were eligible for the FOREST clinical trial (NCT02142751) [13]; 16 consecutive patients hospitalised at University Hospital Virgen Macarena (Sevilla) participated in the trial between July 2013 and October 2016 [14]. The study was approved by the Regional Ethics Committee. Signed informed consent was obtained from all patients. Demographic data (including age, sex, height, and weight of the patient), site of infection, baseline renal function, previous treatments and the fosfomycin minimal inhibitory concentration (MIC) of isolates were recorded. Serum creatinine concentrations were collected as a component of standard-of-care and creatinine clearance was calculated daily using the Cockcroft-Gault equation [15]. The dose of fosfomycin was administered 4g/Q6h (1-hour infusion) according to the clinical trial protocol. Patients with renal impairment (creatinine clearance of 20-40 ml/min) received 4g/Q12h (1-hour infusion) [14].

Pharmacokinetics.

Blood samples were collected 48 hours after the first administration of drug, at 1, 3, 5 and 6 hours after the start of fosfomycin administration for patients with a CrCl >40 mL/min, and 1, 6, 8 and 12 hours in patients with a CrCl 20-40 mL/min.

Plasma fosfomycin concentrations were measured using tandem mass spectroscopy (LC-MS/MS), following a method previously described by Li L *et al* [16]. The assay inter-day coefficients of variation (CV) for fosfomycin in serum were ≤10%, with an accuracy range of 91.5 to 109.9%. The lower limit of quantification (LLOQ) assay for plasma was 1 mg/L, with precision at CV<15%, and accuracy range of 88.5 to 112.8%. The assay was linear over its working range (1-1000 mg/L).

Mathematical Model

The nonparametric adaptive grid (NPAG) algorithm, embedded within the Pmetrics software package [17], was used to build a population pharmacokinetic model. For the population pharmacokinetic analysis, the one- and two-compartment linear models were fitted to the plasma fosfomycin concentration data. Covariate model building was performed using sequential assessment of biologically plausible clinical parameters. Forward inclusion was based upon the aforementioned model selection criteria and significant correlation with one of the pharmacokinetic parameters. Creatinine clearance, weight, age, sex and body mass index (BMI) were explored as covariates for each structural model.

The data were weighted by the inverse of the estimated assay variance. This was determined from the quality control samples used to estimate the inter-day assay variance and given by SD (mg/L) = gamma × (0.059 + 0.0118 × C), where C is the fosfomycin concentration. Gamma represents an estimate of process noise and is expressed as multiples of the assay variance [17].

The fit of each model to the data was assessed using a combination of the following: (i) the log-likelihood value, (ii) the Akaike information criterion (AIC), (iii) the coefficients of determination (r^2) from the linear regression of the observed-

predicted plots before and after the Bayesian step, (iv) minimization of bias and imprecisions of the observed-predicted plots, (v) the normalized prediction distribution errors (NPDE), (vi) the distribution of the weighted residual errors, and (vii) the visual predictive check (VPC) plot.

Simulations and probability of target attainment

Monte Carlo simulations were conducted using 2000-patients, using the Monte Carlo simulator within Pmetrics. For simulations, a semi-parametric sampling method available in Pmetrics [17,18] was used. The final model consisted of 11 support points, and each point was a set of model parameter values and the probability of these values to predict observed fosfomycin concentrations in the population. Each support point then served as the mean for a multivariate normal distribution, weighted by the probability of the point, with covariance equal to the covariance matrix of the full model divided by the number of points (*i.e.* 11). The semi-parametric sampling from this weighted, multivariate, multimodal normal distribution was used to generate a novel population of 2000 parameter sets. For the VPC, fosfomycin regimens of 4g Q6h (dosage used in the FOREST clinical trial for patients with CrCl >40 mL/min) and 4g Q12h for patients with renal impairment (CrCl 20-40 mL/min) were simulated. For the probability of pharmacodynamic target attainment (PTA) analysis, fosfomycin regimens of 4g Q6h and 8g Q8h (mutant prevention dosage observed in a hollow-fiber infection model and also the maximum dosage approved by the Spanish Agency of Medicines and Medical Devices for parenteral fosfomycin) were analysed [5,14,19]. The PTA was assessed over a range of MICs between 0.125 and 1024 mg/L in doubling dilutions. The pharmacodynamic indices targeted for efficacy were obtained from Lepak AJ *et al.* for *E. coli* (*i.e.* $fAUC_{0\text{-}24}$/MIC of 19.3 for static effect and $fAUC_{0\text{-}24}$/MIC of 87.5 for

