PHARMACOKINETICS

Population pharmacokinetics of daptomycin in adult patients undergoing continuous renal replacement therapy

Correspondence Dr Kamal Hamed, Novartis Pharmaceuticals Corporation, 1 Health Plaza, East Hanover, NJ 07936, USA. Tel.: +1 862 778 4780; Fax: +1 973 781 5987; E-mail: kamal.hamed@novartis.com

Received 28 April 2016; Revised 22 July 2016; Accepted 6 September 2016

Xiaoying Xu1, Dmytro Khadzhynov2, Harm Peters2,3, Ricardo L. Chaves4, Kamal Hamed1, Micha Levi1 and Natascia Corti5

1Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA, 2Department of Nephrology, Charité Campus Mitte, Charité – Universitätsmedizin, Berlin, Germany, 3Dieter Scheffner Center for Medical Education and Educational Research, Charité – Universitätsmedizin, Berlin, Germany, 4Novartis Pharma AG, Basel, Switzerland, and 5Department of Clinical Pharmacology and Toxicology, Zurich University Hospital, Zurich, Switzerland

Keywords CRRT, CVVHD, CVVHDF, daptomycin, population pharmacokinetics, renal replacement therapy

AIM
The objective of this population pharmacokinetic (PK) analysis was to provide guidance for the dosing interval of daptomycin in patients undergoing continuous renal replacement therapy (CRRT).

METHODS
A previously published population PK model for daptomycin was updated with data from patients undergoing continuous veno-venous haemodialysis (CVVHD; n = 9) and continuous veno-venous haemodiafiltration (CVVHDF; n = 8). Model-based simulations were performed to compare the 24 h AUC, Cmax, and Cmin of daptomycin following various dosing regimens (4, 6, 8, 10, and 12 mg kg−1 every [Q] 24 h and Q48 h), with the safety and efficacy exposure references for Staphylococcus aureus bacteraemia/right-sided infective endocarditis.

RESULTS
The previously developed daptomycin structural population PK model could reasonably describe data from the patients on CRRT. The clearance in patients undergoing CVVHDF and CVVHD was estimated at 0.53 and 0.94 l h−1, respectively, as compared with 0.75 l h−1 in patients with creatinine clearance (CrCl) ≥ 30 ml min−1. Daptomycin Q24 h dosing in patients undergoing CRRT resulted in optimal exposure for efficacy, with AUC comparable to that in patients with CrCl ≥ 30 ml min−1. In contrast, Q48 h dosing was associated with considerably lower AUC24–48h in all patients for doses up to 12 mg kg−1 and is therefore inappropriate.

CONCLUSIONS
Q24 h dosing of daptomycin up to 12 mg kg−1 provides comparable drug exposure in patients on CVVHDF and in those with CrCl ≥ 30 ml min−1. Daily daptomycin use up to 8 mg kg−1 doses are appropriate for patients on CVVHDF, but higher doses may increase the risk of toxicity.
WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Daptomycin exhibits concentration-dependent bacterial killing.
- It demonstrates a linear PK profile when administered at once-daily doses of 6–12 mg kg\(^{-1}\) and is primarily excreted unchanged by the kidneys.
- Recommendation for dose interval adjustment is available for patients on haemodialysis or continuous ambulatory peritoneal dialysis (Q48 h dosing recommended), but not for patients on CRRT.

WHAT THIS STUDY ADDS

- In contrast to haemodialysis or continuous ambulatory peritoneal dialysis, Q48 h dosing in patients undergoing CRRT is likely to result in exposure levels below the reference range for efficacy every second day and thus be detrimental to patient outcomes.
- Q24 h dosing of daptomycin up to 12 mg kg\(^{-1}\) provides drug exposure in patients on CVVHD comparable to that in patients with CrCl \(\geq 30\) ml min\(^{-1}\).
- Daptomycin doses up to 8 mg kg\(^{-1}\) Q24 h are appropriate for patients on CVVHDF, but higher doses may increase the risk of toxicity.

Introduction

Acute kidney injury in the hospital setting is a common complication often requiring renal replacement therapy [1, 2]. Among the dialysis modalities available in the intensive care unit (ICU), continuous renal replacement therapy (CRRT) is associated with better efficiency and patient tolerability than peritoneal dialysis or intermittent haemodialysis (HD) and often is a preferred and recommended choice in haemodynamically unstable patients [3–5]. Patients undergoing dialysis are at a 100-fold greater risk for invasive methicillin-resistant Staphylococcus aureus infections than the general population, with approximately 85% having invasive devices or catheters at the time of infection [6]. Critically ill patients may show changes in the pharmacokinetic (PK) properties of the drugs being administered, such as clearance, volume of distribution and plasma protein binding [7].

Daptomycin exhibits concentration-dependent bacterial killing, and its 24 h area under the plasma concentration–time curve (AUC) and maximum plasma concentration (C\(_{\text{max}}\)) are the most relevant parameters that correlate with its in vivo efficacy [8]. It demonstrates a linear PK profile when administered at once-daily doses of 6–12 mg kg\(^{-1}\) and is primarily excreted unchanged by the kidneys [9]. Therefore, the major factor affecting daptomycin clearance is renal clearance, with decreased renal function resulting in decreased daptomycin clearance.

In general, drugs that are eliminated primarily by the kidneys are efficiently removed during thrice weekly intermittent HD. However, on days without HD, drug elimination is minimal, necessitating dose adjustment. In contrast, CRRT results in removal of drugs and waste products continuously over 24 h and considerably more efficiently than intermittent HD [10, 11]. Therefore, dosing recommendations based on studies conducted in patients receiving conventional intermittent HD are inappropriate for patients undergoing CRRT. Continuous veno-venous HD (CVVHD) removes substances by ultrafiltration through a semi-permeable membrane and continuous veno-venous haemodiafiltration (CVVHDF) by diffusion. The main determinants of drug clearance in CRRT are ultrafiltration flow rate (CVVHD), dialysate flow rate (CVVHDF) and filter membrane types (CVVHD and CVVHDF). Variations in these factors could explain differences in drug clearance and dosing recommendations [12].

