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CLINICAL MICROBIOLOGY - RESEARCH PAPER

Time-kill curves of daptomycin and Monte Carlo simulation for the treatment of bacteraemia caused by *Enterococcus faecium*

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Abstract

Objectives The aim of this study was to investigate the effect of daptomycin against vancomycin-resistant *Enterococcus faecium* bacteraemia using computer modelling.

Methods Data obtained in vitro from time-kill curves were evaluated by PK/PD modelling and Monte Carlo simulations to determine the logarithmic reduction in the number of colony-forming units (CFU)/mL over 18 days of daptomycin treatment at 6, 8, and 10 mg/kg doses every 24 or 48 h and with variations in creatinine clearance (CL_{CR}) of 15–29, 30–49, and 50–100 mL/min/1.73 m^2. Monte Carlo simulations were performed to evaluate the probability of target attainment (PTA) for an area under the unbound drug concentration-time curve/minimum inhibitory concentration (*f*AUC/MIC) > 36 at the same doses and CL_{CR}.

Results Static time-kill model was employed to investigate the antibacterial efficacy of constant daptomycin concentrations. The time-kill curve analysis was performed using mathematical modelling based on a Hill coefficient factor. There was an expressive reduction (> 2 Log CFU/mL) over 18 days of daptomycin treatment in 75th percentile of individuals with CL_{CR} of 15–100 mL/min/1.73 m^2) with daptomycin 6–10 mg/kg/day, except for daptomycin every 48 h. Using *f*AUC/MIC > 36, PTA was > 90% at MICs ≤ 2 μg/mL.

Conclusions Higher daptomycin doses were associated with higher mortality in time-kill curves. The simulations indicated that independent of the CL_{CR} the therapeutic responses of VRE occur with doses of daptomycin ≥ 6 mg/kg/day and daptomycin every 48 h is insufficient to treat enterococcal bacteraemia.

Keywords Daptomycin · Bacteraemia · *Enterococcus faecium* · PK/PD modelling

Introduction

Daptomycin is the first member of the novel cyclic lipopeptide class, which provides concentration-dependent bactericidal activity against gram-positive microorganisms [1]. Daptomycin binds to the cell membrane of gram-positive pathogens and disrupts their membrane potential with potassium efflux, in a calcium-dependent process [2, 3]. It exhibits linear pharmacokinetics (PK) in the range of 6–12 mg/kg with a half-life of approximately 8 h [1]. Daptomycin was initially approved for use in complicated skin and soft tissue infections and, subsequently, for *Staphylococcus aureus* bacteraemia at a dose of 6 mg/kg/day [1, 4].

Bacteraemia, characterized by the presence of pathogenic bacteria in the bloodstream, is the main cause of morbidity and mortality among infectious diseases due to gram-positive bacteria (*Staphylococcus* spp., *Streptococcus* spp., and *Enterococcus* spp.), mainly in cases of community-acquired infections [5]. *Enterococcus* spp. are the second largest cause of nosocomial infections in the USA (14% of cases), according to the National Healthcare Safety Network (NHSN), and 90% of these are bacteraemias [6]. In Europe and South America, the incidence is lower, ranging from 2 to 20%. In a Brazilian study, the prevalence of vancomycin-resistant Enterococci (VRE) was

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27% [7, 8]. The incidence of VRE bacteraemia has also increased in Canada approximately 6-fold in recent years [9].

Daptomycin is commonly used for the treatment of complicated VRE infections, such as bacteraemia and endocarditis. This drug has potent bactericidal activity in enterococcal infection models and has been used for the treatment of important infections in humans [10]. Extensive clinical experience using this drug to treat enterococcal infections (including bacteraemia) has been reported in the literature. However, there are limited data available from randomized controlled trials that demonstrate efficacy.