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decreasing 1-log the bacterial burden) [12]. The pharmacodynamic indices targeted for resistance suppression (*i.e.* $fAUC_{0\text{-}24}$/MIC of 3136) were obtained from our previous work. Protein binding is negligible for fosfomycin and was ignored in these calculations [20].

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RESULTS

Patients

The demographic and clinical characteristics of the patients are shown in Table 1. All patients received a dose of 4 g of fosfomycin every 6 hours (1-hour infusion), except for 4 patients with creatinine clearance of 20-40 ml/min, who received 4 g every 12 hours.

A total of 64 plasma samples were collected over a single dosing interval at steady state (day 2 or 3 after starting fosfomycin treatment) from 16 enrolled patients. None of the determinations were below de limit of quantification.

Pharmacokinetics and mathematical model

The mean (SD) maximum fosfomycin plasma concentration (Cmax) for patients at steady state was 422.6 mg/L (186.8 mg/L). The comparison between the variability observed in Cmax concentrations between the current study and other previous fosfomycin pharmacokinetic studies is shown in Figure 1. The mean (SD) area under the curve (*f*AUC) for the first 24h, estimated from using the posterior estimates from each patient, was 5215.08 mg/L*h (1972.27 mg/L*h). The fosfomycin concentration-time data were best described by a two-compartment linear model, which was associated with a significant reduction in the log-likelihood value compared with the one-compartment model (LLD=132, $p<0.05$). A linear model using creatinine clearance best described CL. Inclusion of this covariate with an intercept reduced the log-likelihood value by 13 points ($p<0.001$). The incorporation of weight, age, sex or BMI did not improve the model fit. The following final structural model was fitted to the data:

Equation 1:

$$dX_1/dt = R(1) - \left(\frac{intercept + slope \times CrCl}{V_c}\right) \times X_1 - k_{cp} \times X_1 + k_{pc} \times X_2$$

Equation 2:

$$dX_2/dt = k_{cp} \times X_1 - k_{pc} \times X_2$$

Where X_1 and X_2 are the amounts of fosfomycin (in milligrams) in the central compartment and peripheral compartment respectively. R(1) is the infusion rate of fosfomycin into central compartment. The renal clearance of fosfomycin is linearly represented with intercept and slope as parameters and creatinine clearance (CrCl) as covariate. K_{cp} and K_{pc} are the first-order intercompartmental rate constants.

Final population pharmacokinetic parameter estimates are shown in table 2

For the final model, the population and individual observed-versus-predicted plots of the final model are shown in Figure 2. Normalized distribution prediction error (NPDE) results (Q-Q plot and histogram) are summarized graphically in Figure S1. The weighted residual error distributions are shown in Figure S2. Both NPDEs (P=0.599 in the Shapiro-Wilk normality test), the weighted residual error distributions, and VPC plots (Figure 3) suggest that the fit of the model to the data was acceptable. The 11 calculated support points and the covariance matrix in the lower triangular form are shown in Tables S2 and S3, respectively.

