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Precision Daptomycin Dosing: Comparison of 3-, 2-, 1-, and 0-Concentration Sample Strategies

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ABSTRACT

Background: Daptomycin is a once-daily lipopeptide antibiotic with a narrow therapeutic window. As higher doses (8–12 mg/kg) are increasingly used to treat resistant gram-positive infections, achieving therapeutic exposure while minimizing toxicity has become critical. Understanding daptomycin therapeutic drug monitoring (TDM) and what sampling strategy may be most precise and feasible are key to guiding appropriate dosing. The primary objective of this study was to ascertain the precision and bias of a mid-point sample area under the curve over 24-h (AUC_{24}) determination compared to a peak and trough sample AUC_{24} determination using both simple calculation-based methods and a Bayesian model versus no TDM.

Methods: Adult patients receiving daptomycin with at least three steady-state concentrations (peak, mid-point, trough) were included in this analysis. A previously published one-compartment population pharmacokinetic model was applied using Bayesian estimation (Monolix Suite 2024R1). AUC_{24} values were estimated using all three concentrations (AUC_{ref}), and then re-estimated using individual samples (peak, mid-point, or trough) or paired samples (peak + trough). Performance of each strategy was evaluated using regression analysis with the coefficient of determination for precision (R^2) and mean bias.

Results: The cohort included 210 patients (60% male) with a mean (range) age of 66 (18–91) years, body weight 78 (41–140) kg, and BMI 27 (14–51) kg/m^2. A total of 880 daptomycin concentrations were analyzed in patients receiving a mean (range) daptomycin dose of 9 (5–17) mg/kg. The mean (range) AUC_{24} was 869 (385–1692) mg·h/L; only 45.7% of patients achieved the target range of 666 to 939 mg·h/L. A single mid-point sample had similar correlation to AUC_{24} ($R^2 = 0.57$) as trough-only ($R^2 = 0.55$), and greater precision than peak-only ($R^2 = 0.44$). Bayesian estimation with two samples (peak + trough) provided the highest accuracy ($R^2 = 0.87$) and lowest bias.

Conclusions: A mid-interval sampling strategy offers a practical alternative to traditional TDM for daptomycin, enabling more consistent AUC estimation when full sampling is not feasible. A two-sample Bayesian approach remains the most accurate, supporting broader implementation of individualized daptomycin dosing.

Simone Giuliano and Manjunath P. Pai are equal contributors to this work and designated as co-first authors.

1 | Introduction

Daptomycin is a lipopeptide antibiotic commonly used to treat serious gram-positive infections, including bacteremia and endocarditis [1]. Its once-daily dosing and concentration-dependent killing profile make it a convenient and potent agent for inpatient and outpatient care. However, its therapeutic utility is tempered by a narrow therapeutic window, with exposure-dependent toxicities such as skeletal muscle injury and eosinophilic pneumonia increasingly recognized [2]. Elevated daptomycin trough concentrations and total drug exposure, often measured as the 24-h area under the curve (AUC_{24}), have been associated with an increased risk of adverse effects, particularly when AUC_{24} exceeds 939 mg·h/L or trough levels exceed 24.3 mg/L [2, 3].

As clinical practice has moved toward higher dosing of daptomycin, often in the range of 8–12 mg/kg/day to maximize efficacy against resistant pathogens, the need for individualized dosing strategies has become more evident [4–7]. Yet, implementation of therapeutic drug monitoring (TDM) for daptomycin remains limited, largely due to the operational challenges associated with traditional pharmacokinetic sampling [4]. Estimating AUC typically requires multiple concentration measurements, necessitating coordinated sampling efforts, multiple venipunctures, and other workflow factors that may be prohibitive in many healthcare settings [8]. Likewise, availability of the Bayesian software platforms or technical knowledge on the use of model informed precision dosing may be limited to allow for sparse sampling strategies [8]. In response to these barriers, our research group has explored more pragmatic sampling strategies, including the use of a single mid-interval concentration with a nomogram to estimate AUC [9]. We previously identified a mid-point sample collected between 7 and 11 h after dosing to have the potential of simplifying the clinical workflows, reducing costs, and improving access to TDM without sacrificing accuracy [9]. Validation of this approach with a dataset that is independent of the one used for population pharmacokinetic model development is essential for confirmation of reproducibility and supporting generalizability.

The primary objective of this study was to ascertain the precision and bias of a mid-point sample AUC_{24} determination compared to a peak and trough sample AUC_{24} determination using both simple calculation-based methods and a Bayesian model versus no TDM. This work aimed to support the broader implementation of precision dosing for daptomycin through a clinically feasible and validated monitoring strategy.