Translational PK/PD modelling and simulation have emerged as an alternative strategy to characterize the triangular relationship between dose, exposure, and response for identifying the most suitable dosing regimen to be used in a particular clinical setting [11]. Monte Carlo simulation can be considered a valuable technique to guide clinical practice. This statistical algorithm uses computer software to simulate an expanded sample size of a study. Using a PK/PD model and well-defined covariances of the PK/PD parameters of the target population, it is possible to make predictions in different clinical scenarios in the absence of large-scale clinical studies [12]. Predictions can be made for groups of patients with altered PK, such as changes in clearance.

In this study we aimed to (i) investigate the PD effect of daptomycin versus a VRE by evaluating time-kill curves, (ii) model the effect of daptomycin as a function of time, (iii) use the Monte Carlo simulation to predict the reduction in the number of colony-forming units (CFU)/mL with different doses of daptomycin and variations in drug clearance, and (iv) predict the probability of target attainment (PTA) against the VRE using variations in drug doses and clearance.

Methods

Antibiotic, growth media, and microorganism

Daptomycin powder (purity > 97%) was purchased from Sigma-Aldrich and stored at − 20 °C. Stock solutions were freshly prepared daily prior to use and diluted to the desired concentrations with Mueller-Hinton broth (Difco Laboratories, Detroit, MI, USA) supplemented with 50 mg of calcium/L (Ca-MHB). *Enterococcus faecium* ATCC 700221 was donated by Instituto Oswaldo Cruz/Fiocruz, Rio de Janeiro, Brazil. The bacteria were stored at − 70 °C in skim milk. The inocula for minimum inhibitory concentration (MIC) and time-kill curve experiments were prepared in sterile saline solution and adjusted with Ca-MHB to a final concentration of approximately 5×10^5 CFU/mL.

Determination of minimum inhibitory concentration

The MIC of daptomycin for *E. faecium* ATCC 700221 was determined in duplicate according to the Clinical and Laboratory Standards Institute (CLSI) guidelines [13]. The broth in the microdilution wells was read by visual inspection after incubating for approximately 20 h at 35 °C.

Constant concentration time-kill curves

A simple static time-kill model to investigate the antibacterial efficacy of constant daptomycin concentrations for 48 h was used. The model consisted of a 50-mL culture flask containing 30 mL Ca-MHB, incubated at 35 °C with constant shaking. An aliquot (100 μL) of a suspension of the initial inoculation (1×10^8 CFU/mL) was added to the *in* vitro model to produce approximately 5×10^5 CFU/mL. The bacteria were incubated for 1 h before adding different daptomycin concentrations. Multiples of MIC (0.5×, 1×, 3×, 5×, and 10× MIC) were evaluated. A negative control experiment with bacteria and no daptomycin was run simultaneously. Samples were taken at 0, 2, 4, 8, 12, 24, 36, and 48 h. All experiments were conducted in duplicate. Bacterial counts were determined on all countable plates (upper limit for quantification was 200 CFU) by plating 20 μL of 10-fold diluted aliquots on appropriate tryptic soy agar (TSA) plates. Following an incubation of approximately 20 h, the number of CFU/mL was determined.

PK/PD modelling

The time-kill curve analysis and mathematical modelling of the kill curve data were fitted to an E_{max} model employing a non-linear regression software program, Scientist® 3.0 (Micromath, Salt Lake City, UT, USA), according to the following equation [14]:

$$\frac{dN}{dt} = \left[K_0 \cdot \left(1 - \frac{N}{N_{max}}\right) - \left(\frac{K_{max} \cdot C^h}{EC^h{}_{50} + C^h}\right)\right] \cdot N \quad (1)$$

where dN/dt is the change in number of bacteria as a function of time, K_0 (h^{-1}) is the bacterial growth rate constant in the absence of daptomycin, K_{max} (h^{-1}) is the maximum killing rate constant (maximum effect), EC_{50} (μg/mL) is the concentration of daptomycin necessary to produce 50% maximum effect, C (μg/mL) is the concentration of daptomycin at any time (t), N (CFU/mL) is the number of viable bacteria, N_{max} (CFU/mL) is the maximum number of bacteria, and h is the Hill coefficient factor.

