Daptomycin plasma and CSF levels in patients with Health Care-Associated Meningitis.

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Abstract

Background:

There are currently few data concerning the cerebrospinal fluid (CSF) penetration of Daptomycin in patients with health care-associated meningitis. This study aims 1) to better characterize the pharmacokinetics of Daptomycin in humans during a 7 days intravenous (IV) therapy course, and 2) to study the penetration of Daptomycin in the CSF after IV infusion at the dose of 10 mg/Kg.

Results: In this prospective observational study we enrolled nine patients with an implanted external ventricular drainage (EVD) and a diagnosis of a Health Care-Associated Meningitis. Daptomycin was administered at 10 mg/kg for a maximum of 7 days. The pharmacokinetic of Daptomycin was studied using a two-compartment population/pharmacokinetic (POP/PK) model and by means of a non-linear mixed effects modeling approach. A large inter-individual variability in plasma AUC (Range: 574.7-1366.3 h mg/L), paralleled by high peak plasma concentration (Cmax) (all values>60 mg/L) was noted. The inter-individual variability of CSF-AUC although significant (range: 1.17-6.81 h mg/L) was narrower than previously reported and with a late occurrence of CSF-Cmax (range: 6.04-9.54 hrs). The terminal half-life between plasma and CSF was similar. t_{max} values in CSF did not show a high inter-individual variability, and the fluctuations of predicted CSF concentrations were minimal. The mean value for Daptomycin penetration obtained from our model was 0.45%.

Conclusions

Our POP/PK model was able to describe the pharmacokinetics of daptomycin in both plasma and CSF, showing that Daptomycin (up to 7 days at 10mg/Kg) has minimal penetration into CNS. Furthermore, the observed variability of AUC, t_{max} and predicted concentration in CSF was lower than what previously reported in the literature. Based on the present findings, it is unlikely that Daptomycin could reach CSF concentrations high enough to have clinical efficacy; this should be tested in future studies.

Background

Health Care-Associated Meningitis are a serious complication of different neurosurgical procedures associated with significant morbidity and mortality[1–3]. The incidence of these complications varies according to predisposing conditions and risk factors: 1.5% following craniotomy[4], 4% - 17% after internal ventricular catheter insertion[5] and 8% following external ventricular drainage (EVD) insertion[6]. Furthermore, up to 1.4% of head trauma and 5% of external lumbar catheter placement may be associated with central nervous system (CNS) infections.

Gram positive (G^+) cocci, especially Methicillin Resistant Staphylococcus Aureus (MRSA) and Epidermidis (MRSE), are the most common pathogens involved[7]. Their treatment is challenging because of antibiotics resistance and the difficulty to achieve a therapeutic dose of antibiotics in the CNS. Nowadays, treatment options are represented by Vancomycin and Linezolid. The penetration of Vancomycin within the cerebrospinal fluid (CSF) is poor even in the presence of meningeal inflammation [8]. To overcome this pharmacokinetic drawback direct instillation of antimicrobial agents into the ventricles could be necessary. Although this approach has never been standardized and never approved by Food and Drugs Administration, intra-thecal Vancomycin is occasionally necessary in patients with resistant nosocomial EVD-related ventriculitis, as suggested by the guidelines from infectious Disease Society[9]. Other agents such as Fosfomycin [10] and Linezolid [11–14] have been employed in the treatment of nosocomial staphylococcal ventriculitis and meningitis.

More recently, Daptomycin has been approved to treat susceptible G^+ infections of soft tissue and skin infections, right heart endocarditis and bacteremia [15–17]. There are few publications on the pharmacokinetics of Daptomycin at dosage as high as 10 mg/Kg [18] and there are few case reports published on CNS infection treatment with IV Daptomycin [19–22] or by intra-ventricular administration [2323]. The pharmacokinetics of CSF penetration of Daptomycin, which has been

studied in animals, ranges from 4% to 7% [18], whereas only one clinical study evaluated Daptomycin distribution within the CSF after a single IV bolus at the dose level of 10 mg/Kg [24].

Therefore, the aims of this study were 1) to better characterize the pharmacokinetics of Daptomycin in humans during a 7 days IV therapy course, and 2) to study the penetration of Daptomycin in the CSF after IV infusion at the dose level of 10 mg/Kg.

Methods

Study design and Population

This prospective, observational PK study was conducted in a neuro-intensive care unit (NICU) at Spedali Civili University Brescia Hospital, from 2010 to 2012, and in accordance with the Declaration of Helsinki. Ethical approval was obtained (registration number 1723) along with written informed consent for each patient. Ethical approval was also obtained by the Pisa Hospital to use in the present paper the Pisa dataset. The last dataset included patients who required Daptomycin at different dose levels (i.e., 6-10 mg/kg), but who did not suffer from organ or systemic failures, or pathological conditions that could influence the pharmacokinetics of Daptomycin (as well as burn injuries, obesity, etc.).

Inclusion criteria were: ≥ 18 years old with an indwelling external CSF access device and the presence of ventriculostomy-related meningitis (VM) diagnosed according to the CDC (Center for Diseases Control) criteria [25] by an infectious disease specialist, or a systemic infection requiring the use of Daptomycin.

Exclusion criteria were: 1) patients with conditions known or suspected to alter drug's pharmacokinetics (i.e., burned or cystic fibrosis patients), and 2) patients with one of the following: impaired renal function (defined as CLCR <30ml/min), pregnancy, obesity, hepatic failure (Child Class C), documented hypersensitivity to Daptomycin, or significantly elevated Creatine-phosphokinase (CPK) levels at baseline (>250 U/liter).