Monte Carlo simulations and probability of target attainment

The PTA results for 4 g Q6h and 8 g Q8h as 60-min infusions are displayed in Figure 4. Monte Carlo simulations and PTA analysis showed mild improvement by increasing fosfomycin dosing (4g/Q6h vs 8g/Q8h). PTA of 93.9% (4g/Q6h) and 98.2% (8g/Q8h) were achieved for both dosages using a pharmacodynamic target for bacteriostatic effect (*i.e.* $fAUC_{0\text{-}24}$/MIC of 19.3) for MIC =128 mg/L. Alternatively, using a pharmacodynamic target for 1-log decrease (*i.e.* $fAUC_{0\text{-}24}$/MIC of 87.5), PTA of

89.3% (4g/Q6h) and 96.1% (8g/Q8h) were observed for MIC =32 mg/L for both dosages. Setting a target for resistance suppression (*i.e.* $fAUC_{0-24}$/MIC of 3136) an optimal PTA was reached for MIC of 1 mg/L, 83.2% (4g/Q6h) and 93.4% (8g/Q8h).

Following EUCAST (32 mg/L) and CLSI (64 mg/L) susceptibility breakpoints, the PTA were 89-96% and 33-54%, respectively, for decreasing 1-log bacterial burden. However, a PTA of 0% was observed for bacterial resistance suppression for any of the simulated doses (4g/Q6h or 8g/Q8h), irrespective of the susceptibility breakpoints that were used.

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DISCUSSION

The global threat of multidrug resistant bacteria together with the paucity of new active antimicrobials has generated renewed interest in old drugs such as fosfomycin. The World Health Organization has included fosfomycin in "Group 3 - Reserve Group Antibiotics" [21]. This group includes antibiotics that should be reserved as options of "last resort". Such agents should be widely accessible, but their use should be tailored to highly specific patients and settings, when all alternatives have failed (e.g., serious, life-threatening infections due to multi-drug resistant bacteria). However, due to lack of clinical interest in fosfomycin in the past decades, many questions regarding the pharmacokinetic and pharmacodynamic of this drug, and therefore appropriate dosing, remain unanswered.

One of the main findings of the present work is the high variability observed in fosfomycin concentration achieved in patients with B-UTI, who were mostly not critically ill, compared to other previous data from healthy subjects and also from non-critically ill patients, using higher dosages (8g Q8h) [9,22,23]. For example, a mean Cmax of 422.6 mg/L (mean CrCl = 70.4 mL/min) was observed in our study, similar to those in Sauerman *et al*. (mean Cmax of 446 mg/L, mean CrCl = 70.4 mL/min) or Wenzler *et al.* (mean Cmax of 370 mg/L, mean CrCl = 139.6 mL/min). Also, the median trough fosfomycin plasma concentration (Cmin) observed in our patients (178.7 mg/L [range 106.11 to 246.93 mg/L]) is closer to that observed by Parker *et al.* in critically ill patients [10], which was 250 mg/L (range, 76 to 684 mg/L) at steady state. This could be explained, in part, by the renal impairment observed in our population that affects fosfomycin pharmacokinetics (*i.e.* CrCl median of 70.5, which is slightly higher than 59 mL/min observed in Parker *et al*.). Thus, variations in the creatinine clearance could partially explain the differences observed with respect to healthy

subjects [23]. Based on these observations, patients treated with fosfomycin would benefit of a dose individualisation based on creatinine clearance to avoid under or overdosing and thus reducing chance of therapeutic failure or toxicity.

Recent studies performed by Lepak *et al.*[12] and Docobo-Pérez *et al.* [5] provided the pharmacodynamic targets for fosfomycin and enabled Monte Carlo simulation and PTA calculation. These analyses raised several points that deserve emphasis. First, an increase in the fosfomycin dosage, from 4g/Q6h (16g/day) to 8g/Q8h (24g/day, which is the maximum dosage approved by the Spanish Agency of Medicines and Medical Devices) only slightly improves the PTAs [19]. This is of key importance, because a reduction of 8g of fosfomycin per day means a reduction 2.56 g of sodium (every gram contains 0.32 g of sodium) [19], reducing the risk adverse events including hypocalcemia, bradycardia or even heart failure [23,24], which may be particularly relevant for hospitalised patients.

