**Population pharmacokinetics and dosing considerations for the use of daptomycin in adult patients with haematological malignancies**

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**Abstract**

**OBJECTIVES:** To assess the population pharmacokinetics (PopPK) of daptomycin at the conventional dose of 6 mg/kg/daily in a cohort of oncohaematological patients.

**METHODS:** Patients underwent serial blood sampling on day 3 of therapy (before dosing and at 0, 0.5, 1, 2, 3, 5, 7, 9, 12 after dosing) to assess the pharmacokinetic profile of daptomycin. Monte Carlo simulation were performed for defining the probability of target attainment (PTA) of the reference efficacy exposure range (REER) for daptomycin AUC24h (465-761mg∙h/L) and Cmax (66–112mg/L) with 6, 8, 10 and 12 mg/kg/daily.

**RESULTS:** Thirty patients were recruited. A two-compartment open model with first-order intravenous input and first-order elimination was developed. Estimated creatinine clearance (CrCL), serum albumin concentration (Alb), and presence of acute myeloid leukemia (AML) were covarietes included in the final model. Monte Carlo simulation showed that the conventional 6 mg/kg/daily dose resulted in satisfactory drug exposure only in patients with CrCL 50-100 mL/min/1.73 m2, Alb 26-45g/L, and a haematological diagnosis different from AML. Conversely, higher dosages, up to 12 mg/kg daily, were needed to achieve this goal in all of the other tested scenarios. In patients with CrCL 100-150 mL/min/1.73 m2 and Alb <25 g/L, even with the 12 mg/kg/daily dose the proportions of PTA of daptomycin AUC24h below the REER were unacceptably high (>35%). Accordingly, in these scenarios therapeutic drug monitoring could be a useful adjunct for optimized care.

**CONCLUSIONS:** Our study provides a strong rationale for considering daptomycin dosages ≥ 8 mg/kg/daily in several clinical scenarios of oncohaematological patients.

**Introduction**

Bacterial infections are severe life-threatening complications of cytotoxic chemotherapy in neutropenic patients with haematological malignancies.[1](#_ENREF_1) During the last twenty years, bloodstream infections due to Gram-positive microorganisms have become increasingly common in this population,[2](#_ENREF_2) with mortality rates as high as 5%.[3](#_ENREF_3), [4](#_ENREF_4) The prevalence of Gram-positive isolates from blood cultures from febrile oncology and haematology patients was of 18.7%,[5](#_ENREF_5) and increased to 40.9% when considering pathogens yielded from all of the infection sites (blood, lung, skin and soft tissues).[4](#_ENREF_4), [6](#_ENREF_6) Coagulase-negative staphylococci (CoNS) are the most frequent Gram-positive pathogens, with methicillin-resistant (MR) rates of 70-80%.[4](#_ENREF_4), [7](#_ENREF_7) The increase of *vancomycin-resistant Enterococcus* (VRE) is particularly worrisome, with VRE being responsible for up to 41.1% of all Gram-positive bacteremias in oncohaematologic patients..[8](#_ENREF_8" \o "Trubiano, 2015 #62)

Daptomycin is a cyclic lipopeptide antibiotic with potent bactericidal activity against most Gram-positive microorganisms, including*,* MR-CoNS, MR *Staphylococcus aureus* (MRSA) and VRE.[9](#_ENREF_9) Daptomycin is currently used at a dose of 4-6 mg/kg every 24 hours for the treatment of complicated skin and soft tissue infections (cSSTIs), bloodstream infections and endocarditis. ,

Daptomycin is an hydrophilic drug with high plasma protein binding (>90%), relatively small volume of distribution (about 0.1 L/kg), and is primarily eliminated as an unchanged moiety by the kidneys. The elimination half-life is approximately 9 hours.[9](#_ENREF_9), [10](#_ENREF_10) Daptomycin is a valuable alternative to vancomycin because of its extended spectrum of activity and reduced nephrotoxicity.[11](#_ENREF_11), [12](#_ENREF_12)

Patients with haematological malignancies have a number of idiosyncrasices that may alter the pharmacokinetics of hydrophilic antimicrobials such as like daptomycin.[13-15](#_ENREF_13) 12-14 For example, hypoalbuminemia is commonly seen in oncohaematologic patients.[16](#_ENREF_16), [17](#_ENREF_17) In a logistic regression analysis carried out among 948 hospitalized patients, hypoalbuminemia was associated to oncohaematologic diseases with an OR of 2.5.[18](#_ENREF_18) Likewise, augmented renal clearance (ARC), a condition defined as a creatinine clearance (CrCL) > 120 mL/min, has been increasingly described in haematological patients.[19-21](#_ENREF_19)

The aim of this study was to estimate the population pharmacokinetics of daptomycin in a cohort of oncohaematological patients to further establish whether a standard dose of 6 mg/kg/daily results in adequate drug exposure in this patient population.