Study Procedures

Daptomycin was administered as a single daily dose at 10 mg/kg based on total body weight (TBW), over a 40-min IV infusion, for a maximum of 7 days. Daptomycin was associated with Vancomycin plus an anti-Pseudomonal β-lactam (Cefepime in all our patients) as per CDC guidelines [25]. Blood samples (4 ml) were collected just before the start of the infusion (t_0) (minimum plasma concentration, C_{min}) and 1 hr after the end of the infusion that presumably was the time (time to peak, t_{max}) at which Daptomycin could achieve the highest concentrations in tissues (C_{max}). CSF samples (1 ml) were collected using the indwelling EVD from the more proximal port, simultaneously with t_{max} blood sample (CSF C_{max}). After centrifugation (5 minutes at 4000 rpm) aliquots were stored at −80 °C (maximum 4 weeks) and within 45 minutes after sample collection. For each patient serum creatinine and body weight were also collected.

Possible adverse events were recorded as diarrhea, headache, dizziness, rash, abnormal liver function tests, elevated creatinine phosphokinase (CPK), hypotension and dyspnea. Moreover, we did record also severe adverse events: Anaphylaxis/Hypersensitivity Reactions, Myopathy and Rhabdomyolysis (CPK was monitored every two days), Eosinophilic Pneumonia (any patient developed dyspnea with hypoxic respiratory insufficiency, and diffuse pulmonary infiltrates), Clostridium difficile-Associated Diarrhea as reported by Food And Drugs Administration [26].

Concerning the CSF collection, all EVDs were connected to a backer system (Medtronic®) with a continuous and sealed CSF drainage. To avoid CSF dilution, no flushing was performed before the CSF collection. If EVD was blocked by any hematic cloth, hence requiring flushing, samples were not collected on that day.

Bioanalytical methodology

Plasma and CSF levels were assayed by a validated HPLC-MS method based on what described by Baietto *et al.* [27,28]. Briefly, extraction of Daptomycin from plasma and CSF was performed in a PTFE microfuge tube by the addition of 200µl of parent sample followed by 40µL of internal standard working solution and then 200µL of acetonitrile. The tube was vortexed for 10

seconds and then centrifuged at 12,000 rpm for 10 min at 4 °C. One hundred microliters of the supernatant were transferred in a vial and diluted with 400 µL of water mixed with TFA (trifluoracetic acid) solution (98:2, v:v), and then transferred to auto-sampler vials and injected [28]. Limit of quantitation for plasma and CSF Daptomycin level were 1.56 mg/L. Concentrations below the limit of quantitation (BLQ) were considered equal to the limit of quantitation[29]. CSF penetration was determined using the formula: AUC-CSF /AUC-plasma x 100%.

Pharmacokinetic analysis

The pharmacokinetic of Daptomycin was studied using a two-compartment population/pharmacokinetic (POP/PK) model and by means of a non-linear mixed effects modeling approach (NONMEM 7.3 ®).

The plasma/serum and the CSF were represented by compartment 1 and compartment 2, with the quantity of drug in the two compartments denoted as A_1 (elimination rate k_1) and A_2 (elimination rate, k_2.), respectively. The distribution rate of the drug from the plasma compartment to the CSF compartment was denoted as k_{12} (Figure 1). Since there was no transit of drug from CSF to plasma (i.e., $k_{21} = 0$), the plasma compartment could be considered independent from the CSF compartment.

In order to overcome the limited size of the CSF database the pharmacokinetic study was performed in two steps. A one compartment model was first used to estimate the plasma clearance (CL_1) and the plasma volume (V_1). Then, the two-compartment model was used to estimate the CSF clearance (CL_2), and volume (V_2) and the distribution rate k_{12}.

The study was performed utilizing two sets of data provided by the Pisa and Brescia Hospitals. The pharmacokinetic model for the plasma compartment was developed using the Pisa Hospital database. This database included measures for multiple occasions of 54 patients including only plasma concentrations. This one-compartment model (CMP1-Pi) represented an extension of the model previously published by Di Paolo et al. [30] obtained using a proportional plus additive residual error model. The obtained final parameterizations of clearance and volume are:

$CL1 = \theta_1 (CRCL/80)^{\theta 3} e^{\eta 1}$

$V1 = \theta_2 * WT$

where CRCL is the creatinine clearance (CRCL) calculated using the Cockcroft-Gault formula. The results are briefly summarized in supplementary material Table 1 and 2.

To compute the plasma clearance and volume for Brescia database (CMP1-Br) we used a proportional model (rather than proportional plus additive error model), this was due to the limited size of the database. Such a choice allowed us to stabilize the convergence process.

In the second step, given the single CSF measurement for each drug administration, it was decided to compute the CSF compartment with a limited number of parameters, i.e., clearance, volume and distribution rate, parametrized as:

$CL2 = \theta_4 e^{\eta 2}$; $V2 = \theta_5$; $K_{12} = \theta_6$

An inter-individual variability for V_2 and/or for k_{12} could not be included in the model due again to the very limited size of the data available. Because for the two-compartment model we used a non-standard system of ordinary differential equations, the NONMEM subroutine called "ADVAN=6" was utilized and the tolerance value was set to 1e-5. This new model was referred to as CMP12_Br.

As suggested by Kullar et al. [24], the obtained pharmacokinetics quantities have been used to estimate the Daptomycin penetration in CSF using both the Area Under the Curve (AUC) ratio and the Peak Concentration Ratio for the two compartments.

As a side note for Brescia database, because patient 7 had no measurement of CSF concentration we used his/her data for the estimation of the first compartment parameters only. Finally, for two patients the last and last two measures, respectively, have been excluded from the database because the reported value was 10 times or higher than the values reported previously from the same patients (measures considered as outlier). Such a large difference denoted a departure from the steady state conditions assumed for the development of the model.

Statistical analyses and software

We expressed continuous variables as mean (standard deviation, SD) for normal distributed variables or median (interquartile range, IQR) for the non-normal distributed variables. Qualitative variables were expressed as frequency and percentage.

Pharmacokinetic analyses have been performed using NONMEM 7.3®. Bootstrap analyses and visual predictive checks (VPC) have been generated with the "bootstrap" and "vpc" tools of the PsN-Toolkit Ref. 29. Goodness of fit plots have been generated through the combination of the Xpose package and the R software (release 3.3.3). Finally, concentration plots have been obtained using Matlab 2016b®.