An appraisal of the current susceptibility breakpoints for fosfomycin set by EUCAST or CLSI using the pharmacodynamic analyses show that efficacy would be better related with those of EUCAST (*i.e.* susceptible ≤32 mg/L, resistant >32mg/L), rather than those of CLSI (*i.e.* susceptible ≤64 mg/L, resistant ≥256mg/L) [25,26]. However, from the perspective of bacterial resistance suppression, all breakpoints are likely too high. It is also important to note that a number of factors may contribute to the appearance or selection of fosfomycin-resistant subpopulations, such as the mutational status of the bacterial strain (*i.e.* hypermutator phenotype), the presence of high bacterial burden, or the existence of low-resistant mutations that may facilitate the selection of highly resistant mutants [27–29].

There are several limitations of the present study. The sample size was not sufficient to measure the impact of different drug exposures on clinical outcomes. The

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dose of 8g/Q8h have been generated from the mathematical model assuming a linear pharmacokinetic of fosfomycin. Also, the visual predictive check showed some underprediction in the group 4g/Q12h. Given the low renal function in this subset of patients (n=4) and the relatively small cohort of 16 patients, this may also affect the ability of the model to identify other relevant covariates. Moreover, the pharmacodynamic targets for efficacy purposed by Lepak *et al.* in the neutropenic murine thigh infection model and our suggested target for resistance-prevention observed in the hollow-fiber infection model may underestimate the efficacy of fosfomycin for immunocompetent patients and have not been so far validated by other studies. The neutropenic murine thigh infection model evaluated the microbiological efficacy only during the first 24 hours [12]. However, different studies using hollow-fiber infection models have shown microbiological failures occurring later due to the selection of subpopulations with reduced susceptibility or appearance of resistant mutants [5,30]. This suggest that the pharmacodynamic targets that drives the efficacy of fosfomycin in complex infections may need to consider suppression resistant mutants, which is often not considered in the setting of breakpoints [5]. Finally, the existing controversy about how to perform and interpret the fosfomycin susceptibility tests could hinder the use of the MIC as a reliable measure of potency [28,29].

In conclusion, fosfomycin concentrations are highly variable and depended to some extent on the degree of renal dysfunction even for non-critically-ill patients. A regimen of 4g Q6h or 8g Q8h appears effective for the treatment of non-critically ill patients with bacteremic urinary infection caused by multidrug-resistant *E. coli.* However, these regimens may still not be suitable (as monotherapy) for critically-ill patients with a high bacterial burden where the emergence of drug resistance is likely to occur. Higher dosages may increase the probability of toxicity, but would not be

expected to significantly increase efficacy. Our study suggests that revision of both EUCAST and CLSI breakpoints may be required for some clinical contexts and patient subgroups. Finally, all these results must be prospectively validated with further pharmacokinetic and clinical outcome data.

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Transparency declaration

JRB has been scientific advisor for research projects for AstraZeneca and InfectoPharm, and was speaker for Merck at accredited educational activities. JRB and AP received funding for research from COMBACTE-NET (grant agreement 115523), COMBACTE-CARE (gran agreement 115620), and COMBACTE-MAGNET (grant agreement 115737) projects under the Innovative Medicines Initiative (IMI), the European Union and EFPIA companies in kind. WWH has received research funding

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from Pfizer, Gilead, Astellas, AiCuris, Amplyx, Spero Therapeutics, and F2G and acted as a consultant and/or given talks for Pfizer, Basilea, Astellas, F2G, Nordic Pharma, Medicines Company, Amplyx, Mayne Pharma, Spero Therapeutics, Auspherix, Cardeas, and Pulmocide. All other authors have no conflicts to declare.

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Table 1. Baseline patient characteristics of 16 patients with urinary tract bacteraemia due to multidrug-resistant *E. coli*.