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**Materials and methods**

***Study design***

This was a prospective observational single centre study carried out between December 2014 and February 2016 at the Santa Maria della Misericordia Universty Hospital of Udine, Italy. Adult oncohematological patients who received daptomycin 6 mg/kg/day infused over 30 min for documented or suspected Gram-positive infections were eligible for the study. Patients underwent serial blood sampling on day 3 of therapy (before dosing and at 0, 0.5, 1, 2, 3, 5, 7, 9, 12 after dosing) to assess the pharmacokinetic profile of daptomycin. The study was approved by the Regional Ethics Committee and informed written consent was obtained from each patient.

Daptomycin plasma concentrations were analyzed using a validated high performance liquid chromatography (HPLC) method with UV detection, as previously described.[22](#_ENREF_22), [23](#_ENREF_23) Precision and accuracy were assessed by performing replicate analysis of quality control samples against calibration standards. Intra- and inter-assay coefficients of variation were always less than 10%. The lower limit of detection was 0.5 mg/L.

Demographic (age, weight, height) and clinical data (co-administered medications, underlying haematologic disease and type of infection) were collected at patient enrollment. Serum creatinine and serum albumin were measured on the day of pharmacokinetic assessment. Creatinine clearance (CrCL) was estimated by means of the Chronic Kidney Disease Epidemiology (CKD-EPI) formula[24](#_ENREF_24) CrCL estimates between 30 and 100 mL/min/1.73 m2 denoted normal renal function, whereas CrCL estimates > 100 mL/min/1.73 m2 denoted a trend toward ARC. Serum albumin levels of 36-45 g/L denoted normal albuminemia; those between 26 and 35 g/L denoted mild hypoalbuminemia, and those ≤ 25 g/L denoted severe hypoalbuminemia.

***Population pharmacokinetic modeling***

A two-compartment open model with first-order intravenous input and first-order elimination was developed with the non-parametric adaptive grid (NPAG) algorithm within the Pmetrics package for R (Los Angeles, CA, USA).[25](#_ENREF_25) An additive lambda model was chosen for the structure of the error model. Estimates of assay errors were included in the modelling process by using the following polynomial function: SD= C0 + C1Y+C2Y2+C3Y3, where Y are the observed concentrations and SD is the standard deviation of the concentrations.

Population pharmacokinetic modelling was performed in two steps. In the first step, a base model parameterized only for daptomycin volume of distribution (Vd) and clearance (CL) was developed. This exploratory model was used to assess the level of relationship of daptomycin Vd and CL with the patient covariates . In the second step, the covariates were included in the structural model. A forward-backward selection process was implemented for covariate inclusion. A decrease greater than 3.84 points in the log-likelihood across models (i.e., P < 0.05) coupled with a decrease of the AIC and the χ2 in the final model compared with the basic model were used as criteria for retaining a covariate in the final model. Model performance was tested by assessing the goodness-of-fit of the observed-predicted plot and the coefficient of determination of the linear regression of the observed-predicted values of each run.

A visual predictive check (VPC) for the final model was developed to assess the fit of the model-predicted concentration-time profiles with the observed data. The model was considered reliable if at least 95% of the observed concentrations ranged within the 95% confidence interval (CI) of the model-predicted concentration-time profiles.