For the control experiment (without daptomycin), bacterial growth was fitted using the following equation:

$$\frac{dN}{dt} = \left[K_0 \cdot \left(1 - \frac{N}{N_{max}}\right)\right] \cdot N \quad (2)$$

Monte Carlo simulations

The free daptomycin plasma concentrations expected after 6, 8, and 10 mg/kg/day for 18 days were estimated by published population PK parameters [15]. A one-compartment open model with linear elimination was employed. The following parameters of daptomycin were used: clearance = 0.8016 L/h (RSE% 4.71), volume of distribution = 12.29 L (RSE% 5.41), individual creatinine clearance = 0.2026 (RSE% 35.46), and interindividual variability in daptomycin clearance = 20.74 (RSE% 43.69) [15, 16]. To estimate the impact of these doses on the reduction in the CFU, the PK/PD parameters determined in the PK/PD modelling were employed in these simulations.

Monte Carlo simulations (1000-subject) were performed using Berkeley Madonna v 8.3.18 software for each clinical scenario in order to estimate the PTA of an area under the unbound drug concentration-time curve (*f*AUC)/MIC > 36 with various dosing regimens of daptomycin (6, 8, and 10 mg/kg/day). The precise *f*AUC/MIC required for successful outcomes in severe enterococcal infections is unknown. So, the PTA was based on the effective dose for invasive infection in mice (30 mg/kg) corrected by allometric calculation for humans and the free drug fraction [17, 18].

Different scenarios were evaluated including creatinine clearance (CL_{CR}) values of 15–29 mL/min/1.73 m^2, 30–49 mL/min/1.73 m^2, and 50–100 mL/min/1.73 m^2. The Monte Carlo simulation was performed using MIC of 0.06, 0.12, 0.25, 0.5, 1, 2, 4, and 8 μg/mL. The PK/PD susceptibility breakpoint was defined as the highest MIC at which the PTA was ≥ 90% [19].

Results

Determination of minimum inhibitory concentration

For *E. faecium* ATCC 700221, the daptomycin MIC in Ca-MHB was 2 μg/mL. This MIC value was in agreement with, for example, the European Committee on Antimicrobial Susceptibility Testing–reported MIC distributions [20].

PK/PD modelling

The fitted time-kill curves of daptomycin evaluated by the modified E_{max} model are shown in Fig. 1. The data were best explained by a PK/PD model that incorporates the N_{max} term. An additional Hill coefficient (y) factor to better fit the data was employed [21]. The calculated PK/PD parameters of daptomycin are shown in Table 1.

Monte Carlo simulations

The Monte Carlo simulations of the time-kill effects expected of daptomycin against *E. faecium* ATCC 700221 after dosages of 6, 8, and 10 mg/kg/day with different CL_{CR} of 15–29, 30–49, and 50–100 mL/min/1.73 m^2 are depicted in Fig. 2. Different scenarios were simulated for 18 days of daptomycin treatment.

In this study, it was observed that the dose required to reduce the VRE 2 Log (99%) CFU/mL population over 18 days of treatment for 75th percentile of the simulated population was ≥ 6 mg/kg/day, independent on the covariate CL_{CR} employed (15–100 mL/min/1.73 m^2). When compared with the same covariate, although the bacterial death has occurred over time, adjustment of renal function did not lead to complete bacterial death over time (6–10 mg/kg).

When we evaluated individuals with mild renal impairment (CL_{CR} 30–49 mL/min/1.73 m^2), we obtained a mean effect in the population at doses of ≥ 6 mg/kg/day (reduction in 2 Log CFU/mL). A similar effect was observed throughout the doses, at approximately 75th percentile with 6–10 mg/kg when preserved renal function was considered, as shown in Fig. 2. When daptomycin doses were simulated every 48 h, it can be seen that the reduction of 2 Log in CFU/mL drops from 75th percentile to only 25th percentile of the population when compared with a given dose every 48 h. When daptomycin dose of 10 mg/kg per every 48 h was simulated, the reduction of 2 Log CFU/mL was only 50th percentile.