Variable	No. of cases (percentage) except where specified
Male gender	9/16 (56.3)
Age in years, median (range)	68.5 (63-83)
Body mass index ≥25	13 (81.25)
CrCl in mL/min, median (range)	70.5 (30.4-98.6)
McCabe Index	1 (6.3)
Comorbidities	
Diabetes mellitus	9/16 (56.3)
Chronic pulmonary disease	2/16 (12.5)
Cancer	2/16 (12.5)
Community-acquired bacteremia	9/16 (56.3)
ESBL-producing *E. coli*	1/16 (6.3)
MIC of fosfomycin	
0.5 mg/L	1
1 mg/L	8
2 mg/L	2
4 mg/L	1
8 mg/L	2
16 mg/L	2
Outcome	
Early clinical response (day 5)	13/14 (92.86)
Early microbiological response (day 5)	13/14 (92.86)
Microbiological cure	13/14 (92.86)

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Table 2. Final population pharmacokinetic parameter estimates for 16 patients with bacteremic urinary tract infection caused by multidrug-resistant *Escherichia coli* treated with fosfomycin.

Parameter	**Mean**	**SD**	**%CV**	**Median**
Drug Clearance, CL (L/h) CL= (Intercept + (creatinine clearance × slope)	2.430	1.643	67.636	2.209
Intercept (L/h)	1.129	1.176	104.101	0.760
Slope	0.27	0.157	58.005	0.269
Inter-compartmental transfer rate constants				
K_{cp} (h^{-1})	8.275	12.908	155.983	0.140
K_{pc} (h^{-1})	65.419	29.201	44.636	80.612

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Figure 1. Variability observed in fosfomycin concentrations with respect to other pharmacokinetic studies. A) Mean (± standard deviation) maximal plasma fosfomycin concentrations (Cmax) and B) median (± range) trough fosfomycin plasma concentration (Cmin).

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Figure 2. (A) Plot of population predicted concentrations versus observed concentrations. (B) Plot of individual predicted concentrations versus observed concentrations (where the data presented on both the x and y axes are concentrations in milligrams per liter). Continuous line represents the regression line and broken line is the line of identity.

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Figure 3. Monte Carlo simulations (n=2000) and a visual predictive check of the observed (open circles) over the simulated (lines) data is shown after treatment with A) 4g/Q6h fosfomycin (1-hour infusion, patients with CrCl >40) or B) 4g/Q12h fosfomycin (1-hour infusion patients with CrCl 20-40 ml/min). Black lines show the median, the 90% prediction intervals (5th to 95th percentiles) and the interquartile ranges (25th to 75th percentiles). Grey dashed lines represent 95% confidence interval.

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Figure 4. Probability of target attainment for *E. coli* for static effect (fAUC$_{0\text{-}24}$/MIC = 19.3), for 1-log bacterial reduction (fAUC$_{0\text{-}24}$/MIC = 87.5), and for bacterial resistance suppression (fAUC$_{0\text{-}24}$/MIC = 3136) at each fosfomycin MIC. Black dashed lines represents EUCAST and CLSI susceptibility breakpoints for fosfomycin.

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Table S1. Individual pharmacokinetic parameters

Patient	Crcl (L/h)	Int (L/h)	Slope	Vc (L)	K_{cp} (h^{-1})	K_{pc} (h^{-1})
1	1.51	0.26	0.13	11.28	13.45	96.26
2	3.75	0.27	0.43	11.81	3.96	76.87
3	1.79	0.43	0.14	10.00	0.01	92.95
4	5.90	0.52	0.33	31.24	32.91	42.00
5	4.23	1.43	0.27	10.00	0.01	80.25
6	5.10	1.26	0.06	11.44	19.95	55.79
7	3.88	0.12	0.46	12.52	0.97	80.43
8	4.89	2.24	0.22	17.60	0.14	83.15
9	6.42	0.70	0.40	11.68	0.02	84.96
10	9.17	0.12	0.46	12.84	0.01	81.36
11	4.23	2.24	0.22	17.60	0.14	83.15
12	5.92	3.55	0.30	10.00	0.64	1.01
13	1.75	0.09	0.001	16.18	40.66	50.81
14	6.29	3.55	0.30	10.00	0.64	1.01
15	0.83	1.22	0.11	11.13	18.88	53.04
16	1.94	0.05	0.48	12.48	0.01	83.69

See Table 2 and the text for parameter definitions.

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Table S2. Bayesian posterior density results used in all simulations.

