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Original article

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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ABSTRACT

Objectives: To describe the population pharmacokinetics of fosfomycin for patients with bacteraemic urinary tract infection (BUTI). The analysis identified optimal regimens on the basis of pharmacodynamic targets and assessed the adequacy of Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) susceptibility breakpoints for *Escherichia coli*.

Methods: Data of 16 patients with BUTI caused by multidrug-resistant *E. coli* (FOREST clinical trial) received intravenous fosfomycin (4 g every 6 hours) were analysed. A population pharmacokinetic analysis was performed, and Monte Carlo simulations were undertaken using 4 g every 6 hours and 8 g every 8 hours. The probability of pharmacodynamic target attainment was assessed using pharmacodynamic targets for *E. coli* for static effect, 1-log drop in bacterial burden and resistance suppression.

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. Pharmacodynamic target attainment analysis showed mild improvement by increasing fosfomycin dosing (4 g every 6 hours vs. every 8 hours). These dosages showed success for decreasing 1-log bacterial burden in 89% to 96% (EUCAST breakpoints) and 33% to 54% (CLSI breakpoints) of patients, but they were unable to reach bacterial resistance suppression targets.

Conclusions: Fosfomycin concentrations are highly variable—a fact partially explained by renal impairment. The present work supports the use of 4 g every 6 hours as an effective regimen for the treatment of non–critically ill patients with BUTI caused by multidrug-resistant *E. coli*, as higher dosages might increase toxicity but may not significantly increase efficacy. The current information may suggest that fosfomycin susceptibility breakpoints need to be reappraised. **V. Merino-Bohórquez, Clin Microbiol Infect 2018;24:1177**

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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 extended-spectrum β-lactamase– and carbapenemase-producing *Enterobacteriaceae* [2–4] to fosfomycin. Because of 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 support 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 study conducted by Parker et al. [10] in critically ill patients used a population pharmacokinetic methodology. Moreover, several pharmacodynamic studies have been performed to better understand dose exposure–response relationships of fosfomycin [5,11]. For example, Lepak et al. [12] evaluated fosfomycin activity in the neutropenic murine thigh infection model against *Escherichia coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* strains, including a subset with extended-spectrum β-lactamase and carbapenem resistance phenotype. The study showed that the area under the unbound concentration–time curve (*f*AUC) to minimum inhibitory concentration (MIC) ratio (*f*AUC/MIC) is the relevant pharmacodynamic index against these multidrug-resistant, Gram-negative bacteria. 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 (BUTI) and to identify optimal regimens that are based on the recently described pharmacodynamic targets for orders of logarithmic killing and resistance suppression. Such an approach also provides an opportunity to reflect on the adequacy of currently recommended *in vitro* susceptibility breakpoints established by the Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) committees for *E. coli* clinical isolates.

Patients and methods

Study design and patient population

Patients with BUTI due to multidrug-resistant *E. coli* were eligible for the FOREST clinical trial (NCT02142751) [13]; 16 consecutive patients hospitalized at University Hospital Virgen Macarena (Seville) 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, and height and weight), site of infection, baseline renal function, previous treatments and fosfomycin MICs of isolates were recorded. Serum creatinine concentrations were collected as a component of standard of care, and creatinine clearance (CrCl) was calculated daily using the Cockcroft-Gault equation [15]. Fosfomycin was administered 4 g every 5 hours (1-hour infusion) according to the clinical trial protocol. Patients with renal impairment (CrCl 20–40 mL/min) received 4 g every 12 hours (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 at 1, 6, 8 and 12 hours in patients with a CrCl of 20 to 40 mL/min.

Plasma fosfomycin concentrations were measured using tandem mass spectroscopy following a method previously described by Li et al. [16]. The assay interday coefficient of variation for fosfomycin in serum was ≤10%, with an accuracy range of 91.5% to 109.9%. The lower limit of quantification assay for plasma was 1 mg/L, with precision at coefficient of variation <15% and an 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 on the aforementioned model selection criteria and significant correlation with one of the pharmacokinetic parameters. CrCl, weight, age, sex and body mass index 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 interday 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: (a) log likelihood value, (b) Akaike information criterion, (c) coefficients of determination (r^2) from the linear regression of the observed–predicted plots before and after the Bayesian step, (d) minimization of bias and imprecisions of the observed–predicted plots, (e) normalized prediction distribution errors (NPDE), (f) distribution of the weighted residual errors and (g) visual predictive check (VPC) plot.