***Definition of daptomycin reference efficacy exposure range and safety threshold***

I, our study, we adopted the daptomycin reference efficacy exposure range (REER) and safety threshold (ST) proposed by Chaves et al.[26](#_ENREF_26) Based on population pharmacokinetic analysis and simulations, these authors selected as daptomycin REER the interquartile range (IQR) between the 25th and 75th percentile of the simulated steady-state AUC24h (465 - 761 mg∙h/L) and Cmax (66 – 112 mg/L) for patients with infective endocarditis and/or staphylococcal bacteraemias with CrCL ≥ 30 mL/min receiving the standard dose of 6 mg/kg every 24h.[26](#_ENREF_26) Daptomycin ST was defined as the 75th percentiles of the steady-state AUC24h (1422 mg∙h/L) and Cmax (197 mg/L) for daptomycin reported in healthy volunteers with normal renal function who received 12 mg/kg every 24 h. This was the highest dose of daptomycin studied in controlled clinical trials, and showed a favorable safety and tolerability profile.[26](#_ENREF_26), [27](#_ENREF_27)

***Monte Carlo simulation*** ***for estimation of daptomycin doses predicting the probability of target attainment of the reference efficacy exposure range (REER) in oncohaematological patients with various underlying conditions.***

The best performing population pharmacokinetic model was used to conduct Monte Carlo simulations with Pmetrics in order to assess the probability of target attainment (PTA) of the daptomycin REER for AUC24h and Cmax with four incremental dosing regimens (6, 8, 10 and 12 mg/kg every 24 hours) in oncohematological patients. A one-thousand patient Monte Carlo simulation was performed for each of the regimens in relation to any eventual covariate that could have been included in the final model. We considered the optimised regimen as one that ensured the highest percentage of PTA of AUC24h falling within the REER, and a less than 10-15 % of PTA falling below the REER and/or above the ST. Distribution of PTA of Cmax was considered as confirmatory data in supporting the choice.

***Statistical analysis***

The Kolmogorov–Smirnov test was used to assess whether data were normally or non-normally distributed. Accordingly, mean ± SD or median with IQR were used for the descriptive statistics. Categorical variables were compared by the χ2 test while continuous variables were compared using the Student’s t-test or Mann–Whitney test, as necessary. Univariate logistic regression analysis was performed to assess the association between daptomycin underexposure and patients’ clinical variables. A P value < 0.05 was required to achieve statistical significance. All statistical analyses and plotting were performed using R version 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

**Results**

***Patients’ characteristics***

Thirty adult oncohaematological patients were recruited in the study. Demographic and clinical characteristics are summarized in Table 1. Median age was 57 years and most of the patients were females (53.3 %). Median estimate of CrCL was 102.2 mL/min/1.73 m2 and 63.3 % of patients (19/30) had a trend toward ARC. Hypoalbuminemia occurred in 60% of patients (18/30), being mild in 53.3 % of cases (16/30) and severe in 6.7% of cases (2/30). Acute myeloid leukemia was the most frequent underlying haematological malignancy (18/30, 60% of patients). Main reasons for daptomycin treatment were bloodstream infections and skin and soft tissue infections, which accounted overall for 90% of cases (27/30). Microbiological isolates were yielded in 40% of patients (12/30). Additional antibiotics were administered in 53.3 % of cases (16/30).

The median of daptomycin AUC24h and Cmax achieved with the standard 6 mg/kg/daily dose were below the REER (435.8 mg.h/L and 55.42 mg/L, respectively), and almost three-quarters of patients experienced drug underexposure. Following univariate logistic regression analysis, the presence of daptomycin AUC24h under the REER was significantly associated with both the presence of CrCL estimates ≥ 100 mL/min/1.73 m2 (OR = 180, C.I. =10.12 - 3198.80; p < 0.001) and that of AML (OR = 4.9, C.I. = 0.99 - 24.2; p = 0.05). Likewise, a positive trend toward the association was observed with severe hypoalbuminemia, even though this did not reach statistical significance (OR = 3.64, C.I. = 0.77 - 17.01; p = 0.101).

***Population pharmacokinetic analysis***

The final two-compartment model that contained patient covariates described daptomycin concentrations very well. The diagnostic plots for the final covariate model (Figure 1) showed a tight relationship between the observed and the predicted concentrations in plasma, both on a population level (R2 = 0.614; bias = 0.584; imprecision = 4.71) and after the Bayesian step (R2 = 0.936; bias = - 0.117; imprecision = 0.644). The distribution of the observed concentrations in plasma was consistent with that of the predicted concentrations, as suggested by the visual predictive check (VPC) plot (Figure 2).