Support Point	Intercept (L/h)	slope	Vc (L)	K_{cp} (h^{-1})	K_{pc} (h^{-1})	Weighting Fraction
1	0.092	0.001	16.179	40.665	50.809	0.063
2	3.547	0.302	10.003	0.634	1.009	0.096
3	3.559	0.302	10.003	0.643	1.009	0.029
4	0.258	0.127	11.284	13.445	96.261	0.062
5	1.089	0.237	10.275	15.883	45.355	0.034
6	0.022	0.5	11.657	0.004	88.145	0.114
7	1.26	0.058	11.439	19.955	55.786	0.109
8	2.244	0.222	17.602	0.14	83.152	0.131
9	0.43	0.141	10.001	0.009	92.947	0.062
10	0.073	0.47	12.977	0.014	80.972	0.152
11	0.525	0.335	31.241	32.91	41.998	0.063
12	1.431	0.269	10.002	0.009	80.251	0.085

See Table 2 and the text for parameter definitions.

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Table S3. Covariance matrix in the lower triangular form used in all simulations.

Parameter	Intercept (L/h)	slope	Vc (L)	K_{cp} (h^{-1})	K_{pc} (h^{-1})
Intercept (L/h)	1.382				
Slope	-0.033	0.025			
Vc (L)	-0.836	0.023	27.452		
K_{cp} (h^{-1})	-4.156	-1.148	34.544	166.622	
K_{pc} (h^{-1})	-23.017	0.597	-7.398	-96.484	852.674

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Figure S1. Normalized distribution predicted error (NPDE). (A) Q-Q plot of the distribution of the NPDE versus the theoretical normal [N (0, 1)] distribution. (B) Histogram of the distribution of the NPDE with the density of the standard Gaussian distribution overlaid. The results suggest an acceptable fit of the final model to the data.

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Figure S2. A plot of weighted residual error (population predicted concentrations – observed concentration, mg/L) versus population predictions (left) and time of observation (middle); and frequency distribution of the weighted residual errors (right).