Daptomycin is approved for use in complicated skin and skin structure infections at a dose of 4 mg kg\(^{-1}\) every 24 h (Q24 h) and in S. aureus bloodstream infections (S. aureus bacteremia [SAB]), including right-sided infective endocarditis (RIE), at a dose of 6 mg kg\(^{-1}\) Q24 h [13, 14]. The same dose at a reduced frequency of every 48 h (Q48 h) is recommended for patients with a creatinine clearance (CrCl) < 30 ml min\(^{-1}\) (with or without HD or continuous ambulatory peritoneal dialysis [CAPD]), but no formal recommendations have been approved in critically ill patients undergoing CRRT [14, 15]. This analysis aimed to estimate the clearance of daptomycin and to provide guidance for the dosing frequency of daptomycin in critically ill patients undergoing CRRT. Modifications to a previously published population PK model [15] for daptomycin are reported, with additional covariates of two CRRT subtypes (CVVHD and CVVHDF) according to the protocols applied in the respective studies [16, 17]. Simulations were performed using this updated model to assess the optimal daptomycin dosing frequency for critically ill patients undergoing CRRT, and the results were compared with those of previous studies [15–17].

Methods

Patients

In this analysis, demographic and daptomycin PK data from patients on CVVHD (n = 9) or CVVHDF (n = 8) included in two published studies by Corti et al. [16] and Khadzhynov et al. [17] were pooled with the PK database of the base model for daptomycin [15], which had been updated from a previously published and validated PK model for daptomycin [18]. In the base model [15], subjects were categorized as having CrCl ≥ 30 ml min\(^{-1}\) (n = 374), CrCl < 30 ml min\(^{-1}\) but not on-dialysis (n = 11), end-stage renal disease on HD Q48 h or thrice weekly (n = 40), and end-stage renal disease on CAPD (n = 14). This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.
**CRRT procedures**

CVVHD and CVVHDF were performed using a Multifiltrate system (Fresenius Medical Care, Bad Homburg, Germany) with capillary haemofilter AV 1000s (polysulphone; surface area, 1.8 m²) or a Prismaflex ST150 system (Gambro AB, Lund, Sweden) with capillary haemofilter AN69 ST (acylonitrile-sodium-methyl sulphonate; surface area, 1.5 m²) [16], or a Multifiltrate system (Fresenius Medical Care, Bad Homburg, Germany) with a high-flux dialyser (PF140H; surface area, 1.4 m²; Gambro Dialysatoren GmbH, Hechingen, Germany) and using citrate as the anti-coagulation agent [17]. In the Corti et al. study, where possible, total combined filtration and dialysate rates were maintained between 30 and 40 ml kg⁻¹ h⁻¹ [16]. Unless prefilter substitution was necessary, the substitute solutions were reported by Chaves et al. and inter-compartmental clearance (Q), peripheral volume of distribution (Vₚ), and central volume of distribution (Vc) were targeted to achieve a dialysis dose > 30 ml kg⁻¹ h⁻¹ [17].

The base model comprised separate equations (1)–(5), with some shared covariate effects (e.g. CL in different dialysis types); other equations were applied to all populations.

\[
CL_{\text{Dialysisi}} = \theta_{CL} \begin{cases} \text{Temp} \left( ^{\circ}\text{C} \right) & 0^9 \\
37 \left( ^{\circ}\text{C} \right) & 0^9 \text{Sex[Female]} \times 0^9 \text{DIAM[Low flux]} \times 0^{13} \text{DIAM[High flux]} \times 0^{15} \text{IEAC[IEAC 1]}, \\
0^{16} \text{IEAC[IEAC 2]} \cdot 0^{17} \text{IEAC[IEAC 3]} \cdot 0^{18} \text{IEAC[IEAC 4]} \cdot 0^{19} \text{IEAC[IEAC 5]} \cdot 0^{20} \text{CL}\end{cases}
\]

where \( \theta_{CL} \) is \( \theta_1, \theta_{20}, \theta_{21}, \theta_{22}, \) and \( \theta_{23} \) for patients on unknown dialysis, HD, CAPD, CVVHD and CVVHDF, respectively.

\[
V_{CI} = \theta_{CI} e^{\theta_{CI} \eta_{CI}}
\]

where \( \theta_{CI} \) is \( \theta_{24}, \theta_{25} \) and \( \theta_2 \) for CVVHD, CVVHDF and all other patients, respectively.

\[
\theta_i = \theta_{Q2} \left\{ \frac{\text{WT (kg)}}{70 (kg)} \right\} \theta_{Q2} e^{\theta_{Q2} \eta_{Q2}}
\]

where \( \theta_{Q2} \) is \( \theta_{26}, \theta_{27} \) and \( \theta_3 \) for CVVHD, CVVHDF and all other patients, respectively.

\[
V_{Pj} = \theta_{Pj} \left\{ \frac{\text{WT (kg)}}{70 (kg)} \right\} \theta_{Pj} e^{\theta_{Pj} \eta_{Pj}}
\]

where \( \theta_{Pj} \) is \( \theta_{28}, \theta_{29} \) and \( \theta_4 \) for CVVHD, CVVHDF and all other patients, respectively.

\[
D1 = \theta_5
\]
achieve more clinical benefit without increased relevant safety risk. As \( C_{\text{min}} > 24.3 \mu \text{g} \text{ml}^{-1} \) may be associated with elevated creatine phosphokinase (CPK) [21], \( C_{\text{min}} \) was used as an additional safety threshold in this investigation.

### Results

#### Population PK model in patients on CRRT

Data from 459 adult patients from the Chaves et al. [15], Corti et al. [16] and Khazdzhynov et al. [17] studies were included in the present population PK model. Of these patients, 385 had CrCl \( \geq 30 \text{ ml min}^{-1} \), 40 were on HD, 14 were on CAPD, and 17 were on CRRT (CVVHD; 9; CVVHDF; 8). Three patients with unknown dialysis status were excluded from the analysis. A summary of the subject demographic and baseline characteristics of the patients on CVVHD and CVVHDF are presented in supplementary Table S1. A concentration–time profile of 24 h after first dose administration in patients on CVVHD and CVVHDF was co-plotted with all the other patients in the pooled dataset in Figure 1.

The final model and parameter estimates were investigated using a predictive check method, with the basic premise that a model and parameters derived from an observed dataset should produce simulated data that are similar to the original observed data. The model evaluation results provided evidence that both the fixed- and random-effects components of the final model were reflective of the observed data. This CRRT final model, which included CVVHD and CVVHDF as covariates, describes the effect of renal clearance and dialysis type on the daptomycin PK parameters: \( CL, V_c, V_p, \) and \( Q_2 \). The model described the daptomycin concentration–time data reasonably well, allowing an estimation of the PK parameters and covariates affecting the PK properties of daptomycin. Plots of the observed vs. predicted concentrations (both individual and population) and of the conditional weighted residuals vs. time and vs. predicted values were well centred, with relatively few outliers (Figure 2). All final population model parameters are provided in supplementary Table S2.