Simulations and probability of target attainment

Monte Carlo simulations were conducted using data from 2000 patients by using the Monte Carlo simulator within Pmetrics. For simulations, a semiparametric sampling method available in Pmetrics [17,18] was used. The final model consisted of 11 support points; 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 semiparametric 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 4 g every 6 hours (dosage used in the FOREST clinical trial for patients with CrCl >40 mL/min) and 4 g every 12 hours for patients with renal impairment (CrCl 20–40 mL/min) were simulated. For the probability of pharmacodynamic target attainment (PTA) analysis, fosfomycin regimens of 4 g every 6 hours and 8 g every 8 hours (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 et al. [12] for *E. coli* (i.e. *f*AUC$_{0-24}$/MIC of 19.3 for static effect and *f*AUC$_{0-24}$/MIC of 87.5 for decreasing the bacterial burden by 1 log). The pharmacodynamic indices targeted for resistance suppression (i.e. *f*AUC$_{0-24}$/MIC of 3136) were obtained from our previous work. Protein binding is negligible for fosfomycin and was ignored in these calculations [20].

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 four patients with CrCl 20 to 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 was below the limit of quantification.

Pharmacokinetics and mathematical model

The mean (SD) maximum fosfomycin plasma concentration (C_{max}) for patients at steady state was 422.6 mg/L (186.8 mg/L). The comparison between the variability observed in C_{max} concentrations between the current study and other previous fosfomycin pharmacokinetic studies is shown in Fig. 1. The mean (SD) area under the curve (*f*AUC) for the first 24 hours, estimated using the posterior estimates from each patient, was 5215.08 mg*h/L (1972.27 mg*h/L). 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 (LLD) compared to the one-compartment model (LLD = 132, $p < 0.05$). A linear model using CrCl best described drug clearance (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 body mass index did not improve the model fit. The following final structural model was fitted to the data:

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

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

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 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 vs. predicted plots of the final model are shown in Fig. 2. NPDE results (QQ plot and histogram) are summarized graphically in Supplementary Fig. S1. The weighted residual error distributions are shown in Supplementary Fig. S2. Both NPDEs (p 0.599 in the Shapiro-Wilk normality test), the weighted residual error distributions and VPC plots (Fig. 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 Supplementary Tables S1 and S2, respectively.

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

Variable	Value
Male gender	9/16 (56.3%)
Age (years), median (range)	68.5 (63–83)
Body mass index ≥25 kg/m^2	13 (81.25%)
CrCl (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 bacteraemia	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 microbiologic response (day 5)	13/14 (92.86%)*
Microbiologic cure	13/14 (92.86%)*

CrCl, creatinine clearance; ESBL, extended-spectrum β-lactamase; MIC, minimum inhibitory concentration.
*Two values were missed.

Monte Carlo simulations and probability of target attainment

The PTA results for 4 g every 6 hours and 8 g every 8 hours as 60-minute infusions are displayed in Fig. 4. Monte Carlo simulations and PTA analysis showed mild improvement by increasing fosfomycin dosing (4 g every 6 hours vs. 8 g every 8 hours). PTA of 93.9% (4 g every 6 hours) and 98.2% (8 g every 8 hours) were achieved for both dosages using a pharmacodynamic target for bacteriostatic effect (i.e. *f*AUC$_{0-24}$/MIC of 19.3) for MIC = 128 mg/L. Alternatively, using a pharmacodynamic target for 1-log decrease (i.e. *f*AUC$_{0-24}$/MIC of 87.5), PTA of 89.3% (4 g every 6 hours) and 96.1% (8 g every 8 hours) were observed for MIC = 32 mg/L for both dosages. Setting a target for resistance suppression (i.e. *f*AUC$_{0-24}$/MIC of 3136) an optimal PTA was reached for MIC of 1 mg/L, 83.2% (4 g every 6 hours) and 93.4% (8 g every 8 hours).

Following EUCAST (32 mg/L) and CLSI (64 mg/L) susceptibility breakpoints, the PTA were 89% to 96% and 33% to 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 (4 g every 6 hours or 8 g every 8 hours), irrespective of the susceptibility breakpoints that were used.