A Monte Carlo simulation was conducted considering the target PK/PD *f*AUC/MIC > 36 in different clinical scenarios with variable doses (from 6 to 10 mg/kg/day) and clearances (CL_{CR} = 15–29, 30–49, and 50–100 mL/min/1.73 m^2). The distributions of the simulated PTAs are depicted in Fig. 3, which describes the distribution of MICs (frequency %) of the world population to *E. faecium* [20]. The PTA results show that daptomycin with MIC = 2 μg/mL reaches a target probability > 90% for dose range of 6–10 mg/kg/day, independent of the clearance (15–100 mL/min/1.73 m^2). On the other hand, when we considered MIC = 4 μg/mL, the target is attainment only with 10 mg/kg/day and CL_{CR} = 15–29 mL/min/1.73 m^2.

Discussion

Daptomycin is a cyclic lipoprotein drug with potent, concentration-dependent bactericidal activity against gram-positive microorganisms, including methicillin-resistant *S. aureus* (MRSA), methicillin-resistant coagulase-negative staphylococci (MRCoNS), and VRE [22]. The drug has been approved for treatment of complicated skin and soft tissue infections, bloodstream infections, and endocarditis at doses of 4–6 mg/kg/day. However, some studies have revealed therapeutic failure using daptomycin monotherapy to treat