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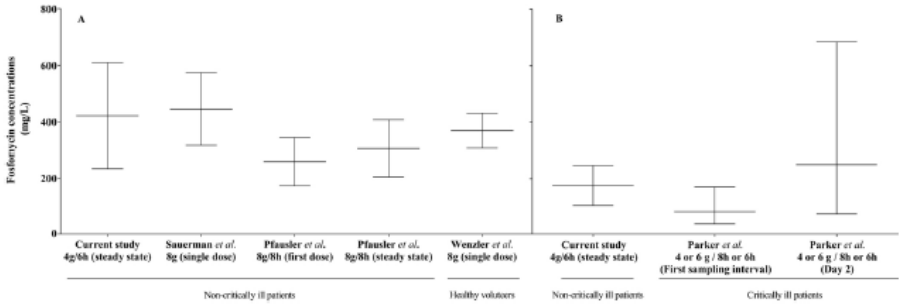
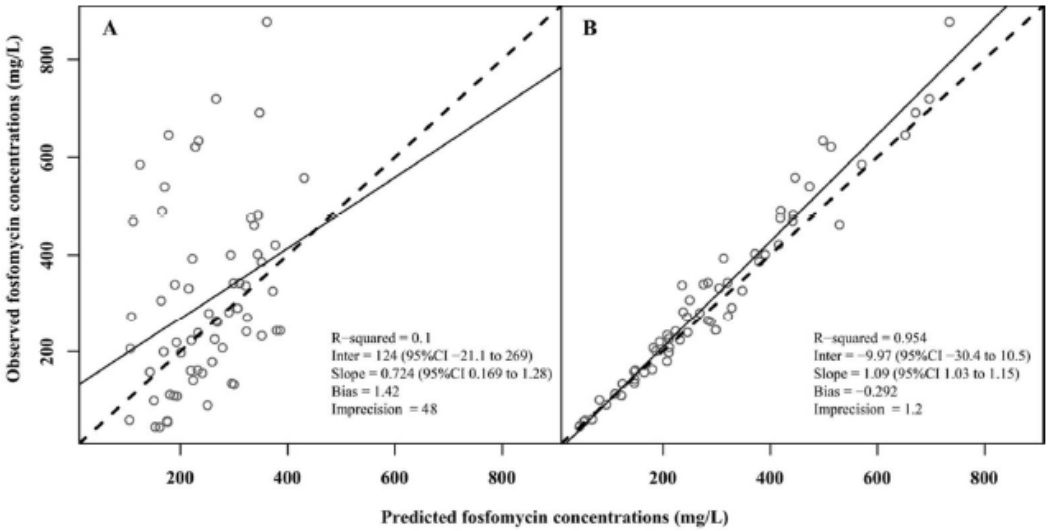
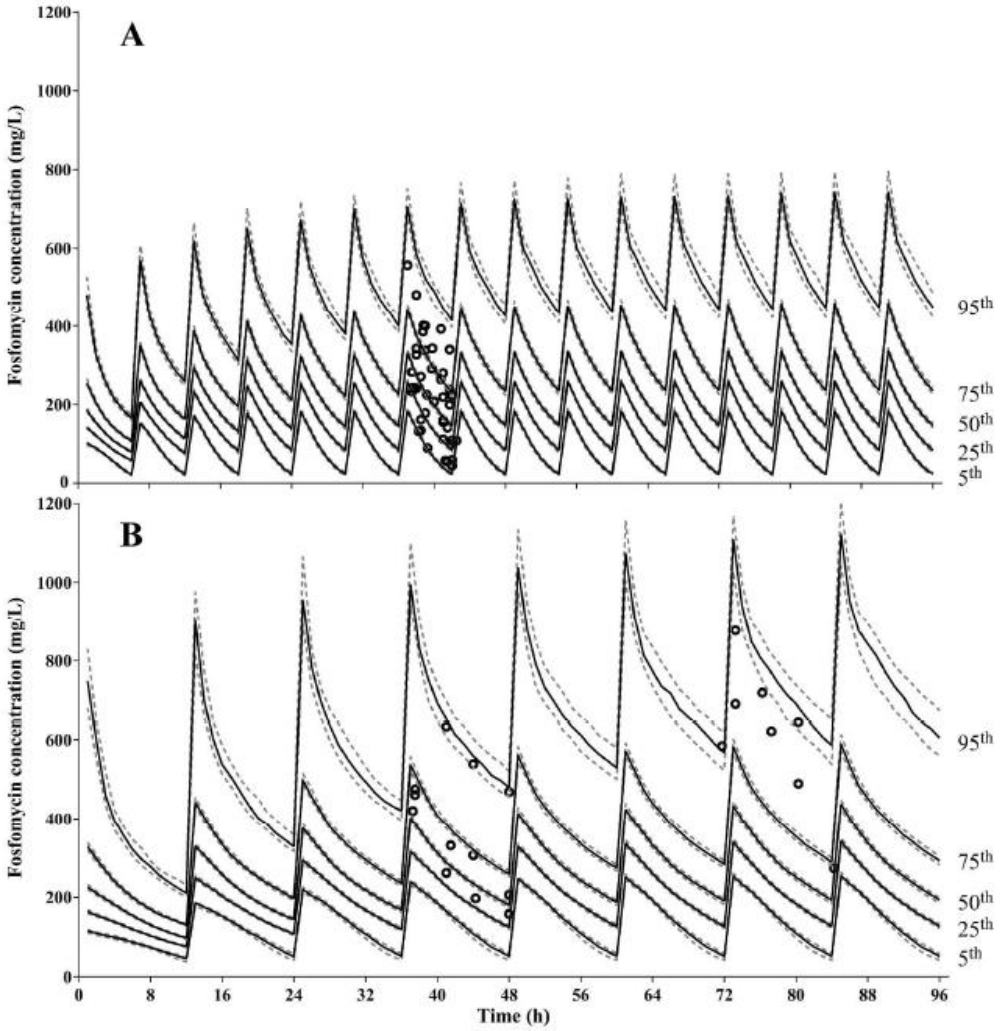
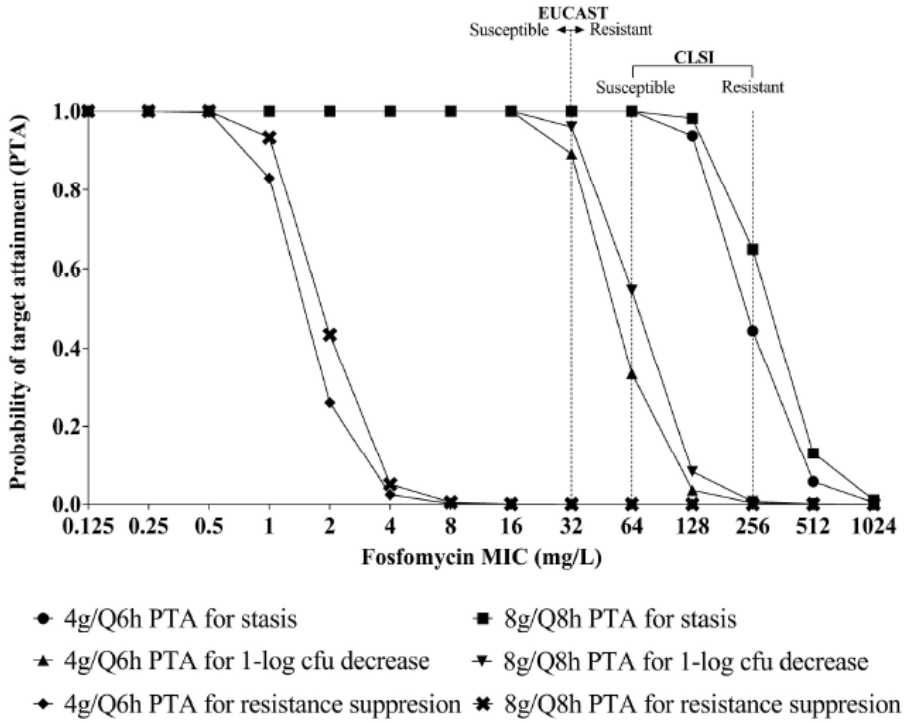