Discussion

The global threat of multidrug-resistant bacteria, together with the paucity of new active antimicrobial agents, 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 multidrug-resistant bacteria). However, as a result of lack of clinical interest in fosfomycin in the past decades, many questions regarding the pharmacokinetics and

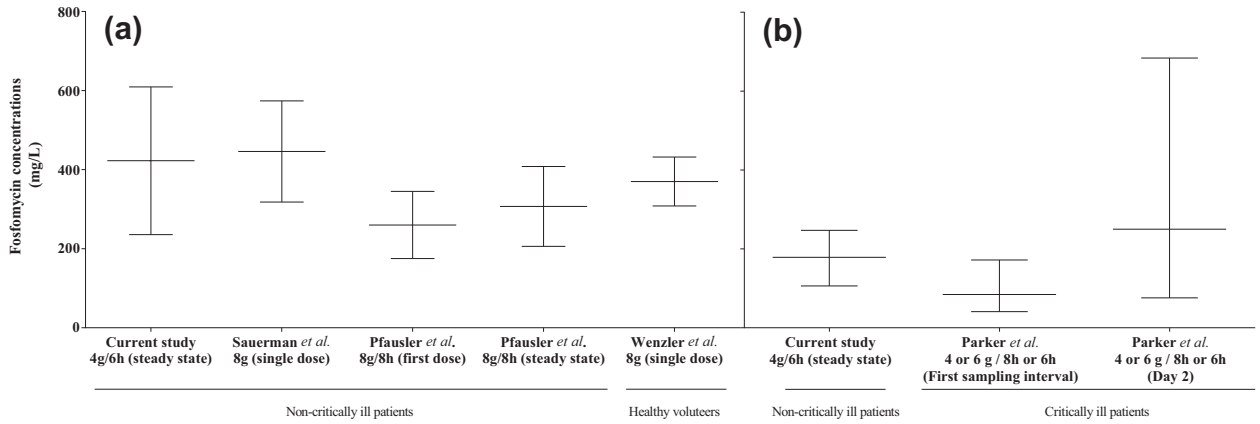

Fig. 1. Variability observed in fosfomycin concentrations with respect to other pharmacokinetic studies. (A) Mean (±standard deviation) maximal plasma fosfomycin concentrations (C_{max}) and (B) median (±range) trough fosfomycin plasma concentration (C_{min}).

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
Intercompartmental 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

SD, standard deviation; CV, coefficient of variation; CL, drug clearance; Kcp and Kpc are intercompartmental transfer rate constants.

pharmacodynamics 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 concentrations observed in patients with BUTI, who were mostly not critically ill, compared to other previously published data from healthy subjects and also from non–critically ill patients, using higher dosages (8 g every 8 hours) [9,22,23]. For example, a mean C_{max} of 422.6 mg/L (mean CrCl = 70.4 mL/min) was observed in our study, similar to those in Sauermann et al. [22] (mean C_{max} of 446 mg/L, mean CrCl = 70.4 mL/min) or Wenzler et al. [23] (mean C_{max} of 370 mg/L, mean CrCl = 139.6 mL/min). Also, the median trough fosfomycin plasma concentration (C_{min}) observed in our patients (178.7 mg/L; range, 106.11–246.93 mg/L) is closer to that observed by Parker et al. [10] in critically ill patients, which was 250 mg/L (range, 76–684 mg/L) at steady state. This could be explained in part by the renal impairment observed in our' population, which 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 CrCl could partially explain the differences observed with respect to healthy subjects [23]. On the basis of these observations, patients treated with fosfomycin would benefit from dose individualization based on CrCl to avoid under- or overdosing, thus reducing the chance of therapeutic failure or toxicity.

Studies by Lepak et al. [12] and Docobo-Pérez et al. [5] provided pharmacodynamic targets for fosfomycin and enabled our Monte Carlo simulation and PTA calculation. These analyses raised several points that deserve emphasis. An increase in the fosfomycin dosage, from 4 g every 6 hours (16 g per day) to 8 g every 8 hours (24 g per day, which is the maximum dosage approved by the Spanish Agency of Medicines and Medical Devices), only slightly improves the PTA [19]. This is of key importance because a reduction of 8 g of fosfomycin per day means a reduction of 2.56 g of sodium (every gram contains 0.32 g of sodium) [19], reducing the