The performance of the different models built for assessing the influence of covariates on daptomycin CL and Vd is reported in Table 2. Estimated CrCL, serum albumin concentration, and AML were significantly correlated with daptomycin CL, whereas body weight was significantly associated with daptomycin Vd. The full multivariable model was as follows:

where TVCL is the typical value of daptomycin CL, TVVd is the typical value of Vd, Alb is serum albumin concentration, and Wt is total body weight. Mean (± SD) and median (IQR) estimates of the pharmacokinetic parameters for the final covariate model are summarized in Table 3.

***Monte Carlo simulation*** ***for estimation of daptomycin doses predicting the probability of target attainment of the reference efficacy exposure range (REER) in oncohaematological patients with various underlying conditions.***

The probability of target attainment (PTA) of the daptomycin REER with incremental doses of 6, 8, 10 and 12 mg/kg/day was simulated in oncohaematological patients according to the underlying clinical conditions that were included as covariates in the final population pharmacokinetic model (CrCL, Alb, diagnosis of AML). Eight different clinical scenarios were simulated in relation to two different classes each for renal function (CrCL 50-100 mL/min/1.73 m2  or 100-150 mL/min/1.73 m2), albuminemia (Alb 26-45 g/L or 15-25 g/L) and type of hematological malignancy (AML or NO AML). The tested scenarios were the following: scenario A, defined as the presence of CrCL 50-100 mL/min/1.73 m2, Alb 26-45 g/L, and NO AML; scenario B, defined as the presence of CrCL 50-100 mL/min/1.73 m2, Alb 26-45 g/L, and AML; scenario C, defined as the presence of CrCL 50-100 mL/min/1.73 m2, Alb 15-25 g/L, and NO AML; scenario D, defined as the presence of CrCL 50-100 mL/min/1.73 m2, Alb 15-25 g/L, and AML; scenario E, defined as the presence of CrCL 101-150 mL/min/1.73 m2, Alb 26-45 g/L and NO AML; scenario F, defined as the presence of CrCL 101-150 mL/min/1.73 m2, Alb 26-45 g/L, and AML; scenario G, defined as the presence of CrCL 101-150 mL/min/1.73 m2, Alb 15-25 g/L, and NO AML; scenario H, defined as presence of CrCL 101-150 mL/min/1.73 m2, Alb 15-25 g/L, and AML.

Consistently, a total of 32 one-thousand Monte Carlo simulation runs were conducted. The distribution of the simulated daptomycin AUC24h and Cmax achievable with the different dosing regimens are depicted in Figure 3 and 4, respectively. In regard to daptomycin AUC24h, the standard 6 mg/kg/daily dose resulted in satisfactory drug exposure (by granting the highest percentage of PTA of AUC24h within the REER, and less than 10-15 % of PTA below the REER and/or above the ST) only for scenario A. Conversely, for all of the other scenarios, higher dosages than the standard one were required for achieving the predefined target (8 mg/kg/daily for the scenario B; 10 mg/kg for the scenarios C and E; 12 mg/kg/daily for the scenarios D, F, G and H). However, it is worth mentioning that in the scenarios G and H, even with the 12 mg/kg/daily dose the proportions of PTA of daptomycin AUC24h below the REER were unacceptably high (35.7 % and 44.0 %, respectively). Accordingly, we believe that in these scenarios therapeutic drug monitoring (TDM) could be a useful adjunct for optimized care.

An algorithm for appropriately choosing the most advisable daptomycin dosing regimen in oncohaematological patients in relation to different classes of underlying haematological disease, creatinine clearance estimates and albumin levels is depicted in Figure 5.

**Discussion**

The present study developed a population pharmacokinetic model for daptomycin in hospitalized patients with haematological malignancies, and simulated the PTA of the REER in plasma with four incremental drug-dosing regimens. Our intention was to identify the best regimens for achieving appropriate drug exposure in oncohematological patients according to various underlying conditions.

The final model accounted for up to 94% of the variability in drug concentrations and adequately fitted daptomycin concentration-time data, providing reliable estimates of the pharmacokinetic parameters. Daptomycin CL and Vd showed wide inter-individual variability across different patient populations. Daptomycin CL ranged from 0.56 L/h to 1.81 L/h in patients with bone and joint infections[28](#_ENREF_28) and in those with sepsis and SA bacteremia[29](#_ENREF_29), respectively. Likewise, Vd ranged from 4.44 L[30](#_ENREF_30) to 12.29 L.[31](#_ENREF_31) Overall, our pharmacokinetic estimates are consistent with those reported by the largest population pharmacokinetic study of daptomycin carried out in patients with CrCL estimates > 80 mL/min (median CL of 0.86 L/h and Vd of 4.44 L).[30](#_ENREF_30) Covariate analysis found that CrCL, AML and ALB may affect the clearance of daptomycin in oncohematological patients.