Results

We enrolled nine neurosurgical patients (4 male, 5 female) for a total of 87 CSF and 99 plasma samples, with a mean ± SD of 5.56 ± 1.67 study/days per patient. Table 1 shows individual patients' baseline and clinical characteristics. The underlying diseases were intracerebral hemorrhage (n=2), subarachnoid hemorrhage (n=3), cerebral malignancy (n=2) and traumatic brain injury (n=1). Two patients died (patient 3 and 8). In supplementary materials Table 3 we reported the available CSF parameters collected along with the CSF microbiological results.

Median Daptomycin dosage was 650 mg (IQR, 150 mg). Daptomycin at 10 mg/kg was well tolerated with no adverse events (severe e non severe) noted during the 7 days drug course.

Pharmacokinetic model building

Concerning the pharmacokinetics, the results of run CMP1-Br model (basic model) and CMP12-Br model (the final model) are summarized in Supplementary materials Table 1. The obtained values confirm that the final model developed for the plasma compartment of Daptomycin using the Pisa database fits very well the Brescia database. We report in Figure 2 the goodness of fit plots for model CMP12-Br and in Figure 3 the visual predictive check for models CMP1-Br and CMP12-Br. Bootstrap results are shown in Supplementary materials Table 2, while diagnostic plots confirm that

the estimates of the pharmacokinetics quantities are reliable. In Supplementary materials Figure 1 and 2, the concentration C_1 and C_2 of Daptomycin in compartments 1 (plasma) and 2 (CSF) are plotted for each patient. It can be observed that the variation of concentration in compartment 2 is relatively small compared to compartment 1. Since the concentration in compartment 2 undergoes "moderate changes", having a single data point for each occasion can be considered acceptable, though not optimal.

Table 2 reports values of the principal pharmacokinetic parameters estimated from the POP/PK model. A large inter-individual variability in systemic exposure was evident (AUC range: 574.7 up to 1366.3 h mg/L), paralleled by C_{max} (values always higher than the limit of 60 mg/L). The mean value for Daptomycin penetration obtained from our POP/PK model was about 0.45%.

It is worth noting that the reduced penetration of daptomycin into CSF is witnessed by the late occurrence of C_{max}, ranging from 6.04 up to 9.54 h after the start of infusion (Table 2), despite the terminal half-life in plasma and CSF were similar (8.51±2.71 h and 7.77±3.74 h, respectively). Finally, t_{max} values in CSF did not show a high inter-individual variability, and the fluctuations of predicted CSF concentrations were minimal (Supplementary materials Figure 2).

Discussion

To the best of our knowledge this study presents the first investigation and description of the penetration of Daptomycin in the CNS by a POP/PK approach in human during a 7-day course therapy. Although the limited number of CSF samples available, the developed POP/PK model is reliable enough to fit plasma and CSF drug concentrations. The most intriguing finding is related to the low penetration rate of Daptomycin in CSF and the low inter-individual variability of predicted CSF concentrations.

It is well known that in absence of an intense meningeal inflammation, as in the case of EVD related meningitis, the penetration of antibacterial drugs into CNS is very limited [31] with the exception of meropenem that has the best penetration in the CNS. In our patients, the final POP/PK

model suggests a very limited penetration of Daptomycin within the CNS compartment (only 0.45% of plasma concentrations). This value is slightly lower than the only other one available in the literature, i.e, 0.8% reported by Kullar and colleagues [24]. It is worth noting that our model seems to be more accurate. Indeed, the coefficient of variation (CV) for our estimate is 48.13%, against the value of 87.5% reported by Kullar's study. Similar observation can be made regarding the C_{max} values in plasma and CSF. Moreover, the inter-individual variability in our patients is nearly halved with respect to the former study by Kullar and coworkers. The possible explanation of that striking difference could be the larger population of patients available to set up the plasma PK model, on which the CSF modeling was based.

In addition, all patients in the present study have received a standardized combination of Daptomycin and Vancomycin plus an antibiotic against the G- cocchi (notably reducing the meningeal inflammation), where just a few did in the Kullar's protocol. Finally, we have studied the Daptomycin CSF penetration over a mean (± SD) of 5.6 days (±1.57) course, where Kullar *et al.* administered a single drug dose.

Even though we found a difference in Daptomycin penetration between our patients and the Kullar's population, this difference should be contextualized in the clinical frame, with special reference to minimal inhibitory concentration (MIC) values of daptomycin, the highest doses of the drug and the administration of dexamethasone. Indeed, Daptomycin MIC values for G^+ microorganisms (e.g., S. aureus, S. pneumoniae, etc.) generally range between 0.1 and 1 mg/L. CSF C_{max} concentration achieved in our patients (0.21 ± 0.11 mg/L), as well as the one found by Kullar et al. (0.461 ± 0.51 mg/L at the same time point,), could be effective only in the case of low MIC, whereas the dose of 10 mg/Kg is highly effective in the plasma compartment (being the C_{max} mean value of 81.89 ± 9.28 mg/L). Therefore, the effective treatment could be attained by prescribing daily doses higher than 10 mg/kg. However, although severe adverse events were not observed in the present study, the further increase in drug daily doses could expose the patient to the risk of possible severe toxicity[32]. To the best of our knowledge, there are no studies that have evaluated a

higher Daptomycin dosage. Moreover, it is worth noting that the present patients did not receive Dexamethasone, which is known to affect the distribution of daptomycin into CSF[33].

The low rate of Daptomycin CNS penetration in our patients was associated to the high values of CSF t_{max} predicted by the final model (6-9.5 hrs). This finding was in agreement with the pharmacokinetics of other antimicrobial drugs that have a low rate of distribution within the CNS[29] because of their hydrophilic nature. Moreover, Daptomycin distribution is limited to the intercellular space, as suggested by the calculated plasma volume in the present population (0.14 L/kg). This value was similar to the previous reported in studies enrolling patients with severe infections[30,34], hence higher than value reported by Dvorchik and colleagues[35].