#### Model-predicted vs. observed concentrations of daptomycin in patients undergoing CVVHD and CVVHDF

The final model describes the daptomycin concentration–time data, allowing estimation of the PK parameters and covariates affecting the PK profile of daptomycin. The

| $CL_{\text{Not-on-dialysis}}$ | $\theta_6 \left\{ CLC_0 \left( \text{ml min}^{-1} \right) \right\}^{0.7} \cdot \left\{ \text{Temp} \left( ^\circ \text{C} \right) \right\}^{0.9} \cdot \theta_8 \left[ \text{Female} \right] \cdot \theta_{15} \left[ \text{IEAC[IEAC 1]} \right] \cdot \theta_{16} \left[ \text{IEAC[IEAC 2]} \right] \cdot \epsilon_{\text{CL,i}}$ |
|-----------------------------|---------------------------------------------------------------------------------------------------------------------------------|

The symbols represent the following parameters: \( \eta \), NONMEM inter-individual error; \( \theta \), NONMEM fixed-effect parameter; \( A_1 \), amount in central compartment (mg); \( CL \), clearance; \( CL_{\text{Dialyse}} \), clearance in dialysis patients (l h\(^{-1} \)); \( CL_{\text{Not-on-dialysis}} \), clearance in not-on-dialysis patients (l h\(^{-1} \)); \( CLC_0 \), creatinine clearance at baseline (ml min\(^{-1} \)); \( CP \), concentration in the central compartment (mg l\(^{-1} \)); \( DIAM \), dialysis membrane; \( D_1 \), duration of zero order infusion (h); \( i \), individual; \( INFN \), presence of Gram-positive infection; \( TEMP \), temperature \( ^\circ \text{C} \); \( WT \), weight at baseline (kg). IEAC, independent external adjudication committee (1 = LIE, 2 = complicated RIE, 3 = uncomplicated RIE, 4 = complicated bacteraemia and 5 = uncomplicated bacteraemia).

### Simulations and references for drug exposure

As the number of patients was small in the CRRT subpopulations, a practical parametric bootstrap approach was used in the simulations. A set of individual parameters from the final model (MAP Bayes parameter estimates) with the same number of patients in the original study were sampled (with replacements). The mean \( C_{\text{min}}, C_{\text{max}}, \text{AUC}_{0-24}, \) and \( \text{AUC}_{24-48} \) were computed for each set, following different dosing regimens (4, 6, 8, 10, and 12 mg kg\(^{-1} \) Q24 h or Q48 h) in patients undergoing CVVHD or CVVHDF dialysis. Overall, 100 sets of parameters were drawn to calculate the variability in the PK summary parameters. The simulations were performed in R version v3.3 using the package Rackage v0.5 [19]. Simulated data were presented as means with 95% confidence intervals around the means.

Exposure references for efficacy and safety were derived from controlled clinical trials of daptomycin that demonstrated its efficacy in SAB [20] and tolerability at daily doses up to 12 mg kg\(^{-1} \) [9], as previously published [15]. Daptomycin exposure in patients representative of those in the pivotal IE/bacteraemia study [20], that is patients with SAB/RIE and CrCl \( > 30 \text{ ml min}^{-1} \) treated with 6 mg kg\(^{-1} \) once daily, served as the exposure reference (AUC\(_{0-24h}\) of 465–761 \( \mu \text{g} \text{h ml}^{-1} \)) and \( C_{\text{max}} \) of 66–112 \( \mu \text{g ml}^{-1} \) [15]. The reference for safety threshold (AUC\(_{0-24h}\) of 1422 \( \mu \text{g} \text{h ml}^{-1} \)) was the 75th percentile of the steady state AUC\(_{0-24h}\) reported in healthy volunteers with normal renal function who received daptomycin at 12 mg kg\(^{-1} \) Q24 h, the highest well-tolerated dose used in controlled clinical trials [9, 15]. From a clinical point of view, any individual patient with 24 h AUC or \( C_{\text{max}} \) above the upper efficacy boundary, but not exceeding the safety threshold, may
individual and population predicted vs. observed concentrations of daptomycin in individual patients on CVVHD \((n = 9;\) NONMEM ID, 5001–5009) and CVVHDF \((n = 8;\) NONMEM ID, 6001–6005 and 6007–6009) are shown in Figure 3. In general, the population and individual predictions superimposed the observed data except for one subject \((6003)\), where the model appeared to slightly overpredict the data on Day 1 but not on Days 3 and 5, most likely due to an experimental error on Day 1.

**Model-predicted PK parameters of daptomycin in patients undergoing CVVHD and CVVHDF**

The PK parameter values for a typical subject \((70 \text{ kg male with } \text{CrCl} \geq 30 \text{ ml min}^{-1})\) were \(\text{CL}_{\text{Not-on-dialysis}} = 0.75 \text{ l h}^{-1}, V_c = 4.86 \text{ l}, V_p = 3.20 \text{ l},\) and \(Q_2 = 3.69 \text{ l h}^{-1}\) (Table 2). These point estimates of the parameters and the estimates of unexplained inter-individual variability were consistent with those estimated previously in the base model without the patients on CRRT shown in Table 2 \((\text{e.g. } 11.4 \text{ ml h}^{-1} \text{ kg}^{-1}, \text{or } 0.80 \text{ l h}^{-1} \text{ at } 70 \text{ kg})\) \([15]\). This similarity was also noted for patients on HD \((0.22 \text{ l h}^{-1} \text{ vs. } 3.43 \text{ ml h}^{-1} \text{ kg}^{-1} \text{ or } 0.24 \text{ l h}^{-1} \text{ at } 70 \text{ kg})\) and CAPD \((0.24 \text{ l h}^{-1} \text{ vs. } 2.98 \text{ ml h}^{-1} \text{ kg}^{-1} \text{ or } 0.21 \text{ l h}^{-1} \text{ at } 70 \text{ kg})\) when compared with the base model \([15]\). These results increase the confidence in the estimation of the PK parameters for the CRRT patients.