A
B
Fosfomycin concentrations (mg/L)
800
600
400
200
0
Current study 4g/6h (steady state)
Sauerman et al. 8g (single dose)
Pfausler et al. 8g/8h (first dose)
Pfausler et al. 8g/8h (steady state)
Wenzler et al. 8g (single dose)
Current study 4g/6h (steady state)
Parker et al. 4 or 6 g / 8h or 6h (First sampling interval)
Parker et al. 4 or 6 g / 8h or 6h (Day 2)
Non-critically ill patients
Healthy volutoers
Non-critically ill patients
Critically ill patients


A
B
Observed fosfomycin concentrations (mg/L)
200
400
600
800
R−squared = 0.1
Inter = 124 (95%CI −21.1 to 269)
Slope = 0.724 (95%CI 0.169 to 1.28)
Bias = 1.42
Imprecision = 48
R−squared = 0.954
Inter = −9.97 (95%CI −30.4 to 10.5)
Slope = 1.09 (95%CI 1.03 to 1.15)
Bias = −0.292
Imprecision = 1.2
Predicted fosfomycin concentrations (mg/L)


A
B
Fosfomycin concentration (mg/L)
Time (h)
95th
75th
50th
25th
5th
0
200
400
600
800
1000
1200
0
8
16
24
32
40
48
56
64
72
80
88
96



Probability of target attainment for E. coli for static effect (fAUC0-24/MIC = 19.3), for 1-log bacterial reduction (fAUC0-24/MIC = 87.5), and for bacterial resistance suppression (fAUC0-24/MIC = 3136) at each fosfomycin MIC. Black dashed lines represents EUCAST and CLSI susceptibility breakpoints for fosfomycin.

196x157mm (300 x 300 DPI)

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