Our study has some obvious limitations associated with the reduced number of enrolled patients and the administration of other antibiotics, which in turn hampers a possible correlation analysis between Daptomycin pharmacokinetics and clinical outcomes. However, the treatment of severe CNS infections is often based on drugs other than Daptomycin and in some selected cases by the intraventricular administration of drugs, which overcomes the problem of blood-brain barrier permeability. Moreover, the study did not consider CSF protein and plasma level, which may influence drug pharmacokinetics because Daptomycin is highly bounded to proteins (from 90 to 93%). Therefore, the decreased level of protein founded in critically ill patients could lead to an increased free fraction of Daptomycin that may exert a greater bactericidal effect and be responsible for a higher renal clearance. At the same time the presence of an external ventricular device leads to a CSF drainage, affecting the drug clearance.

Conclusions

In conclusion, the POP/PK model was able to describe the pharmacokinetics of daptomycin in both plasma and CSF, showing that doses of 10 mg/kg administered for up to 7 days were associated with a minimal penetration into CNS. Furthermore, the observed variability of AUC, t_{max} and predicted concentration in CSF was lower than what previously reported in the literature[24]

while the observed variability of plasma quantities was instead comparable. Based on the present findings, it is unlikely that Daptomycin could reach concentrations high enough to result in a therapeutic effect for Health Care-Associated Meningitis. Further studies with larger databases are recommended to confirm the present results and to establish the Daptomycin clinical efficacy.

DECLARATIONS

List of Abbreviations:

Cerebrospinal fluid (CSF), central nervous system (CNS), Methicillin Resistant Staphylococcus Aureus (MRSA), Methicillin Resistant Staphylococcus Epidermidis (MRSE), Gram positive (G^+), external ventricular drainage (EVD), population/pharmacokinetic (POP/PK), Area Under the Curve (AUC), Center for Diseases Control (CDC), Creatine-phosphokinase (CPK), creatinine clearance (CRCL), standard deviation (SD).

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained (registration number 1723, Spedali Civili di Brescia, University of Brescia) along with written informed consent for each patient.

Consent for publication

Not applicable

Availability of data and material

The dataset is available in Github repository, https://github.com/pivadoc/DaptomycinDataset.git

Competing interests

All the authors declare to do not have any Competing Interest.

Funding

None to declare.

Author contribution

Study conception and design – Piva, Signorini. Acquisition of data – Togni, Piva, Signorini for clinical data, D'Avolio, Baietto for Daptomycin CSF and plasma dosage. Interpretation of results –

All authors. In particular, Di Paolo, Galeotti, Ceccherini and Cordoni for the POP/PK model elaboration. Drafted manuscript – Piva, D'avolio, Di Paolo, Galeotti, Ceccherini, Cordoni. Critically revised the manuscript – All authors.

All the authors approved the manuscript.

Tables and Figures Legend

Figure 1: Schematic representation of the final two-compartment model developed in the present study. Cmpt 1= Compartment 1 (Plasma/serum compartment), cmpt2=Compartment 2 (CSF Compartment). A1= quantity of Daptomycin in compartment 1 with k_1 denoting its elimination rate. A2= quantity of Daptomycin in compartment 2 with k_2 denoting its elimination rate. k_{12} denote distribution rate of Daptomycin between serum and CSF.

Figure 2: Goodness of fit plots for model CMP12-Br. Population (left) and individual (right) prediction values (Panel A) and individual weighted residuals (Panel B) plotted against observations (OBS) and individual prediction (IPRED), respectively. Symbols, individual values; red line, LOWESS line.

Figure 3: Visual predictive check plots for model CMP1-Br (panel A.) and CMP12-Br (Panel B.) obtained by resampling 1000 time the original database. Symbols, individual measured values of daptomycin concentrations; red lines, median (continuous line) and 95% confidence intervals (dashed lines) of measured values; box, 95% confidence intervals of median (pale pink) and 95%CI (pale blue).

Supplementary materials content:

Supplementary material Table 1: Summary of results for model CMP1_Pi.

Supplementary material Table 2: Summary of results for models CMP1-Br and CMP12-Br.

Notes: Model equations: CMPT1 CL_1 (L/h) = θ_1 $(CRCL/80)^{\theta_3}$ $\exp(\eta_1)$, V_1 (L) = $\theta_2 \cdot WT$;

CMPT2 CL_2 (L/h) = θ_4 $\exp(\eta_2)$, V_2 (L) = θ_5, k_{12} (1/h) = θ_6.

RSE%, relative standard error, i.e. standard error/mean x 100; CI, confidence interval; CMPT1 (plasma compartment), CMPT2 (CSF compartment).

Supplementary material Table3: CSF characteristics of collected samples.

Supplementary materials Figure 1: Plot of concentration of plasma compartment (C_1) for each patient vs time.

Supplementary materials Figure 2: Plot of concentration of CSF compartment (C_2) for each patient vs time.

Table 1: Patient demographics and clinical characteristics. Cr = Creatinine (mg/dL); CLCR (ml/min) = Clearance of Creatinine calculated using Cockcroft – Gault formula. SD= Standard Deviation. * refer to patients died. IVH= Intraventricular Hematoma; IPH= Intraparenchymal hemorrhage; SAH= Subarachnoid hemorrhage; TBI= Traumatic Brain Injury. Data are represented as Mean ± SD. All patients received Vancomycin + Cefepime as per CDC guidelines.

Patients ID	**Days of study**	**Weight (Kg)**	**Cr**	**CLCR**	**Dose (mg)**	**Diagnosis**
1	5	80	0.86	95	800	Neurinoma
2	7	65	0.4	148	650	IVH + IPH
3	5	45	0.32	91	450	Hydrocephalus
4	7	80	0.32	197	800	IPH
5	7	60	0.65	108	600	SAH
6	6	70	0.44	114	700	SAH
7	3	85	0.86	174	850	TBI
8	7	48	0.53	44	500	Astrocytoma
9	3	60	0.99	27	600	SAH
	5.56 ± 1.67	56.89 ± 14.17	0.59± 0.25	110.88± 55.85	661± 138.69	

Table 2. Main pharmacokinetic parameters of daptomycin in plasma (compartment 1) and CSF (compartment 2). The AUC and C_{max} CSF/plasma ratio values are also presented, suggesting a poor passage of the drug from plasma to the liquor.