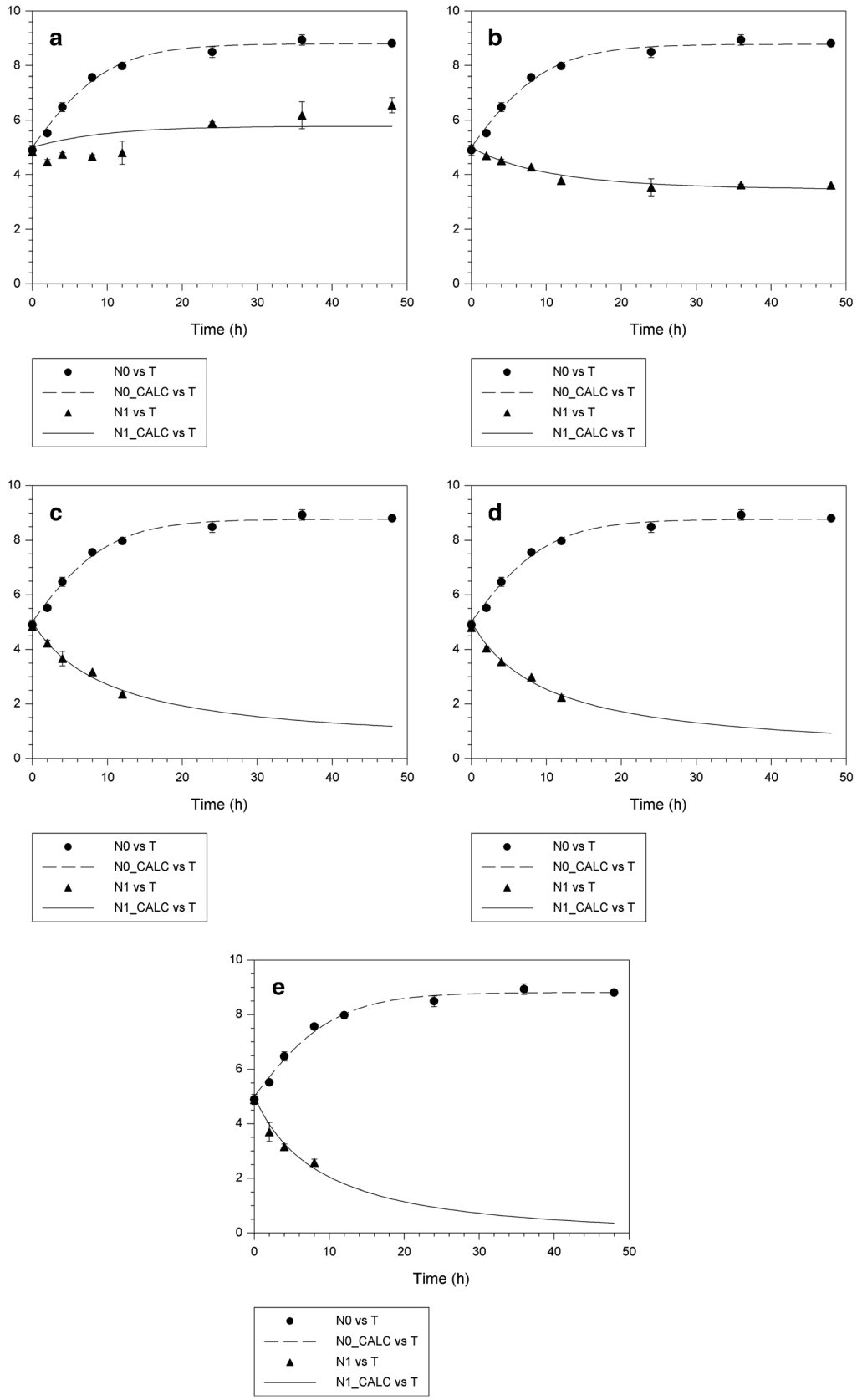

Fig. 1 Effect of daptomycin on *Enterococcus faecium* ATCC 700221 growth at various multiples of the minimum inhibitory concentration (MIC). **a** 0.5× MIC = 1 μg/mL; **b** 1× MIC = 2 μg/mL; **c** 3× MIC = 6 μg/mL; **d** 5× MIC = 10 μg/mL, and **e** 10× MIC = 20 μg/mL. •, control without drug; ▲, with daptomycin, $n = 2$ experiments/group. Mean values are plotted with errors bars indicating standard deviations

Table 1 PK/PD parameters of daptomycin against *Enterococcus faecium* ATCC 700221 at different multiples of the minimum inhibitory concentration (2 μg/mL)

Parameters	Multiples MIC					Average	SD
	0.5× MIC	1× MIC	3× MIC	5× MIC	10× MIC		
K_0 (h^{-1})	0.159	0.176	0.168	0.167	0.170	0.168	0.005
N_{max} (CFU/mL)	8.837	8.762	8.799	7.796	8.788	8.596	0.45
K_{max} (h^{-1})	0.029	0.052	0.097	0.101	0.148	0.086	0.044
EC_{50} (μg/mL)	1.448	0.760	0.894	0.976	1.075	1.031	0.246
h	3.924	0.739	1.447	2.063	0.958	/	/

E. faecium bloodstream infections with MIC > 2 mg/L [23–25]. In our study, we also observed that daptomycin monotherapy 6–10 mg/kg/day failed to PTA 90% with MIC