2 | Methods

2.1 | Patient Enrollment and Data Collection

The study was approved by the Ethics Committee of the Azienda Ospedaliero-Universitaria of Udine (Prot IRB: 290/2024). Signed informed consent was waived due to the retrospective nature of this investigation, in accordance with national legislation and institutional requirements. Adult patients who received daptomycin for a documented or presumed serious gram-positive infection were evaluated. Only patients with three sample measurements (peak, mid-point and trough concentration) after administration of daptomycin were included in this study. This study excluded pediatric patients, pregnant women, patients for whom TDM sampling times differ from those investigated in this study, and patients not treated with daptomycin long enough (3 doses) to ensure achievement of steady-state plasma concentrations. Daptomycin dosing, TDM, clinical conditions, demographic characteristics, and serum creatinine data were collected retrospectively.

2.2 | Daptomycin AUC Estimation

Our previously published one-compartment daptomycin population pharmacokinetic model was used as the Bayesian model [9]. Briefly, this model includes body weight as a covariate of the central compartment volume (V), and creatinine clearance using the Cockcroft–Gault equation as a covariate of clearance (CL), and includes a proportional error model. A differential for AUC_{24} estimation was included in the structural model. Bayesian estimation was performed using the Monolix Suite (version 2024R1; Lixoft, Antony, France) by computing the *Maximum* a posteriori (MAP) estimate with inclusion of the population priors for V and CL, using the final covariate structural model detailed in the Supporting information of our previous publication [9]. The full data set of at least three samples per patient was used to compute the reference AUC_{24} (AUC_{ref}). The data set was then depleted to only include a single concentration (peak, trough, or mid-point), or two concentrations (peak and trough) to reestimate the AUC_{24}. The AUC_{24} was also calculated using a formula-based method with the peak and trough concentration data as previously reported [10].

2.3 | Statistical Analysis

Continuous variables were described with mean and standard deviation, as well as minimum and maximum values by sex. The percentage of patients achieving an AUC_{24} of 666–939 mg·h/L was computed [2]. Ordinary least squares regression was performed to compute the precision (R^2) and mean bias (95% confidence interval) between the dose (mg and mg/kg), individual concentration measurements, formula estimated AUC, and Bayesian estimated AUC against the AUC_{ref}.

3 | Results

3.1 | Patient Characteristics

A total of 210 patients (60% male) with a mean (minimum, maximum) age of 66 (18, 91) years, weight 78 (41, 140) kg, and BMI 27 (14, 51) kg/m^2 were evaluated and had at least three steady-state daptomycin concentrations obtained for analysis (Table 1). Daptomycin was used for documented gram-positive (predominantly *Staphylococcus* spp.)-related prosthetic infections (33%), skin and skin structure infections (20%), and bloodstream infections (17%).

TABLE 1 | Study population variables by sex.

Variable	Female ($N=84$)	Male ($N=126$)	Total ($N=210$)
Age, years	67 (18), [27–93]	65 (15), [18–91]	66 (17), [18–91]
Weight, kg	70 (18), [41–138]	84 (19), [50–140]	78 (19), [41–140]
Height, cm	163 (7), [140–177]	177 (8), [147–190]	172 (8), [140–190]
Body Mass Index, kg/m^2	26 (7), [17–51]	27 (6), [14–43]	27 (7), (14–51)
Dose (mg)	591 (165), (350–1050)	725 (155), [350–1200]	671 (158), [350–1200]
Dose (mg/kg)	9 (1), [6–11]	9 (2), [5–17]	9 (2), (5–17)
Creatinine Clearance[a] (mL/min)	80 (36), [12–157]	108 (45), [19–274]	96 (42), [12–274]

Note: Data presented as mean (standard deviation), (minimum, maximum).
[a]Clearance calculated using Cockcroft Gault equation with total body weight.

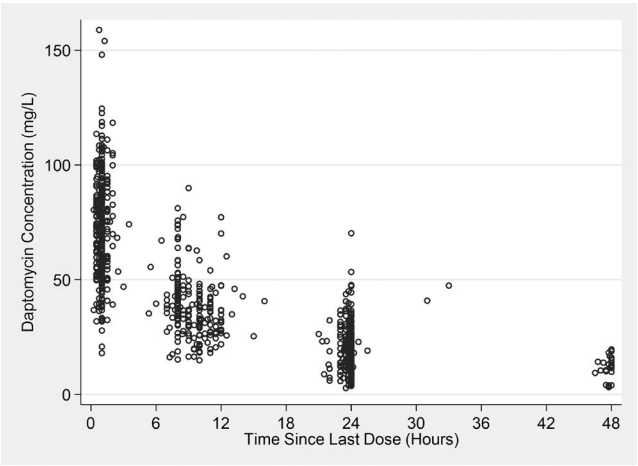

FIGURE 1 | Scatter plot of the observed concentrations over the time since last dose to illustrate the distribution of data for areas under the curve estimation.