Patients	PLASMA				CSF				CSF/Serum ratio	
	AUC (hxmg/L)	C_{max} (mg/L)	t_{max} (h)	$t_{1/2}$ (h)	AUC (hxmg /L)	C_{max} (mg/L)	t_{max} (h)	$t_{1/2}$ (h)	AUC (%)	C_{max} (%)
1	965.9	83.87	0.67	9.38	4.00	0.19	8.60	7.15	0.41	0.23
2	574.7	72.15	0.67	5.58	1.51	0.09	6.74	4.54	0.26	0.12
3	728.9	76.36	0.67	7.08	2.61	0.14	7.67	6.17	0.35	0.18
4	590.7	72.55	0.67	5.74	1.17	0.08	6.04	3.43	0.20	0.10
5	713.4	75.91	0.67	6.93	2.98	0.15	7.90	7.21	0.42	0.20
6	1148.7	90.21	0.67	11.16	6.27	0.29	9.30	9.41	0.55	0.32
8	962.7	85.92	0.67	8.98	8.73	0.39	9.54	15.64	0.91	0.46
9	1366.3	98.15	0.67	13.27	6.81	0.31	9.30	8.60	0.50	0.32
Mean	881.4	81.89	0.67	8.51	4.26	0.21	8.14	7.77	0.45	0.24
SD	280.4	9.28		2.71	2.73	0.11	1.28	3.74	0.22	0.12

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Legends of figures

Figure 1. Schematic representation of the final two-compartment model developed in the present study. Cmpt 1, compartment 1 (plasma/serum compartment); cmpt2, compartment 2 (CSF compartment); A1, quantity of daptomycin in compartment 1 with k1 denoting its elimination rate; A2, quantity of daptomycin in compartment 2 with k2 denoting its elimination rate. k12 denotes distribution rate of daptomycin between serum and CSF

Figure 2 Goodness-of-fit plots for model CMP12-Br. Population (left) and individual (right) prediction values (Panel A) and individual weighted residuals (Panel B) plotted against observations (OBS) and individual prediction (IPRED), respectively. Symbols, individual values; red line, LOWESS line (Color figure online)

Figure 3. Visual predictive check plots for model CMP1-Br (panel A.) and CMP12-Br (Panel B.) obtained by resampling 1000 times the original database. Symbols, individual measured values of daptomycin concentrations; red lines, median (continuous line) and 95% confidence intervals (dashed lines) of measured values; box, 95% confidence intervals of median (pale pink) and 95% CI (pale blue) (Color figure online)