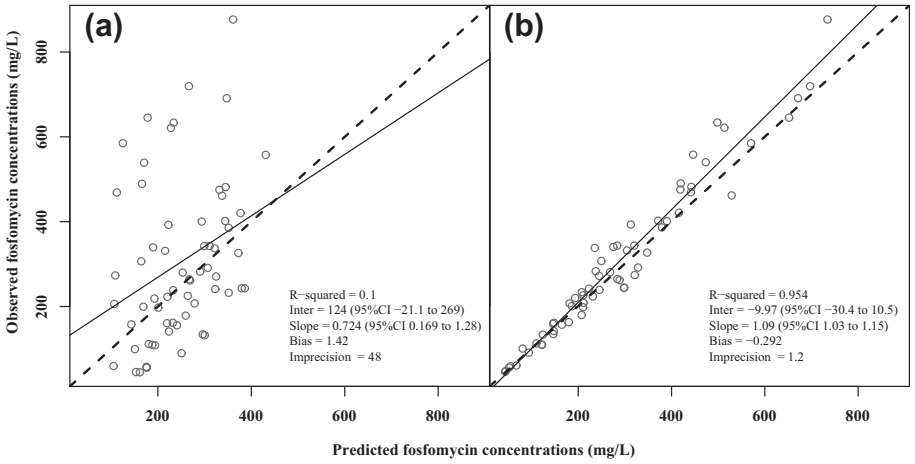

Fig. 2. (A) Plot of population predicted concentrations vs. observed concentrations. (B) Plot of individual predicted concentrations vs. observed concentrations (where data presented on both *x*- and *y*-axes are concentrations in milligrams per liter). Continuous line represents regression line; broken line, line of identity.