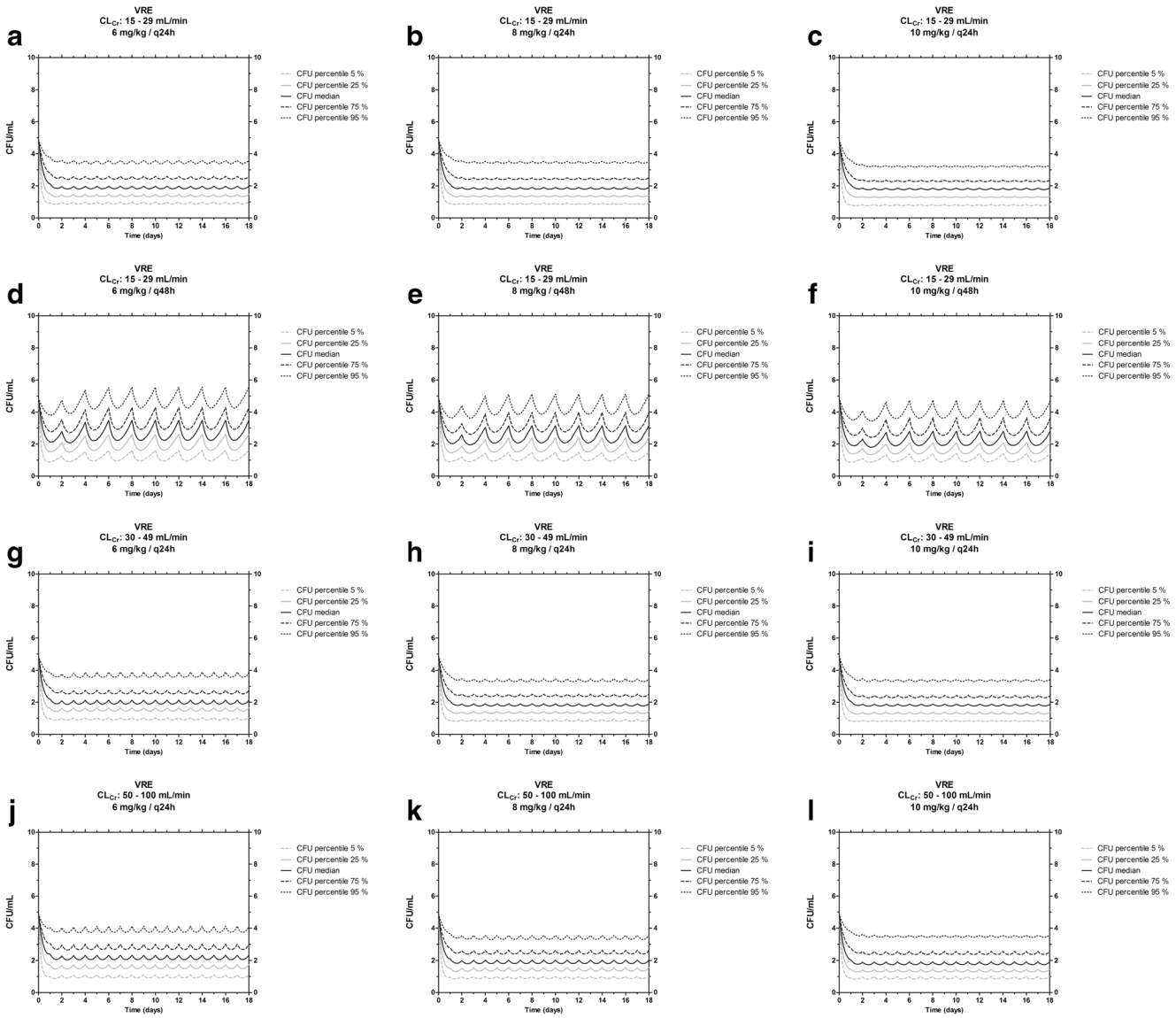

Fig. 2 PK/PD Monte Carlo simulations of clinical *Enterococcus faecium* responses to daptomycin with creatinine clearance as covariate. (—) CFU 5th percentile; (—) CFU 25th percentile; (—) CFU median; (—) CFU 75th percentile; (—) CFU 95th percentile. **a**, **b**, and **c** CL_{CR} 15–29 mL/min/1.73 m^2 for 6, 8, and 10 mg/kg/day, respectively; **d**, **e**, and **f** CL_{CR} 15–29 mL/min/1.73 m^2 for 6, 8, and 10 mg/kg/48 h, respectively; **g**, **h**, and **i** CL_{CR} 30–49 mL/min/1.73 m^2 for 6, 8, and 10 mg/kg/day, respectively; and **j**, **k**, and **l** CL_{CR} 50–100 mL/min/1.73 m^2 for 6, 8, and 10 mg/kg/day, respectively