Figure 1

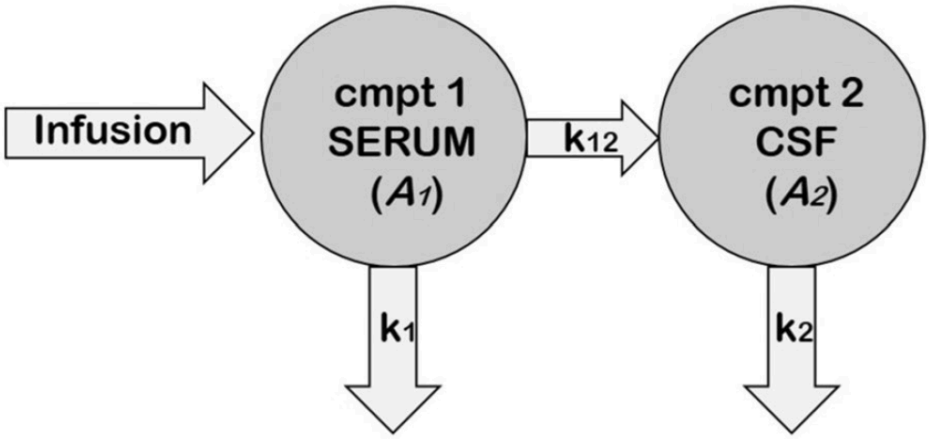


Figure 2, Panel A

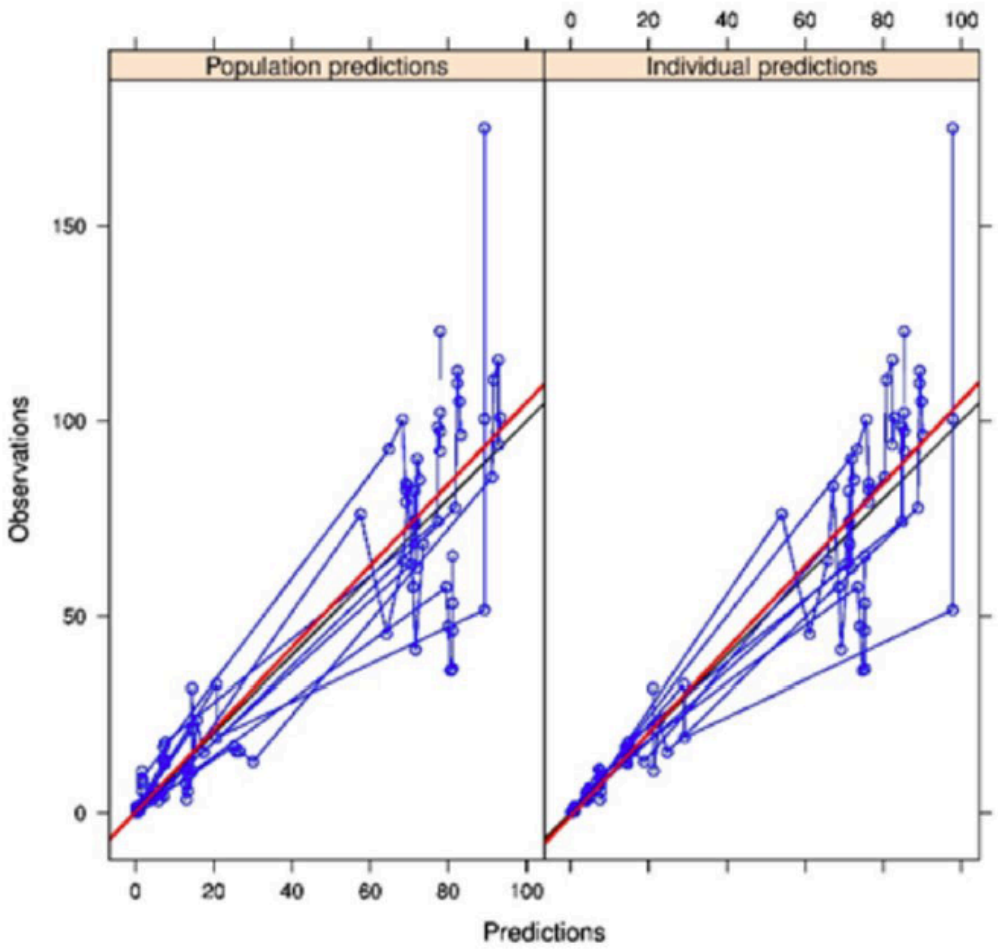


Figure 2, Panel B

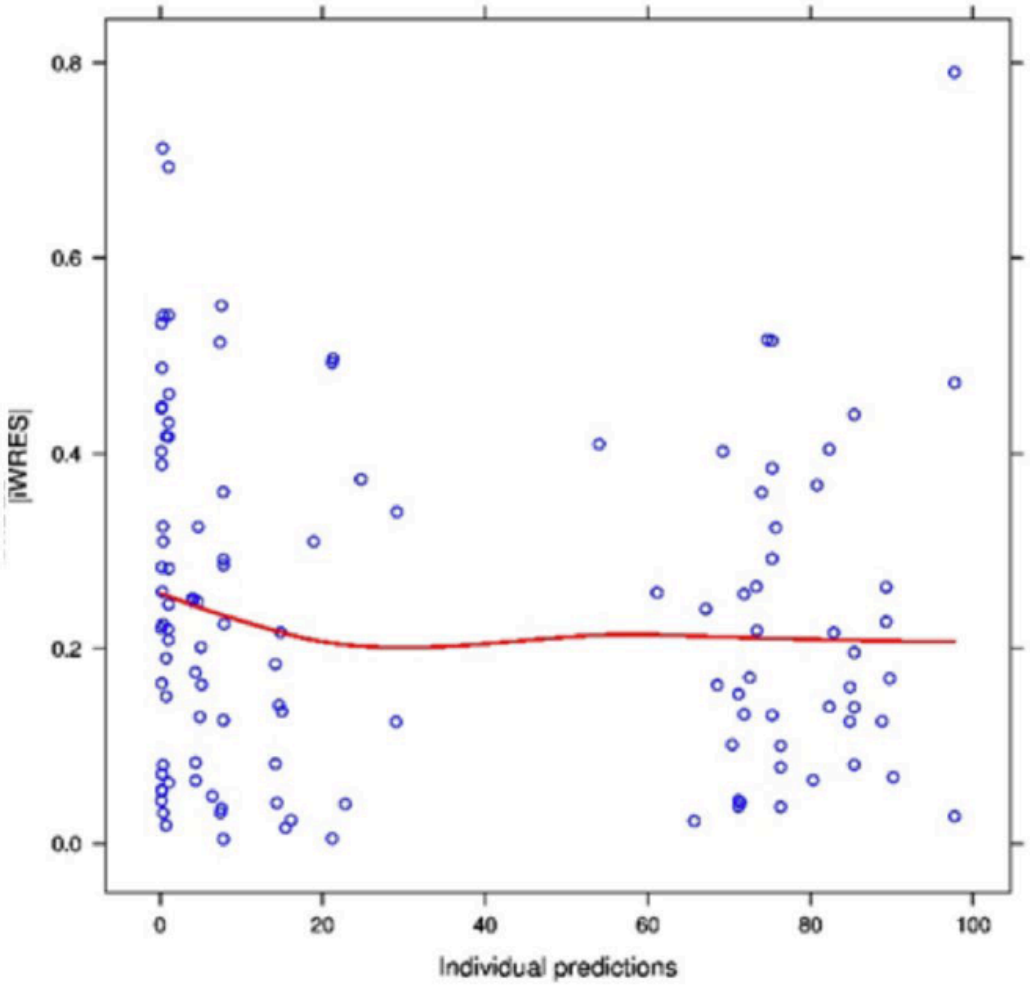


Figure 3, Panel A

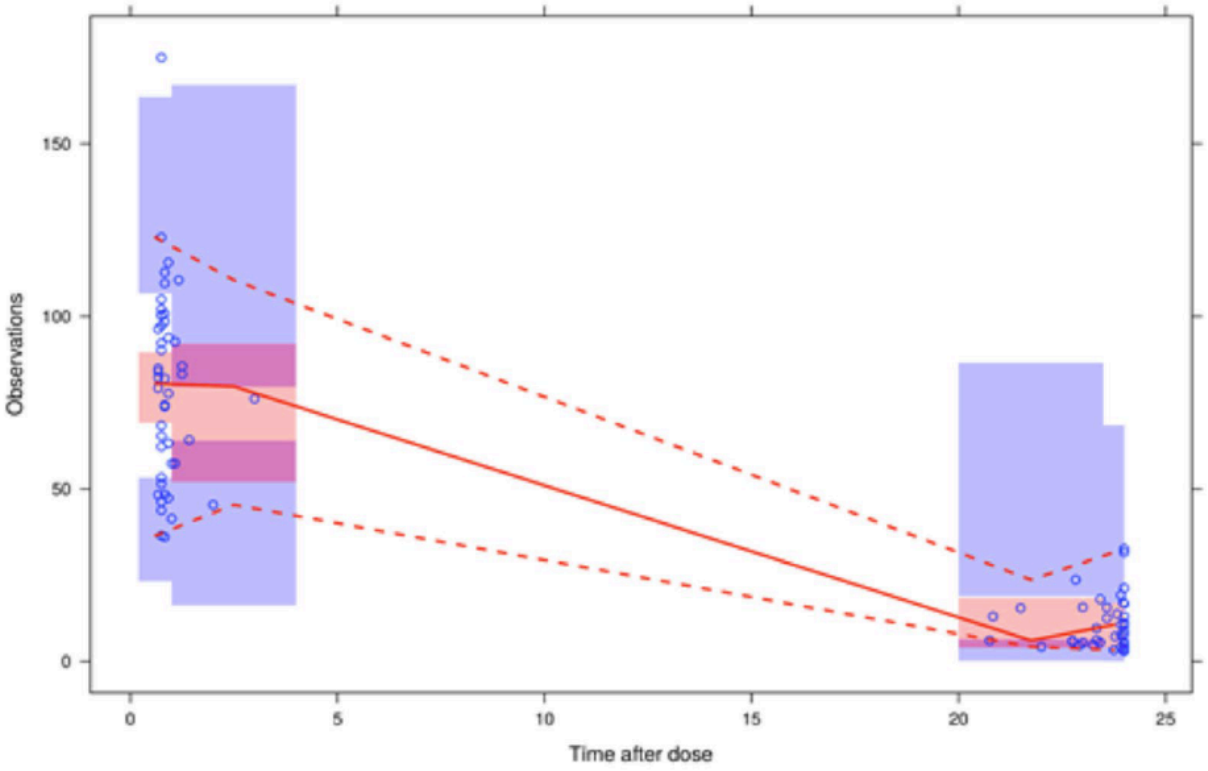
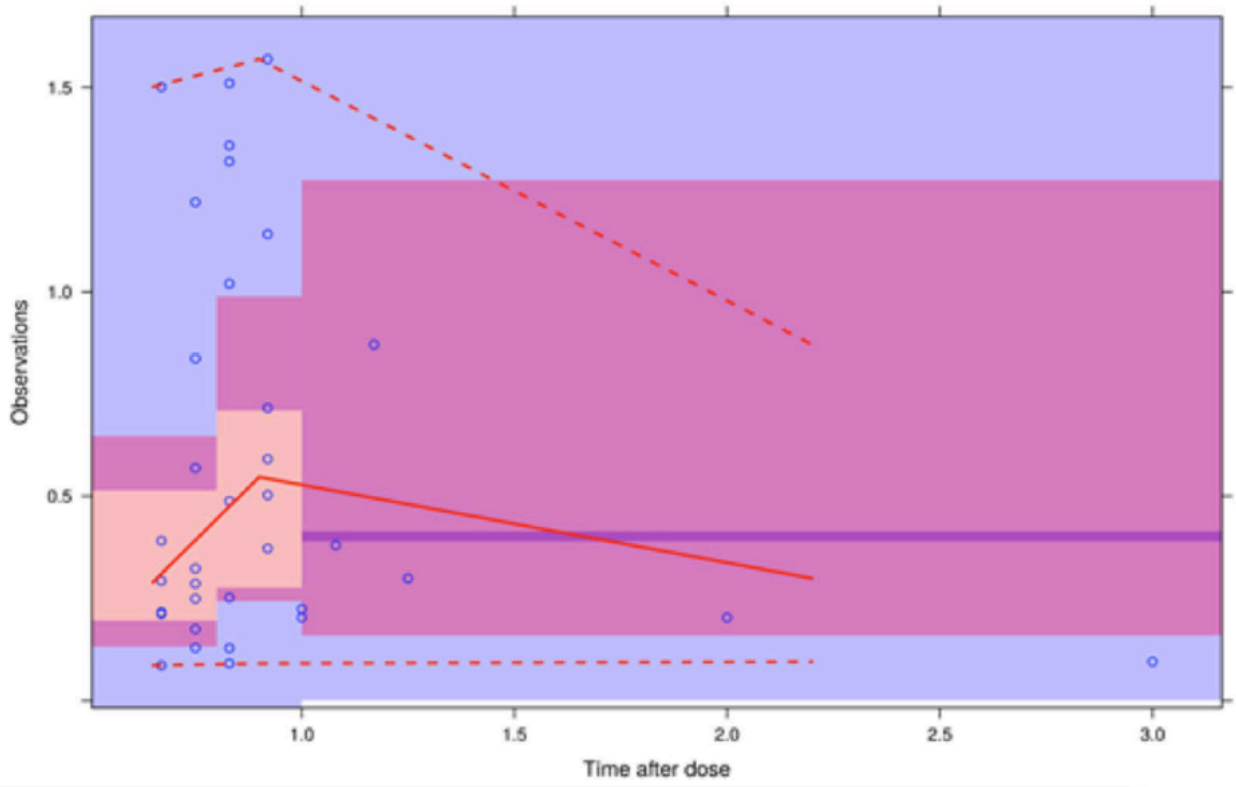


Figure 3, Panel B



Supplementary material Table 1: Summary of results for model CMP1_Pi.

			Bootstrap (4000 samples)	
Parameter	Median Value	RSE %	Median	5%-95% CI
θ_1 (L/h)	0.57	4.8	0.87	0.81-0.94
θ_2 (L/Kg)	0.19	5.9	0.19	0.17-0.20
θ_3	0.24	35.5	0.24	0.09-0.39
ω_1	0.22	32.3	0.22	0.15-0.28
σ_{pro}	0.32	13.6	0.32	0.28-0.35
σ_{add}	2.65	36.9	2.60	1.69-3.41

Supplementary material Table 2: Summary of results for models CMP1-Br and CMP12-Br.

Notes: Model equations: CMPT1 CL_1 (L/h) = θ_1 $(CRCL/80)^{\theta_3}$ $\exp(\eta_1)$, V_1 (L) = $\theta_2 \cdot WT$; CMPT2 CL_2 (L/h) = θ_4 $\exp(\eta_2)$, V_2 (L) = θ_5, k_{12} (1/h) = θ_6.