3.2 | Pharmacokinetic Analysis

The mean (min, max) daptomycin dose was 9 [5, 17] mg/kg or absolute doses of 671 [350, 1200] mg (Table 1). The vast majority (92%) of patients received the dose every 24 h, with the remainder receiving the dose every 48 h due to reduced kidney function. The median (5th, 95th percentile) number of doses prior to measurement was 6 [3, 11]. A total of 880 daptomycin concentrations were measured, and a distribution of these measurements is illustrated in Figure 1. As shown, data are clustered around the expected sampling times for peak, mid-point, and trough concentrations. The AUC_{ref} was a mean [min, max] of 869 [385, 1692] mg·h/L, and only 45.7% of patients were within the AUC target of 666 to 939 mg·h/L.

As expected, the AUC_{ref} increased with increasing dose, though the correlation of this relationship was weaker with dosing by weight rather than on an absolute dose basis ($R^2=0.06$ for weight-based vs. 0.13 for absolute values) (Figure 2). The relationships of a single concentration measurement to AUC_{ref} are illustrated in Figure 3 and show that in relative terms the correlation was similar with mid-point ($R^2=0.57$) and trough ($R^2=0.55$) concentrations. Use of a peak concentration or calculation of AUC using both a peak and trough concentration led to similar correlations with AUC_{ref} ($R^2=0.44$). In contrast to these simpler translations to AUC, generation of Bayesian estimates of AUC had stronger but similar correlations with single sample concentrations ($R^2=0.62$–0.67). Use of a two sample strategy (peak and trough) yielded the best correlation ($R^2=0.87$) to AUC_{ref} (Figure 4). Taken together, Table 2 summarizes both the precision and bias of these 0-, 1-, and 2-sample strategies relative to the referent three-sample-based AUC_{ref} determination. The Bayesian methods had no mean bias, as was the case with use of a single mid-point sample for AUC determination.

4 | Discussion

This study evaluated the precision of current daptomycin dosing strategies and TDM approaches for estimating AUC_{24}, in order to achieve safe and efficacious exposure thresholds. Our findings indicate that conventional dosing without individualized monitoring yields the least precise AUC predictions. Daptomycin's efficacy is closely tied to adequate exposure and the toxicity risk increases with overexposure, which reinforces the need for precision dosing to optimize patient outcomes [2, 3]. Our analysis demonstrates that standard weight-based dosing without TDM can lead to less predictable AUCs, corroborating concerns that this approach may not reliably attain target exposures. Likewise, the use of fixed doses of daptomycin is an incremental improvement over weight-based dosing but also cannot guarantee optimal exposure profiles [11]. Both empiric dosing strategies highlight the need for TDM to gain precision.

In the context of TDM, we explored how the timing and number of plasma samples affect AUC estimation. A key finding is that a single mid-interval concentration (approximately 7–11 h post dose) provides the most accurate one-sample AUC estimate, surpassing the precision of using only a peak or only a trough level. The peak samples in this analysis were collected 30–60 min post a 30-min daptomycin infusion in almost all instances but ultimately do not reflect the true maximum concentration. A mid-interval sample captures the drug's disposition during the elimination phase, offering a balanced representation of total exposure. By contrast, a single trough (immediately before the next dose) may be susceptible to variability at the tail end of the dosing interval and does not inform the higher concentration range, whereas a single peak (just after infusion) could represent