Several other authors found that CrCL is a major covariate affecting daptomycin CL,[28](#_ENREF_28), [30](#_ENREF_30), [31](#_ENREF_31) and dose adjustments have been recommended for patients with CrCL estimates < 30 mL/min. However, renal insufficiency is a rather infrequent occurrence in hematological patients, among whom mean and median values of CrCL are frequently higher than 100 mL/min/1.73 m2,[20](#_ENREF_20), [32](#_ENREF_32) especially among AML patients.[19](#_ENREF_19)

Augmentation of renal CL has been documented for several hydrophilic antibiotics among AML patients. A 20 % increase of amikacin CL was documented among 207 AML patients,[33](#_ENREF_33) and similar findings for the aminoglycosides were also reported by other authors.[34-36](#_ENREF_34) We and other authors showed that also ceftazidime CL may be increased in AML patients with febrile neutropenia.[15](#_ENREF_15), [37](#_ENREF_37) Consistently, conventional doses of hydrophilic antimicrobials were shown to be inadequate in AML patients. A prospective randomized controlled study was focused on describing piperacillin exposure in febrile neutropenic patients (38% of whom with AML) with a median CrCL of 84 mL/min/1.73 m2. It was shown that the conventional dose of piperacillin/tazobactam (4.5 g every 8 h every 6 h may) did not offer adequate exposure especially among patients with ARC (31% of the study population).[21](#_ENREF_21) Likewise, Lamoth et al. demonstrated that the recommended 2 g daily dose of imipenem was inadequate in ensuring appropriate exposure in febrile neutropenic oncohaematological patients (64.9 % of whom with AML) with a median CrCL of 105 mL/min.[20](#_ENREF_20)

The finding that the diagnosis of AML may by itself be an independent covariate in increasing daptomycin CL is in agreement with that of other authors, which found that AML was an independent predictor of CL increase for both amikacin[33](#_ENREF_33) and vancomycin. It has been hypothesized that in the early time post-chemotherapy the influence of AML on drug CL might be due to glomerular hyperfiltration in response to the huge renal load of proteic cellular catabolites deriving from massive cellular lysis of circulating cells.[38](#_ENREF_38) Other authors suggested that glomerular hyperfiltration might be due to increased cardiac output and systemic inflammatory response promoted by febrile neutropenia.[39](#_ENREF_39)

Albuminemia was the third covariate that improved the predictive performance of our population pharmacokinetic model in estimating daptomycin CL. For antibiotics highly bound to plasma protein, like daptomycin and teicoplanin, severe hypoalbuminemia, by increasing the amount of the free moiety, may promote significant increases of drug CL.[40](#_ENREF_40), [41](#_ENREF_41) Severe hypoalbuminemia is a frequent occurrence among oncoheaematological patients,[18](#_ENREF_18) and our group showed that conventional doses of teicoplanin are often inadequate among AML patients with severe hypoalbuminemia.[14](#_ENREF_14)

Monte Carlo simulations showed that the conventional 6 mg/kg daily dose of daptomycin may be inadequate in several clinical scenarios of oncohaematological patients. Simulation granted attainment of the daptomycin REER only in patients with normal renal function, normal albuminemia or mild hypoalbuminemia, and a diagnosis of haematological disease different from AML. Conversely, higher dosages, up to 12 mg/kg daily, were needed to achieve this goal in all of the other tested scenarios. The most challenging of these was that of AML patients with ARC and severe hypoalbuminemia. Our analysis suggests that when ARC and severe hypoalbuminemia coexist, even the 12 mg/kg/daily dose may not be sufficient in oncohematiological patients. Considering the high probability of drug underexposure predicted by our model in these clinical scenarios, we believe that TDM should be at least considered in this setting. Some limited experience showed the potential usefulness of this approach in routine clinical practice.[22](#_ENREF_22), [29](#_ENREF_29)

The need for high daptomycin dosages ≥ 8 mg/kg/daily has been advocated by several authors, mainly in other patient populations.[27](#_ENREF_27), [29](#_ENREF_29), [42-45](#_ENREF_42) However, the majority of these claims were empirical, and were not supported by robust population pharmacokinetic analysis, as we did for oncohaematological patients in this study.