RSE%, relative standard error, i.e. standard error/mean x 100; CI, confidence interval; CMPT1 (plasma compartment), CMPT2 (CSF compartment).

				Bootstrap (4000 samples)	
CMPT	Parameter	Median Value	RSE %	Median	5%-95% CI
1	θ_1 (L/h)	0.57	13.9	0.57	0.45-0.75
1	θ_2 (L/Kg)	0.14	7.7	0.14	0.13-0.16
1	θ_3	0.61	26.9	0.61	0.24-1.00
2	θ_4 (L/h)	0.20	34.5	0.18	0.01-0.23
2	θ_5 (L)	2.03	38.8	1.36	0.57-83.10
2	θ_6	4.02e-4	39.8	3.69e-4	1.8e-5-4.67e-4
1	ω_1	0.30	36.2	0.26	0.17-0.36
2	ω_2	0.47	54.8	0.46	0.23-0.75
1	σ_1	0.28	26.9	0.27	0.21-0.33
2	σ_2	0.38	14.9	0.38	0.33-0.43

Notes: Model equations: CMPT1 CL_1 (L/h) = θ_1 $(CRCL/80)^{\theta_3}$ $\exp(\eta_1)$, V_1 (L) = $\theta_2 \cdot WT$; CMPT2 CL_2 (L/h) = θ_4 $\exp(\eta_2)$, V_2 (L) = θ_5, k_{12} (1/h) = θ_6. RSE%, relative standard error, i.e. standard error/mean x 100; CI, confidence interval; CMPT1 (plasma compartment), CMPT2 (CSF compartment).

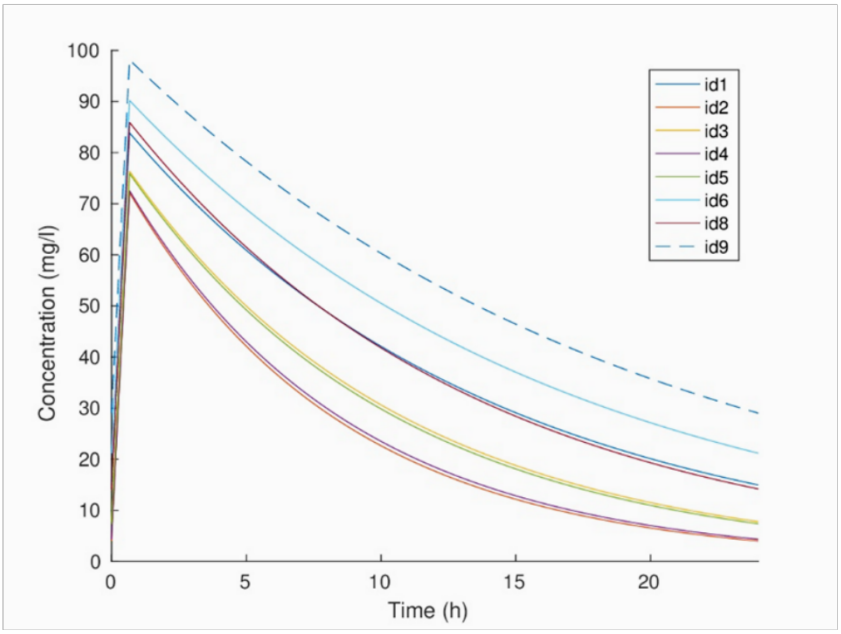
Supplementary materials Table 3: CSF characteristics of collected samples

Patients		CSF-Colture	CSF-Protein	CSF-Glucose	CSF-WBC	CSF-Neutrophils	CSF-Lymphocyte	CSF-Color	CSF-Aspect
1									
	1	E.Fecalis	350	1	256	99%		Torpid	Sediment present
	2								
	3								
	4	E.Fecalis	222	46	123	99%		Torpid	Sediment present
	5								
	6								
	7	Negative	68	99	100	99%		Slightly torpid	Sediment present
2									
	1	Negative	N/A	24	3000			hematic	
	2								
	3	Negative	260	53	150	99%		Slighlty Hematic	Clear with hematic sediment
3									
	1	Negative	215	22	86	99%		Torpid	Sediment present
	2								
	3								
	4	Negative	191	38	4			No color	Clear
	5	Negative							
4									
	1	Negative	350	65	604	75%	25%	Hematic	Clear with hematic sediment
	2		108	56	520			Hematic	Clear with hematic sediment
	3								
	4								
	5	Negative	92	59	1700	99%		Slightly hemaitc	Clear with scarce hematic sediment

	6								
	7	Negative	38	61	152	99%		Slightly Xantocromic	Clear with scarce hematic sediment
5		NA							
6									
	1	Coagulase- Negative Staphylococci	225	55	310	99%		pinkish	Clear with hematic sediment
	2								
	3								
	4								
	5	Coagulase- Negative Staphylococci	180	63	240	99%		pinkish	Clear with hematic sediment
	6								
7									
	1	Negative	88	45	25	99%			
	2								
	3	Negative	53	66	4			pinkish	Clear with hematic sediment
8									
	1	MRSE	161	35	180	50%	45%	Xantocromic	Clear with hematic sediment
	2								
	3								
	4								
	5								
	6								
	7	Negative	1222	40	170	73%	25%	Xantocromic	Clear with hematic sediment
	13	Negative	218	46	12				
	17	Negative	116	40	16	18%	77%	Slightly xantocromic	Clear with hematic sediment
	20	Negative	134	50	76				
	25	Negative	143	41	44				
9									
	1								

	2								
	3	MRSE	160	32	84			Xantocromic	Clear with hematic sediment
	4								
	7		150	22	68	68%	20%	Xantocromic	Clear with hematic sediment
	13	MRSE	220	20	36				
	21	MRSE	102	32	2				
	26		75	42	0			Xantocromic	Clear with hematic sediment
	31		77	36	4			Clear	Clear

Supplementary materials Figure 1



Supplementary materials Figure 2