Table 2 and Figure 4 show the model-predicted typical total \(\text{CL}\) of daptomycin in patients undergoing different dialysis methods vs. patients not on dialysis. In patients undergoing CVVHD, the \(\text{CL} (0.94 \text{ l h}^{-1})\) was 1.25-fold greater than that in patients with \(\text{CrCl} \geq 30 \text{ ml min}^{-1} (0.75 \text{ l h}^{-1})\) and was approximately 4.3 and 3.9-fold greater than that in typical HD \((0.22 \text{ l h}^{-1})\) and CAPD \((0.24 \text{ l h}^{-1})\), respectively. The total \(\text{CL}\) in patients undergoing CVVHDF \((0.53 \text{ l h}^{-1})\) was 29% lower than the estimated total \(\text{CL}\) in patients with \(\text{CrCl} \geq 30 \text{ ml min}^{-1}\) and was slightly more than 2-fold greater than that in typical HD and CAPD patients.

Interestingly, both \(V_c\) and \(V_p\) in both CVVHD and CVVHDF patients were higher than those of the not-on-dialysis patients. The \(Q_2\) value in CVVHD was much higher than that of the not-on-dialysis patients; however, in CVVHDF, it was lower than that of the not-on-dialysis patients \((\text{Table 2})\). Individual estimated daptomycin PK parameters for CVVHD and CVVHDF patients are
out a potentially increased risk of toxicity. With a 95% CI, this
error was 11%.

Depending on the daptomycin concentration profile (Figure 1)
summarized in supplementary Table S3. Shrinkage between
subject variability for CL, Vc, Qd, and Vd was 10.0%, 7.52%,
28.5% and 40.9%, respectively. The residual inter-subject
error was 11%.

Simulations of AUC in patients undergoing
CVVHD and CVVHDF
The predicted means with 95% confidence intervals of the
AUC at steady state (AUCss) Cmax and Cmin for Q24 h and
Q48 h dosing in patients undergoing CRRT are summarized
in Table 3.

Daptomycin dosing Q24 h at 4–12 mg kg⁻¹ resulted in a
mean systemic exposures of 335–999 μg h ml⁻¹ and
508–1475 μg h ml⁻¹ in patients undergoing CVVHD and
CVVHDF, respectively. If dosed at 4–12 mg kg⁻¹ Q48 h, the
mean systemic exposure was 272–799 μg h ml⁻¹ on the first
day after dosing and 63–182 μg h ml⁻¹ on the second day in
CVVHD patients, and the mean systemic exposure was
383–1129 μg h ml⁻¹ and 126–361 μg h ml⁻¹ on the first and
second days, respectively, in CVVHDF patients.

The mean AUCss was predicted to be above the lower
boundary of the efficacy threshold for SAB/RIE but below the
safety threshold in CVVHD (at 8–12 mg kg⁻¹) and CVVHDF (at 6–12 mg kg⁻¹)
patients during the first day, but fall below the lower bound-
ary of the efficacy threshold on the second day at all dose
levels (4–12 mg kg⁻¹).

Simulations of Cmax and Cmin in patients
undergoing CVVHD and CVVHDF
Daptomycin dosing Q24 h at 4–12 mg kg⁻¹ resulted in a
mean Cmax of 46–137 μg ml⁻¹ and 57–169 μg ml⁻¹ in patients
undergoing CVVHD and CVVHDF, respectively. With Q48 h
dosing, daptomycin at 4–12 mg kg⁻¹ resulted in a mean Cmax
of 42–124 μg ml⁻¹ and 49–147 μg ml⁻¹ in patients undergo-
ing CVVHD and CVVHDF, respectively (Table 3). The mean
Cmax in the CVVHDF (at 6–12 mg kg⁻¹ Q48 h or at
8–12 mg kg⁻¹ Q48 h) patients was above the lower boundary
of the efficacy threshold for SAB/RIE, but below the safety
threshold. Regardless of Q24 h or Q48 h dosing, CVVHDF
(at 6–12 mg kg⁻¹) patients achieved mean Cmax above the
lower boundary of the efficacy threshold for SAB/RIE but
below the safety threshold. Daptomycin dosing Q24 h at
4–12 mg kg⁻¹ resulted in a mean Cmin of 6.2–18.0 μg ml⁻¹
and 11.0–32.2 μg ml⁻¹ in patients undergoing CVVHD and
CVVHDF, respectively. With Q48 h dosing, daptomycin at
4–12 mg kg⁻¹ resulted in a mean Cmin of 1.2–3.5 μg ml⁻¹
and 3.1–8.8 μg ml⁻¹ in patients undergoing CVVHD and
CVVHDF, respectively (Table 3). Although the mean Cmin is
below 24.3 μg ml⁻¹ in patients undergoing CVVHDF who
received 6–8 mg kg⁻¹ Q24 h, some patients will have a Cmin
> 24.3 μg ml⁻¹ based on 95% CI. With Q24 h dosing, dap-
tomycin at 10–12 mg kg⁻¹ resulted in a mean Cmin > 24.3 μg ml⁻¹
in patients undergoing CVVHDF. All patients on CVVHD
and CVVHDF receiving 4–12 mg kg⁻¹ of daptomycin maintained
a Cmin < 24.3 μg ml⁻¹ with daptomycin dosing Q48 h.

Discussion
A previously reported population PK model for daptomycin
was used as a framework to analyse the PK profiles in patients
undergoing CRRT. The present population PK model reason-
ably describes daptomycin concentration profiles in patients
undergoing CVVHD or CVVHDF.

Our analysis suggests that the clearance in CVVHDF pa-
tients was 29% lower, while the clearance in CVVHD patients
was 25% higher than that in patients with CrCl ≥ 30 ml
min⁻¹. This finding was consistent with the reports of Churchwell
et al. [22] and Clark et al. [23]. In the Churchwell et al.
report [22], continuous haemofiltration and CVVHDF led to
higher daptomycin clearance compared with HD in a bovine
model. The main factors affecting clearance were filter surface
and ultrafiltrate and dialysis flow rates. In the Clark et al.
report [23], drug clearance was significantly reduced in con-
tinuous haemofiltration by prefilter fluid replacement. This
could possibly explain the lower daptomycin clearance ob-
served in CVVHDF patients compared with those in CVVHD
patients in the present analysis. In the study by Corti et al.,
higher flow rates were used in CVVHD patients compared
with those in CVVHDF patients, resulting in higher clearance
in these patients [16]. Furthermore, prefilter solute substitu-
tion in four of their patients could also account for decreased
filter clearance. Although these results should be interpreted with caution due to the small sample size, the overall estimated higher clearance of daptomycin in CRRT patients is consistent with the CRRT procedure, wherein drugs and waste products are removed more efficiently on a continuous basis than with thrice-weekly intermittent HD [10, 11]. Previous studies have also shown that clearance of daptomycin by CRRT accounted for approximately 40–50% of the total drug clearance [16, 17, 24], which is comparable to the amount of drug cleared by the kidneys in patients with normal renal function (34–54%) [25].