We are aware of some potential weaknesses of our study. We recognize that the small sample size coupled with the heterogeneity of the patient case-mix might limit the generalizability of the findings. Additionally, some of the interindividual pharmacokinetic variability of daptomycin might not be predicted accurately by our model, as non-renal CL may account for up to 40 % of daptomycin CL.[10](#_ENREF_10) However, the robust population pharmacokinetic analysis is a strength of our work.

In conclusion, our study provides a strong rationale for considering the need for high daptomycin dosages ≥ 8 mg/kg/daily in several clinical scenarios of oncohaematological patients. Additionally, it provides a user-friendly algorithm that may help clinicians in choosing the most advisable dosing regimen in relation to some clinical conditions of frequent occurrence among these patients. We are currently planning a prospective study based on real-time TDM of daptomycin to assess the reliability of this algorithm in clinical practice.

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| Table 1. Demographic characteristics of the population | | | |
| Total number of patients | | | 30 |
| Age (years) | | | 57 (50.3 – 62.5) |
| Gender (male/female) | | | 14/16 |
| Weight (kg) | | | 69.0 (50.0 – 109.0) |
| BMI (kg/m2) | | | 23.9 (18.8 – 39.7) |
| Creatinine clearance (mL/min/1.73 m2) | | | 102.2 (68.2 – 123.2) |
| Albumin (g/L) | | | 33.6 (18.7 – 41.3) |
| Daptomycin AUC24h (mg∙h/L) | | | 435.8 (155.6 – 1006.1) |
| Daptomycin Cmax (mg/L) | | | 55.42 (47.0 – 68.9) |
| Duration of therapy (days) | | | 7 (4 – 16) |
| Time post chemotherapy (days) | | | 12 (9 – 16) |
| Type of hematologic disease | | |  |
|  | | acute myeloid leukemia | 18 (60.0) |
|  | | acute lymphocytic leukemia | 3 (10.0) |
|  | | multiple myeloma | 3 (10.0) |
|  | | lymphoma | 3 (10.0) |
|  | | chronic myeloid leukemia | 1 (3.3) |
|  | | idiopathic myelofibrosis | 1 (3.3) |
|  | | idiopathic thrombocytopenic purpura | 1 (3.3) |
| Type of infections | | |  |
|  | blood stream infection | | 15 (50.0) |
|  | soft and skin tissue infection | | 11 (36.7) |
|  | fever of unknown origin | | 2 (6.7) |
|  | soft and skin tissue infection and blood stream infection | | 1 (3.3) |
|  | thrombophlebitis | | 1 (3.3) |
| Organisms isolated | | |  |
|  | *Staphylococcus* spp. | | 12 (40) |
|  | viridans streptococci | | 2 (6.7) |
|  | *Enterococcus faecalis* | | 1 (3.3) |
| Additional antibiotics | | |  |
|  | piperacillin/tazobactam | | 8 (26.7) |
|  | meropenem | | 3 (10.0) |
|  | levofloxacin | | 2 (6.7) |
|  | amikacin | | 2 (6.7) |
|  | trimethoprim/sulfamethoxazole | | 1 (3.3) |
| Data for continuous variables are presented as median (IQR) and data for dichotomous variables are presented as number (%). | | | |

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| Table 2. Runrecord of the most significant models evaluated in this study with their relative performance indicators | | | | | | | | | | |
| Model type | Parameter | Covariate | Functional form | Log likelihood | AIC | χ2 compared  to base model | Statistics for observed vs. individual predictive analysis | | |
| *R*2 | Bias | Imprecision |
| Base Model | - | - | - | -1869 | 1880 | NA | 0.902 | -0.143 | 0.652 |
| Covariate Models | CL | Alb | Power | -1777 | 1789 | 3.07 E-9 | 0.929 | -0.175 | 0.651 |
|  | CL | AML | Additive shift | -1743 | 1755 | 1.83 E-10 | 0.937 | -0.120 | 0.643 |
|  | CL | CrCL | Power | -1734 | 1746 | 5.12 E-10 | 0.937 | -0.148 | 0.674 |
|  | Vd | Wt | Power | -1743 | 1755 | 3.07 E-9 | 0.936 | -0.114 | 0.644 |
| Full Multivariable Model | CL, Vd | Alb, AML, CrCL, Wt | Power and  additive shift | -1727 | 1743 | 3.07 E-9 | 0.937 | -0.117 | 0.644 |
| Alb, serum albumin concentration; AML, acute myeloid leukemia; CrCL, creatinine clearance; CL, total clearance of daptomycin; Vd, volume of distribution of the central compartment; Wt, total body weight. | | | | | | | | | | |