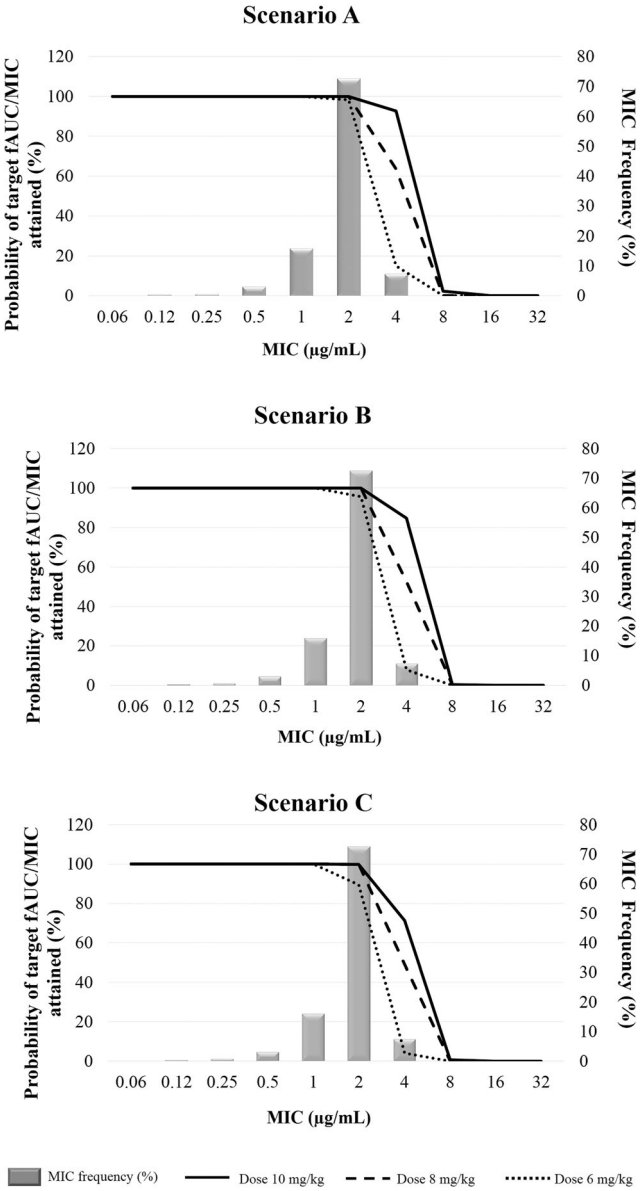

Fig. 3 Distributions of the simulated PTA of *f*AUC/MIC > 36 achievable with different daptomycin dosing regimens in various clinical scenarios of bacteraemia for *Enterococcus faecium*. Scenario A: CL_{CR} 15–29 mL/min/1.73 m^2. Scenario B: CL_{CR} 30–49 mL/min/1.73 m^2. Scenario C: CL_{CR} 50–100 mL/min/1.73 m^2. Doses are given as mg/kg in the legends. MIC frequency is shown as a bar graph. Probability of target *f*AUC/MIC attained is shown as a line plot. (EUCAST, 2017)

= 4 μg/mL. There are no consistent data regarding therapeutic failures of bacteraemias caused by VRE strains [26].

The MIC of an antimicrobial drug is often used as a clinical marker of its antimicrobial effect. However, the MIC is an arbitrary measurement since microorganism growth is determined at only one point in time after 18- or 24-h exposure to a constant antimicrobial concentration. In contrast, time-kill curves of microorganisms following in vitro exposure of antimicrobial drug concentrations more closely reflect the in vivo situation. Thus, describing these observations with mathematical PK/PD modelling provides additional information on the effects of antimicrobials over time and allows simulations and predictions of effect in situations of changes in dosages and concentrations of exposure of the drug to the microorganism. Generally, a mechanism-based antimicrobial PK/PD model includes equations describing the growth of microorganisms (the microorganism submodel), the effect of antimicrobial drugs (the antimicrobial submodel), and changes in drug concentrations (the pharmacokinetic submodel) [27–29].

Thus, the PK/PD model employed in the study uses the time-kill curves data to describe the effect of bacterial death as a function of time, as well as the information of concentration changes, when multiples of the MIC are used as described in the parameters in the PK/PD model equation.

The success of an antimicrobial treatment depends on the drug, characteristics of the host and microorganism. In the present study, a modelling application using vancomycin-resistant *E. faecium* bacteraemia with MIC = 2 μg/mL for daptomycin was proposed. In the PK/PD modelling, the Hill coefficient E_{max} model adequately described the experimental data, not requiring more sophisticated models, although these have also been evaluated.