With Q24 h dosing, mean AUC$_{ss}$ in patients on CVVHD (at 6–12 mg kg$^{-1}$) and CVVHDF (at 4–10 mg kg$^{-1}$) was above the lower boundary of the efficacy threshold for SAB/RIE but below the safety threshold every day. Q48 h dosing resulted in appropriate drug levels in a similar proportion of patients in the first 24 h (AUC$_{0–24h}$); however, all patients receiving doses up to 12 mg kg$^{-1}$ Q48 h had AUC below the reference range for efficacy in SAB/RIE every second day (AUC$_{24–48h}$). Drug concentrations decrease over time and are markedly lower on the second day after Q48 h dosing. Adequate efficacy is at risk every second day after Q48 h dosing.

Results of this analysis show that the difference in mean $C_{\text{max}}$ following Q24 h and Q48 h dosing in patients undergoing the same CRRT method is <15%. CVVHD (at 6–12 mg kg$^{-1}$ Q24 h and at 8–12 mg kg$^{-1}$ Q48 h) patients achieved $C_{\text{max}}$ above the lower boundary of the efficacy threshold for SAB/RIE but below the safety threshold. Regardless of Q24 h or Q48 h dosing, CVVHDF (at 6–12 mg kg$^{-1}$) patients achieved mean $C_{\text{max}}$ above the lower boundary of the efficacy threshold but below the safety threshold. Similarity in $C_{\text{max}}$ between the Q24 h and Q48 h dosing regimens in this simulation is expected at the same dose level. However, the clinical relevance of ‘missing’ $C_{\text{max}}$ every second day, which is associated with Q48 h dosing, has not been well investigated and its potential impact remains unclear. Nevertheless, Q24 h dosing of

---

**Figure 2**

Goodness-of-fit diagnostic plots: A) DV vs. PRED for CVVHD patients; B) DV vs. IPRED for CVVHD patients; C) DV vs. PRED for CVVHDF patients; D) DV vs. IPRED for CVVHDF patients; E) Weighted residuals vs. PRED; F) Weighted residuals vs. time in h. Black cross, CVVHD patients; grey circle, all other patients in parts A & B. Red triangle, CVVHDF patients; grey circle, all other patients in parts C & D. Black circle, CVVHD patients; red circle, CVVHDF patients; grey circle, all other patients in parts E & F. CVVHD, continuous veno-venous haemodialysis; CVVHDF, continuous veno-venous haemofiltration; DV, observation; IPRED, individual prediction; PRED, population prediction.
Daptomycin in CRRT patients provided comparable systemic exposure (AUC) to that with Q24 h dosing in patients with CrCl ≥ 30 ml min⁻¹. In contrast, daptomycin dosing Q48 h was associated with a high risk of considerably low systemic exposure every second day after dosing in CRRT patients and thus may be detrimental to clinical outcomes. This is valid for all daptomycin doses evaluated in controlled clinical trials – up to 12 mg kg⁻¹.

Excessive drug exposure may be a safety concern. The AUC and C_max results obtained indicate that doses up to 12 mg kg⁻¹ in patients undergoing CVVHD do not exceed the defined safety threshold in randomized clinical trials, regardless of the dosing interval. Additionally, the mean C_min of doses up to 12 mg kg⁻¹ in CVVHD also remain clearly below the safety threshold (> 24.3 μg ml⁻¹), which may be associated with a higher risk of CPK elevation in plasma.

Figure 3
Model-predicted vs. observed daptomycin concentrations in patients undergoing CVVHD and CVVHDF. Solid line, individual prediction; dashed line, population prediction; blue dots in part A, observed data from the Khadzhynov et al. [17] (5001–5008) and Corti et al. [16] (5009) studies; red dots in part B, observed data from the Corti et al. study [16]. CVVHD, continuous veno-venous haemodialysis; CVVHDF, continuous veno-venous haemodiafiltration.
However, the mean AUC and $C_{\text{max}}$ results in patients undergoing CVVHDF and receiving doses of 10–12 mg kg$^{-1}$ Q24 h are close to or above these safety thresholds. Therefore, careful safety monitoring in patients undergoing CVVHDF is indicated, especially in clinical situations demanding the use of high daptomycin doses (≥10 mg kg$^{-1}$) once daily, as suggested in recent treatment guidelines and expert recommendations in Europe and the USA [26–31]. CPK levels in the blood are a sensitive marker of daptomycin-related muscle toxicity, and regular monitoring during therapy is recommended in all patients with renal impairment regardless of the dose regimen.

Other authors have also shown that Q24 h dosing is a more appropriate dosing strategy in patients undergoing CRRT without the risk of exposure above the target ranges [32, 33]. Preiswerk et al. [32] showed that daptomycin exposure in critically ill patients undergoing CRRT after once-daily dosing was similar to that in ICU patients with normal renal function. In the study by Rudiger et al. [33], nine critically ill patients undergoing CVVHDF were administered 4–6 mg kg$^{-1}$ of daptomycin in a once-daily dosing regimen (effluent flow 30–40 ml kg$^{-1}$ h$^{-1}$). No daptomycin accumulation was seen in any of the patients. The $C_{\text{max}}$ and $C_{\text{min}}$ were rather variable, and ranged between 24.7–69.7 μg ml$^{-1}$ and 2.7–11.9 μg ml$^{-1}$, respectively, with the 4 mg kg$^{-1}$/day dose ($n = 4$); between 34.7–35.7 μg ml$^{-1}$ and 3–3.7 μg ml$^{-1}$, respectively, with the 5 mg kg$^{-1}$/day dose ($n = 2$); and between 20.5–61.7 μg ml$^{-1}$ and 1.5–15.9 μg ml$^{-1}$, respectively, with the 6 mg kg$^{-1}$/day dose ($n = 2$). Based on these findings, the authors concluded that 6 mg kg$^{-1}$ Q24 h could be insufficient in patients undergoing CVVHDF compared with the plasma concentrations attained in healthy volunteers. Overall, our results are largely consistent with those from Preiswerk et al. [32] and Rudiger et al. [33], who also concluded that daily-dosing regimens with daptomycin are more appropriate than dosing every second day in CRRT patients.