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| Table 3. Parameter estimates of daptomycin for the final covariate two-compartment population pharmacokinetic model | | | | |
|  | Mean | SD | Coefficient of variation (%) | Median (IQR) |
| CL (L/h) | 1.02 | 0.45 | 44.10 | 0.89 (0.73 – 1.19) |
| Vd (L) | 4.84 | 2.34 | 48.30 | 4.29 (3.58 – 4.76) |
| *k*cp (h-1) | 19.04 | 2.16 | 11.33 | 19.89 (18.72 – 19.90) |
| *k*pc (h-1) | 19.40 | 1.89 | 9.73 | 19.90 (19.90 – 19.90) |
| CL, total clearance of daptomycin; *k*cp and *k*pc, first-order intercompartmental transfer rate constant connecting the central and peripheral compartments; Vd, volume of distribution of the central compartment. | | | | |

**Figure Legends:**

**Figure 1.** Diagnostic plot for the final covariate model. Shown are observed versus population predicted concentrations (left) and individual predicted concentrations (right) in plasma. Solid lines refer to linear regression between observed and predicted concentrations. Dashed lines are the identity lines between observed and predicted concentrations.

**Figure 2.** Visual predictive check plot of daptomycin plasma concentrations versus time for the final covariate model. Gray shadings display predicted intervals of simulated data.

**Figure 3.** Notched box (median and 25th to 75th percentile) and whisker (5th and 95th percentiles) plots of simulated daptomycin AUC24h according to eight different clinical scenarios (scenario A: CrCL 50-100 ml/min/1.73m2, albumin 26-45 g/L, NO AML; scenario B: CrCL 50-100 ml/min/1.73m2, albumin 26-45 g/L, AML; scenario C: CrCL 50-100 ml/min/1.73m2, albumin 15-25 g/L, NO AML; scenario D: CrCL 50-100 ml/min/1.73m2, albumin 15-25 g/L, AML; scenario E: CrCL 101-150 ml/min/1.73m2, albumin 26-45 g/L, NO AML; scenario F: CrCL 101-150 ml/min/1.73m2, albumin 26-45 g/L, AML; G) CrCL 101-150 ml/min/1.73m2, albumin 15-25 g/L, no AML; H) CrCL 101-150 ml/min/1.73m2, albumin 15-25 g/L, AML. The gray shaded area identifies the daptomycin reference effective exposure range (REER). The dashed line identifies the safety threshold (ST).

**Figure 4.** Notched box (median and 25th to 75th percentile) and whisker (5th and 95th percentile) plots of simulated Cmax according to eight different clinical scenarios (scenario A: CrCL 50-100 ml/min/1.73m2, albumin 26-45 g/L, NO AML; scenario B: CrCL 50-100 ml/min/1.73m2, albumin 26-45 g/L, AML; scenario C: CrCL 50-100 ml/min/1.73m2, albumin 15-25 g/L, NO AML; scenario D: CrCL 50-100 ml/min/1.73m2, albumin 15-25 g/L, AML; scenario E: CrCL 101-150 ml/min/1.73m2, albumin 26-45 g/L, NO AML; scenario F: CrCL 101-150 ml/min/1.73m2, albumin 26-45 g/L, AML; G) CrCL 101-150 ml/min/1.73m2, albumin 15-25 g/L, no AML; H) CrCL 101-150 ml/min/1.73m2, albumin 15-25 g/L, AML. The gray shaded area identifies the daptomycin reference effective exposure range (REER). The dashed line identifies the safety threshold (ST).

**Figure 5.** Algorithm for choosing the most advisable daptomycin dosing regimen in oncohaematological patients in relation to different classes of underlying haematological disease, of creatinine clearance estimates and of albumin levels (AML, acute myeloid leukemia; CrCL, creatinine clearance; Alb; albumin concentration; \* therapeutic drug monitoring suggested).