Chuang et al. [30] found in their clinical study that higher doses of daptomycin (≥ 9 mg/kg) produced significantly higher bacterial death against vancomycin-resistant *E. faecium* in bacteraemia than did smaller doses. This is consistent with our study, in which doses of 10 mg/kg/day produced higher clinical responses with respect to bacterial death (> Log UFC/mL reduction).

In difficult to treat infections, high doses (> 6 mg/kg/day) could be more effective because of the pharmacokinetics and the possibility of faster bacterial eradication, also preventing the emergence of multidrug-resistant strains. International societies such as the Infectious Diseases Society of America (IDSA) recommend the use of 10 mg/kg/day in persistent MRSA bacteremia where vancomycin has failed; and clinical studies also suggest the dose of 8–10 mg/kg/day for infections such as sepsis, bacteremia, septic arthritis, and osteomyelitis. Extreme caution should be exercised in treating obese patients with high doses, as they will be exposed to concentrated doses with lower volume of distribution [31–33].

Our results are also comparable with those of Casapao et al. [34] who demonstrated that high doses of daptomycin (mean of 8.2 mg/kg) over an average of 10 days produced an excellent death curve of VRE strains in cases of bacteraemia [33]. Crank et al. [35] conducted a comparative study between the use of daptomycin and linezolid in cases of VRE bacteraemia and found no evidence of superiority between the drugs with respect to bacterial mortality, even at high doses.

When we simulated MIC using the same therapeutic doses in strains with higher MICs (> 2 μg/mL), we observed greater failure to kill the bacteria. Chong et al. [26] concluded the same from their study between 2006 and 2014, comparing VRE isolates obtained from patients with haematologic malignancies with MIC for daptomycin of 2 μg/mL versus 3–4 μg/mL and all cases of bacteraemia that were caused by *E. faecium* with higher MICs required higher doses of the drug for a therapeutic response. These findings are corroborated by those of Shukla et al. [24], who observed in a multicentre retrospective study of immunosuppressed patients antibiotic failure when MIC values for daptomycin remained at 3–4 μg/mL. In the present study, the bacterial reduction over the 18-day treatment for patients with altered renal function was evaluated, and it was observed that, in individuals with chronic renal disease (CL_{CR} of 15–29 mL/min/1.73 m^2), there was a response dose (6–10 mg/kg/day) in 75% of the simulated population. When adjusting for renal function with the usual doses every 48 h, we observed a regrowth of the isolates in doses of 6–8 mg/kg with only 25th percentile reduction of 2 Log CFU/mL.

Daptomycin at high doses may compromise the treatment of bacteremias because of the mitochondrial toxicity of the drug with increased creatinekinase (CPK) levels [31–33], but this toxicity is not so frequent in clinical practice, suggesting that daptomycin is effective and well tolerated at higher doses and in combination therapy [36]. We should also consider that high-dose daptomycin therapy has been proven to be effective for reducing the risk of selection of daptomycin-resistant strains.

There are some limitations to the current study, as the data presented were modelled considering only a static time-kill model and just one enterococcal strain. Therefore, our study demonstrates, through the simulations described, that therapeutic responses of VRE bacteraemia (reduction of 2 Log CFU/mL) occur with doses of daptomycin ≥ 6 mg/kg/day in strains with MIC = 2 μg/mL, independent of the CL_{CR}. Therefore, when the dosing interval is 48 h, the dosing, even higher, is ineffective to treat bacteraemia. When the PTA approach is considered with MIC = 2 μg/mL, the optimum target is reached with daptomycin ≥ 6 mg/kg/day. When *E. faecium* has higher MIC (≥ 4 μg/mL), these results suggest that daptomycin monotherapy is not sufficient to treat bacteraemia.

Authors' contributions All authors were involved in the content development of the manuscript, reviewed all drafts, and approved the final version.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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