Contrary to the aforementioned Q24 h dosing recommendations, a few authors have recommended Q48 h dosing.

### Table 2

**Daptomycin typical PK parameters by dialysis type**

| Dialysis type | Estimated parameters from final model | Estimated parameters from base model [15] |
|---------------|--------------------------------------|------------------------------------------|
|               | CL (l h$^{-1}$) (SE) | $V_c$ (l) (SE)$^a$ | $Q_2$ (l h$^{-1}$) (SE)$^a$ | $V_p$ (l) (SE)$^a$ | CL (l h$^{-1}$) (%CV) | $V_c$ (l) (%CV) | $Q_2$ (l h$^{-1}$) (%CV) | $V_p$ (l) (%CV) |
| Not-on-dialysis | 0.75 (0.03) | 0.75 (3) |
| HD | 0.22 (0.06) | 4.86 (0.04) | 3.69 (0.06) | 3.20 (0.03) | 0.24 (1) | 4.89 (3%) | 3.64 (4%) | 3.19 (3%) |
| CAPD | 0.24 (0.08) | 0.21 (1) |
| CVVHD | 0.94 (0.06) | 5.74 (0.08) | 7.11 (0.15) | 4.89 (0.07) | –– | –– | –– | –– |
| CVVHDF | 0.53 (0.14) | 6.53 (0.06) | 2.88 (0.35) | 3.85 (0.16) | –– | –– | –– | –– |

$^a$ $V_c$, $V_p$ and $Q_2$ were estimated separately for CVVHD and CVVHDF.

CAPD, continuous ambulatory peritoneal dialysis; CL, clearance; CVVHD, continuous veno-venous haemodialysis; CVVHDF, continuous veno-venous haemodiafiltration; HD, haemodialysis; PK, pharmacokinetics; $Q_2$, inter-compartmental clearance; SE, standard error; $V_c$, central volume of distribution; $V_p$, peripheral volume of distribution.

### Figure 4

Model-predicted total clearance of daptomycin in different patient populations. Note: Three patients in whom it was unknown whether or not they were on dialysis were excluded from this analysis. Boxplot: whiskers (5th and 95th percentiles); box (25th and 75th percentiles); line (median). CAPD, continuous ambulatory peritoneal dialysis; CVVHD, continuous veno-venous haemodialysis; CVVHDF, continuous veno-venous haemodiafiltration; HD, haemodialysis.
frequency [24, 34, 35]. Although the PK simulation results from the Vilay et al. [24] study are generally consistent with previously published results, the authors used \( AUC_{0-24h} \) as an exposure indicator without considering that daptomycin concentration decreases over time and is markedly lower in patients on dialysis the second day after \( Q_{48h} \) dosing, as demonstrated by our results and those of others [15, 36]. The use of \( AUC_{0-24h} \) as an exposure indicator does not accurately indicate the needed exposure to ensure efficacy at every 24 h interval. The same limitation applies to the reports by Falcone et al. [35] and Wenisch et al. [34], in which \( Q_{48h} \) dosing was used.

Since the mean time for clearance of methicillin-resistant \( S. aureus \) infection with daptomycin therapy in patients with IE/bacteraemia is > 1 week [20], exposure to suboptimal antimicrobial concentrations on any day of treatment could be associated with treatment failure and the development of antimicrobial resistance [15]. The risk of suboptimal antimicrobial concentrations and resistance also increases with the occurrence of biofilms on the surfaces of catheters and foreign devices that are frequently used in CRRT patients [37]. Hence, appropriate systemic exposure every day is crucial to avoid detrimental effects in patients.

The \( Q_{24h} \) dosing interval recommendation based on this investigation is applicable to comparable \( CVVHD \) and \( CVVHDF \) procedures (e.g. high-flux filter with 1.4–1.8 m² surface, blood flow of 100–200 ml min \(^{-1} \) and target dialysis flow rate of 30–40 ml kg \(^{-1} \) h \(^{-1} \)). Although this represents common practice in the ICU, cases may exist wherein the dialysis procedure could differ largely from this procedure and therefore the dose recommendation will possibly not be applicable under those conditions. Regardless of the daptomycin dose, frequent monitoring of blood CPK levels is indicated in all patients with renal impairment to ensure that this drug is used safely.

In conclusion, the clearance of daptomycin in patients undergoing CRRT is similar to that in patients with normal renal function (CrCl ≥ 30 ml min \(^{-1} \)). The final model predicts that administration of daptomycin \( Q_{24h} \) will result in exposure levels to achieve adequate efficacy, generally without the risk of increased toxicity (except for doses ≥ 10 mg kg \(^{-1} \) in \( CVVHDF \)). In contrast, \( Q_{48h} \) dosing in patients undergoing

### Table 3

Simulation of \( AUC, \) \( C_{\text{max}} \) and \( C_{\text{min}} \) in patients on \( CVVHD \) and \( CVVHDF \) using \( Q_{24h} \) and \( Q_{48h} \) dosing frequencies