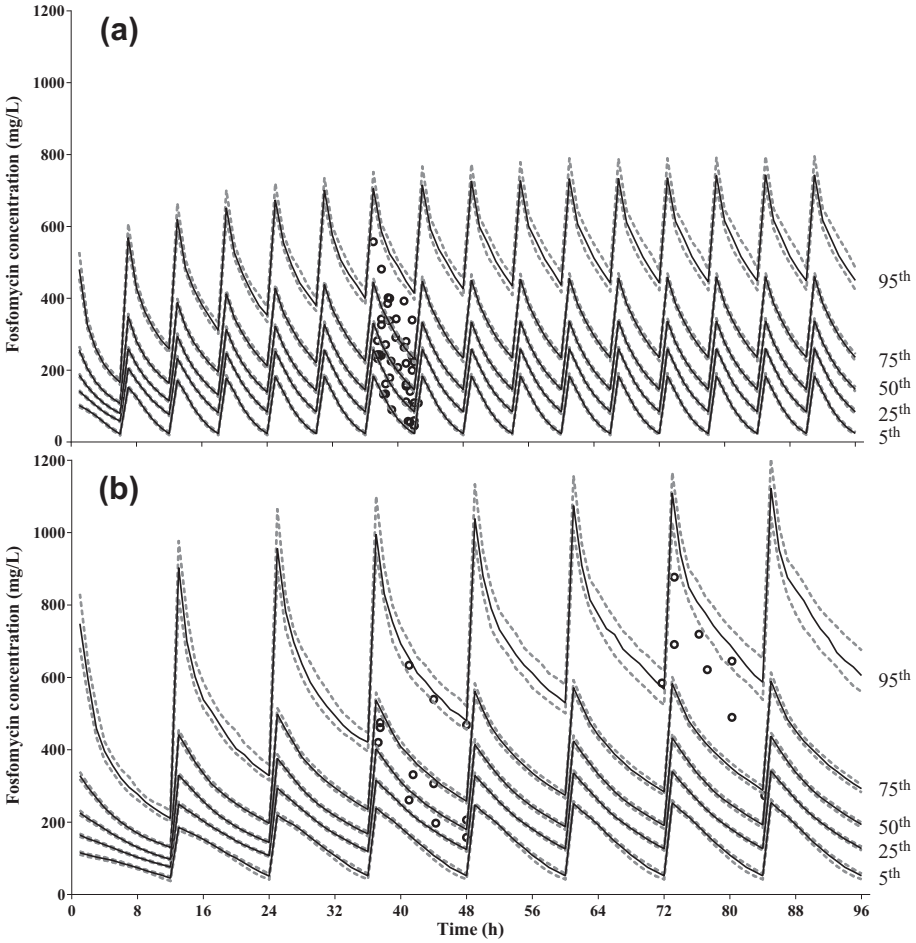

Fig. 3. Monte Carlo simulations ($n = 2000$) and visual predictive check of observed (open circles) over simulated (lines) data after treatment with (A) 4 g every 6 hours of fosfomycin (1-hour infusion, patients with CrCl >40 mL/min) or (B) 4 g every 12 hours of fosfomycin (1-hour infusion patients with CrCl 20–40 mL/min). Black lines indicate median, 90% prediction intervals (5th to 95th percentiles) and interquartile ranges (25th to 75th percentiles). Grey dashed lines represent 95% confidence interval.

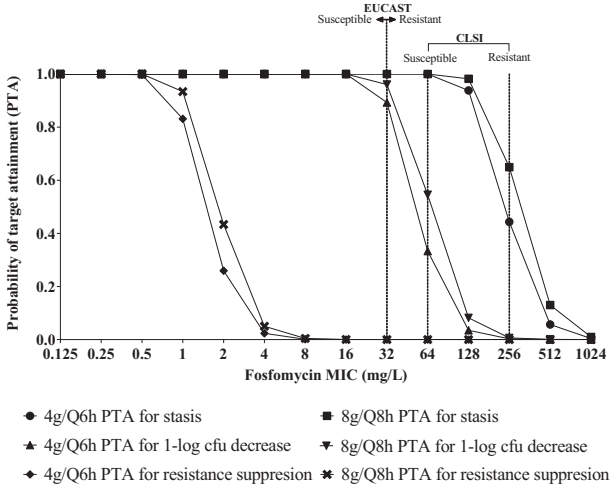

Fig. 4. Probability of target attainment for *Escherichia coli* for static effect ($fAUC_{0-24}$/MIC = 19.3), for 1-log bacterial reduction ($fAUC_{0-24}$/MIC = 87.5) and for bacterial resistance suppression ($fAUC_{0-24}$/MIC = 3136) at each fosfomycin MIC. Black dashed lines represent EUCAST and CLSI susceptibility breakpoints for fosfomycin. CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; *f*AUC, unbound concentration–time curve; MIC, minimum inhibitory concentration.

risk of adverse events, including hypocalcaemia, bradycardia or even heart failure [23,24], which may be particularly relevant for hospitalized patients.

An appraisal of the current susceptibility breakpoints for fosfomycin set by EUCAST and CLSI using the pharmacodynamic analyses reveals that efficacy would be better related to EUCAST breakpoints (i.e. susceptible ≤32 mg/L, resistant >32 mg/L) rather than CLSI breakpoints (i.e. susceptible ≤64 mg/L, resistant ≥256 mg/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 dosage of 8 g every 8 hours has been generated from the mathematical model assuming a linear pharmacokinetic of fosfomycin. Also, the VPC showed some underprediction in the group provided with 4 g every 12 hours. 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. [12] 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 microbiologic efficacy only during the first 24 hours. However, different studies using hollow fiber infection models have shown microbiologic failures occurring later as a result of the selection of subpopulations with reduced susceptibility or appearance of resistant mutants [5,30]. This suggests that the pharmacodynamic targets that drive the efficacy of fosfomycin in complex infections may need to consider suppression-resistant mutants, which are often not considered in the setting of breakpoints [5]. Finally, the existing controversy about how to perform and interpret fosfomycin susceptibility tests could hinder the use of MIC as a reliable measure of potency [28,29].

In conclusion, fosfomycin concentrations are highly variable and depend to some extent on the degree of renal dysfunction, even for non–critically ill patients. A regimen of 4 g every 6 hours or 8 g every 8 hours appears effective for the treatment of non–critically ill patients with bacteraemic 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.

Transparency declaration

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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 COMBACTENET (grant agreement 115523), COMBACTECARE (grant agreement 115620) and COMBACTEMAGNET (grant agreement 115737) projects under the Innovative Medicines Initiative (IMI), the European Union and EFPIA companies in kind. WWH has received research funding from Pfizer, Gilead, Astellas, AiCuris, Amplyx, Spero Therapeutics and F2G and has 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. The other authors report no conflicts of interest relevant to this article.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.cmi.2018.02.005.

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