| Dose (mg kg \(^{-1} \)) | 4    | 6    | 8    | 10   | 12   |
|------------------------|------|------|------|------|------|
| \( Q_{24h} \) dosing    |      |      |      |      |      |
| \( CVVHD \)             |      |      |      |      |      |
| Mean \( AUC_{0-24h} \) \( \mu g \) ml \(^{-1} \) | 335 (285, 387) | 498 (412, 563) | 673 (563, 750) | 839 (717, 942) | 999 (854, 1146) |
| Mean \( C_{\text{max}} \) \( \mu g \) ml \(^{-1} \) | 46 (40, 51) | 69 (61, 75) | 92 (81, 101) | 115 (102, 130) | 137 (122, 157) |
| Mean \( C_{\text{min}} \) \( \mu g \) ml \(^{-1} \) | 6.2 (4.8, 7.6) | 9.0 (6.9, 10.9) | 12.0 (9.6, 14.8) | 15.4 (12.4, 17.9) | 18.0 (14.6, 22.5) |
| \( CVVHDF \)            |      |      |      |      |      |
| Mean \( AUC_{0-24h} \) \( \mu g \) ml \(^{-1} \) | 508 (359, 681) | 712 (527, 1017) | 1000 (671, 1289) | 1203 (819, 1813) | 1475 (1082, 1896) |
| Mean \( C_{\text{max}} \) \( \mu g \) ml \(^{-1} \) | 57 (46, 69) | 82 (68, 103) | 113 (90, 133) | 139 (112, 180) | 169 (142, 196) |
| Mean \( C_{\text{min}} \) \( \mu g \) ml \(^{-1} \) | 11.0 (6.7, 16.5) | 15.4 (9.6, 24.8) | 21.7 (12.1, 30.7) | 26.5 (14.8, 45.3) | 32.2 (20.0, 44.3) |
| \( Q_{48h} \) dosing    |      |      |      |      |      |
| \( CVVHD \)             |      |      |      |      |      |
| Mean \( AUC_{0-24h} \) \( \mu g \) ml \(^{-1} \) | 272 (235, 307) | 404 (354, 450) | 542 (460, 607) | 684 (571, 761) | 799 (692, 899) |
| Mean \( AUC_{24h} \) \( \mu g \) ml \(^{-1} \) | 63 (47, 77) | 93 (74, 113) | 126 (95, 161) | 158 (118, 194) | 182 (141, 222) |
| Mean \( C_{\text{max}} \) \( \mu g \) ml \(^{-1} \) | 42 (36, 48) | 62 (55, 68) | 82 (72, 92) | 104 (89, 117) | 124 (108, 142) |
| Mean \( C_{\text{min}} \) \( \mu g \) ml \(^{-1} \) | 1.2 (0.9, 1.6) | 1.8 (1.4, 2.3) | 2.4 (1.7, 3.3) | 3.1 (2.1, 3.9) | 3.5 (2.5, 4.5) |
| \( CVVHDF \)            |      |      |      |      |      |
| Mean \( AUC_{0-24h} \) \( \mu g \) ml \(^{-1} \) | 383 (278, 493) | 558 (439, 708) | 759 (574, 997) | 936 (751, 1243) | 1129 (891, 1479) |
| Mean \( AUC_{48h} \) \( \mu g \) ml \(^{-1} \) | 126 (63, 182) | 180 (102, 267) | 244 (132, 387) | 304 (183, 466) | 361 (212, 567) |
| Mean \( C_{\text{max}} \) \( \mu g \) ml \(^{-1} \) | 49 (41, 57) | 73 (63, 85) | 98 (83, 117) | 121 (107, 145) | 147 (126, 174) |
| Mean \( C_{\text{min}} \) \( \mu g \) ml \(^{-1} \) | 3.1 (1.3, 5.0) | 4.5 (2.0, 7.3) | 6.1 (2.6, 10.6) | 7.8 (3.7, 12.7) | 8.8 (4.3, 15.7) |

- \( a \) Apply for the first day.
- \( b \) Apply for the second day.

Efficacy exposure reference is \( AUC_{0-24h} \) of 465–761 \( \mu g \) ml \(^{-1} \) and safety threshold is \( AUC_{0-24h} \) of 1422 \( \mu g \) ml \(^{-1} \). Data are presented as mean (95% CI). \( AUC \), area under the plasma concentration–time curve; \( AUC_{ss} \), area under the plasma concentration–time curve at steady state; \( C_{\text{max}} \), maximum plasma concentration; \( C_{\text{min}} \), minimum plasma concentration; \( CVVHD \), continuous veno-venous haemodialysis; \( CVVHDF \), continuous veno-venous haemodiafiltration; \( Q_{24h} \), every 24 h; \( Q_{48h} \), every 48 h.
CRRT is likely to result in exposure levels below the efficacy requirement every second day and thus be detrimental to patient outcomes.

**Competing Interests**

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: X.X., K.H. and M.L. are employees of Novartis Pharmaceuticals Corporation and R.L.C. is an employee of Novartis Pharma AG; these authors may thus be eligible for Novartis stock and stock options. HP has received research funding and lecture honoraria from Novartis and Fresenius Medical Care AG & Co. N.C. has been a member of the advisory board of Novartis and has received travel and accommodation grants from Novartis. D.K. has no disclosures to provide.

The analysis was sponsored by Novartis Pharma AG, Basel, Switzerland. This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

The authors acknowledge Geetanjali Tonpe and Anupama Tamta (Novartis Healthcare Pvt. Ltd., Hyderabad, India) for providing medical writing assistance for this manuscript.

**Contributors**

All authors had full access to all data and take responsibility for the integrity of the data and accuracy of analyses. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors. D.K., H.P. and N.C. had collected data from patients undergoing CVVHD and CVVHDF in two previous studies. X.X., K.H. and M.L. planned the update of a previously published population PK model. X.X. and M.L. updated the model. All authors actively participated in the preparation of the manuscript and provided critical review at each step. All authors read and approved the final manuscript.

**References**

1. Li PK, Burdmann EA, Mehta RL. World Kidney Day Steering C. Acute kidney injury: global health alert. Kidney Int 2013; 83: 372–6.

2. Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S, et al. Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA 2005; 294: 813–8.

3. Pannu N, Gibney RN. Renal replacement therapy in the intensive care unit. Ther Clin Risk Manag 2005; 1: 141–50.

4. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract 2012; 120: c179–84.

5. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney Int 2012; 2: 11–38.

6. Centers for Disease Control and Prevention. Invasive methicillin-resistant *Staphylococcus aureus* infections among dialysis patients—United States, 2005. MMWR Morb Mortal Wkly Rep 2007; 56: 197–9.

7. Boucher BA, Wood GC, Swanson JM. Pharmacokinetic changes in critical illness. Crit Care Clin 2006; 22: 255–71.

8. Safdar N, Andes D, Craig WA. *In vivo* pharmacodynamic activity of daptomycin. Antimicrob Agents Chemother 2004; 48: 63–8.

9. Benvenuto M, Benziger DP, Yankelev S, Vigliani G. Pharmacokinetics and tolerability of daptomycin at doses up to 12 milligrams per kilogram of body weight once daily in healthy volunteers. Antimicrob Agents Chemother 2006; 50: 3245–9.

10. Clark WR, Mueller BA, Alaka KJ, Macias WL. A comparison of metabolic control by continuous and intermittent therapies in acute renal failure. J Am Soc Nephrol 1994; 4: 1413–20.

11. Mueller BA, Pasko DA, Sowinski KM. Higher renal replacement therapy dose delivery influences on drug therapy. Artif Organs 2003; 27: 808–14.

12. Susla GM. The impact of continuous renal replacement therapy on drug therapy. Clin Pharmacol Ther 2009; 86: –5.

13. Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. Cubicin (Daptomycin) Prescribing Information 2015 [online]. Available at https://www.merck.com/product/usa/pi_circulars/c/cubicin/cubicin_pi.pdf (last accessed 1 October 2016).

14. Novartis Pharmaceuticals UK Ltd. Cubicin powder for concentrate for solution for injection or infusion. Summary of Product Characteristics, 2015. Available at http://www.medicines.org.uk/emc/medicine/17341 (last accessed 1 October 2016).

15. Chaves RL, Chakraborty A, Benziger D, Tannenbaum S. Clinical and pharmacokinetic considerations for the use of daptomycin in patients with *Staphylococcus aureus* bacteraemia and severe renal impairment. J Antimicrob Chemother 2014; 69: –10.

16. Corti N, Rudiger A, Chiesa A, Marti I, Jetter A, Rentsch K, et al. Pharmacokinetics of daily daptomycin in critically ill patients undergoing continuous renal replacement therapy. Chemotherapy 2013; 59: 143–51.

17. Khadzhykov D, Słowiński T, Lieber I, Spies C, Puhlmann B, König T, et al. Plasma pharmacokinetics of daptomycin in critically ill patients with renal failure and undergoing CVVHD. Int J Clin Pharmacol Ther 2011; 49: 656–65.

18. Dvorchik B, Arbeid RD, Chung J, Liu S, Knebel W, Kastrissios H. Population pharmacokinetics of daptomycin. Antimicrob Agents Chemother 2004; 48: 2799–807.

19. Wang W, Hallow KM, James DA. A tutorial on RxODE: simulating differential equation pharmacometric models in R. CPT Pharmacometrics Syst Pharmacol 2016; 5: 3–10.

20. Fowler VG Jr, Boucher HW, Corey GR, Abrutyn E, Karchmer AW, Rupp ME, et al. Daptomycin versus standard therapy for bacteraemia and endocarditis caused by *Staphylococcus aureus*. N Engl J Med 2006; 355: 653–65.

21. Bhavnani SM, Rubino CM, Ambrose PG, Drusano GL. Daptomycin exposure and the probability of elevations in the creatine phosphokinase level: data from a randomized trial of patients with bacteraemia and endocarditis. Clin Infect Dis 2010; 50: 1568–74.

22. Churchill MD, Pasko DA, Mueller BA. Daptomycin clearance during modeled continuous renal replacement therapy. Blood Purif 2006; 24: 548–54.
23 Clark WR, Turk JE, Kraus MA, Gao D. Dose determinants in continuous renal replacement therapy. Artif Organs 2003; 27: 815–20.

24 Vilay AM, Grio M, Depestel DD, Sowinski KM, Gao L, Heung M, et al. Daptomycin pharmacokinetics in critically ill patients receiving continuous venovenous hemodialysis. Crit Care Med 2011; 39: 19–25.

25 Woodworth JR, Nyhart EH Jr, Brier GL, Wolny JD, Black HR. Single-dose pharmacokinetics and antibacterial activity of daptomycin, a new lipopeptide antibiotic, in healthy volunteers. Antimicrob Agents Chemother 1992; 36: 318–25.

26 Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. Clin Infect Dis 2011; 52: e18–55.

27 Gould IM, Cauda R, Esposito S, Gudiol F, Mazzei T, Garau J. Management of serious meticillin-resistant Staphylococcus aureus infections: what are the limits? Int J Antimicrob Agents 2011; 37: 202–9.

28 Vidaillac C, Steed ME, Rybak MJ. Impact of dose de-escalation and escalation on daptomycin’s pharmacodynamics against clinical meticillin-resistant Staphylococcus aureus isolates in an in vitro model. Antimicrob Agents Chemother 2011; 55: 2160–5.

29 Gudiol F, Aguado JM, Almirante B, Bouza E, Cercenado E, Dominguez MA, et al. Diagnosis and treatment of bacteremia and endocarditis due to Staphylococcus aureus. A clinical guideline from the Spanish Society of Clinical Microbiology and Infectious Diseases (SEIMC. Enferm Infecc Microbiol Clin 2015; 33: 625e1–e23.

30 Gudiol F, Aguado JM, Pascual A, Pujol M, Almirante B, Miro JM, et al. Consensus document for the treatment of bacteremia and endocarditis caused by methicillin-resistant Staphylococcus aureus. Sociedad Espanola de Enfermedades Infecciosas y Microbiologia Clinica. Enferm Infecc Microbiol Clin 2009; 27: 105–15.

31 Mensa J, Barberan J, Llinares P, Picazo J, Bouza E, Alvarez-Lerma F, et al. Guidelines for the treatment on infections caused by methicillin-resistant Staphylococcus aureus. Rev Esp Quimioter 2008; 21: 234–58.

32 Preiswerk B, Rudiger A, Fehr J, Corti N. Experience with daptomycin daily dosing in ICU patients undergoing continuous renal replacement therapy. Infection 2013; 41: 553–7.

33 Rudiger A, Rentsch K, Maggiorini M, Corti N. Daptomycin pharmacokinetics in critically ill patients undergoing continuous renal replacement therapy. Crit Care Med. author reply 4–5 2011; 39: 1243–4.

34 Wenisch JM, Meyer B, Fuhrmann V, Saria K, Zuba C, Dittrich P, et al. Multiple-dose pharmacokinetics of daptomycin during continuous venovenous haemodiafiltration. J Antimicrob Chemother 2012; 67: 977–83.

35 Falcone M, Russo A, Cassetta MI, Lappa A, Tritapepe L, Fallani S, et al. Daptomycin serum levels in critical patients undergoing continuous renal replacement. J Chemother 2012; 24: 253–6.

36 Patel N, Cardone K, Grabe DW, Meola S, Hoy C, Manley H, et al. Use of pharmacokinetic and pharmacodynamic principles to determine optimal administration of daptomycin in patients receiving standardized thrice-weekly hemodialysis. Antimicrob Agents Chemother 2011; 55: 1677–83.

37 Hall-Stoodley L, Costerton JW, Stoodley P. Bacterial biofilms: from the natural environment to infectious diseases. Nat Rev Microbiol 2004; 2: 95–108.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site:

http://onlinelibrary.wiley.com/doi/10.1111/bcp.13131/suppinfo.

Table S1 Detailed patient demographic and baseline characteristics – CVVHD and CVVHDF populations

Table S2 All population model parameter estimates of the final model

Table S3 Daptomycin individual estimated PK parameters in CVVHD and CVVHDF patients