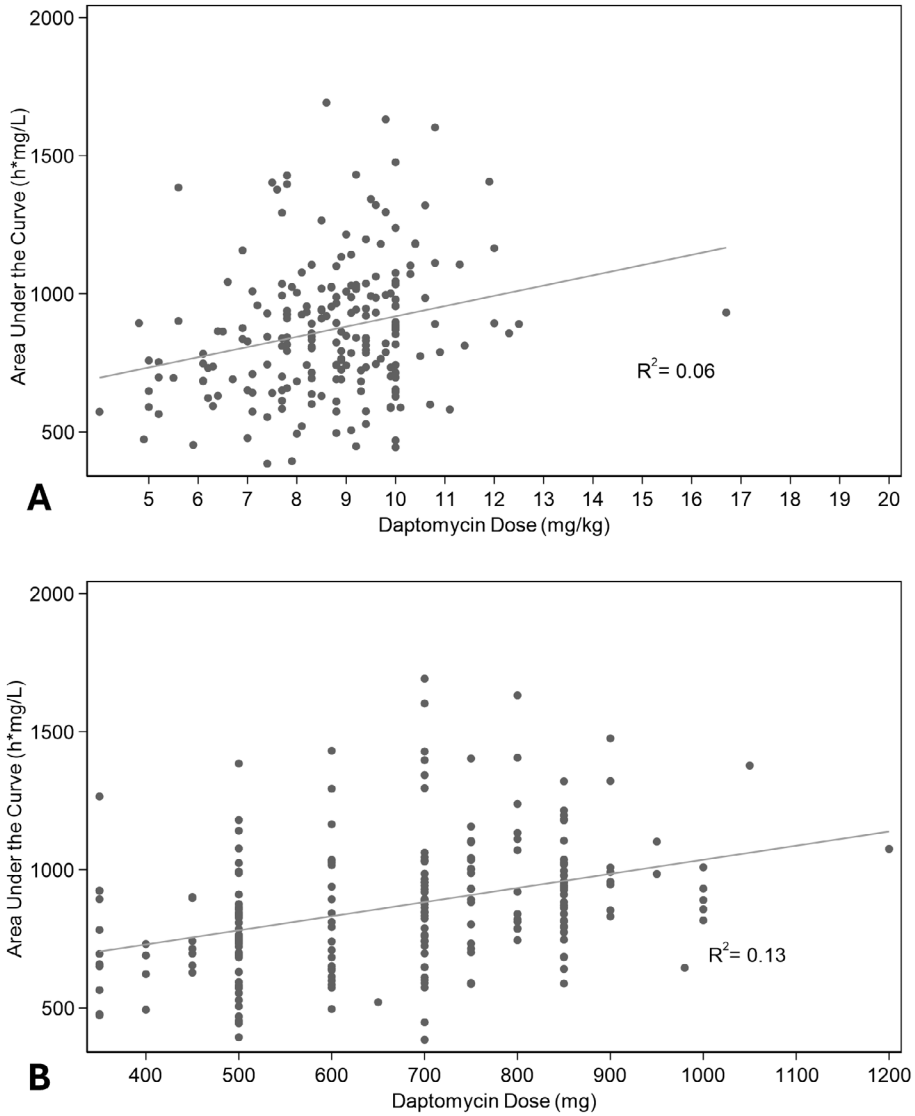

FIGURE 2 | Scatter plot with linear fit of the area under the curve versus dose as (A) weight-based in mg/kg and (B) in absolute values in mg.

the distribution phase but not the full elimination. Our findings are consistent with recent Bayesian analyses demonstrating the value of mid-interval sampling. A recent study demonstrated that among various single-sample strategies, a sample taken approximately 6 h after infusion start yielded the lowest bias (≈2 mg·h/L) and only 6% imprecision in AUC prediction, outperforming single trough or single peak measurements [12]. Thus, if only one concentration can be obtained for daptomycin dose individualization, timing the sample in the 7–11 h post dose window appears to maximize AUC estimation accuracy.

This insight is particularly relevant in clinical settings where drawing multiple samples is impractical; a well-timed single level can still substantially improve dosing precision relative to no monitoring. Furthermore, in our previous work, we demonstrated that a single blood sample taken 7–11 h post dose may provide a reliable early estimate of drug exposure immediately after the administration of the first dose of daptomycin [9]. This approach could be particularly useful in critical care settings where high doses of daptomycin are administered. In these cases, it could be used not necessarily to assess target attainment, but rather to estimate the patient's risk of exposure to potentially toxic concentrations from the very first hours of therapy initiation.

Finally, our study confirms that Bayesian modeling with two concentration measurements (specifically, peak and trough levels) provides the most accurate and least biased AUC estimates relative to other evaluated methods in this study. Incorporating both an early sample (reflecting peak or initial distribution) and a late sample (trough) allows the Bayesian estimator to refine the patient's pharmacokinetic parameters more effectively than one sample alone. We observed that the two-sample Bayesian approach had minimal bias and the highest precision among all methods tested, essentially converging on the true AUC with very small error. This advantage of 2-point TDM is consistent with findings by Tuloup et al. (2023), who reported that a two-sample strategy (trough + mid-level) produced AUC estimates virtually identical to those from a full three-sample profile. In that analysis, using two optimally timed samples resulted in only approximately 3% imprecision, whereas even the best single sample had about 6% imprecision [12]. Likewise, a recent

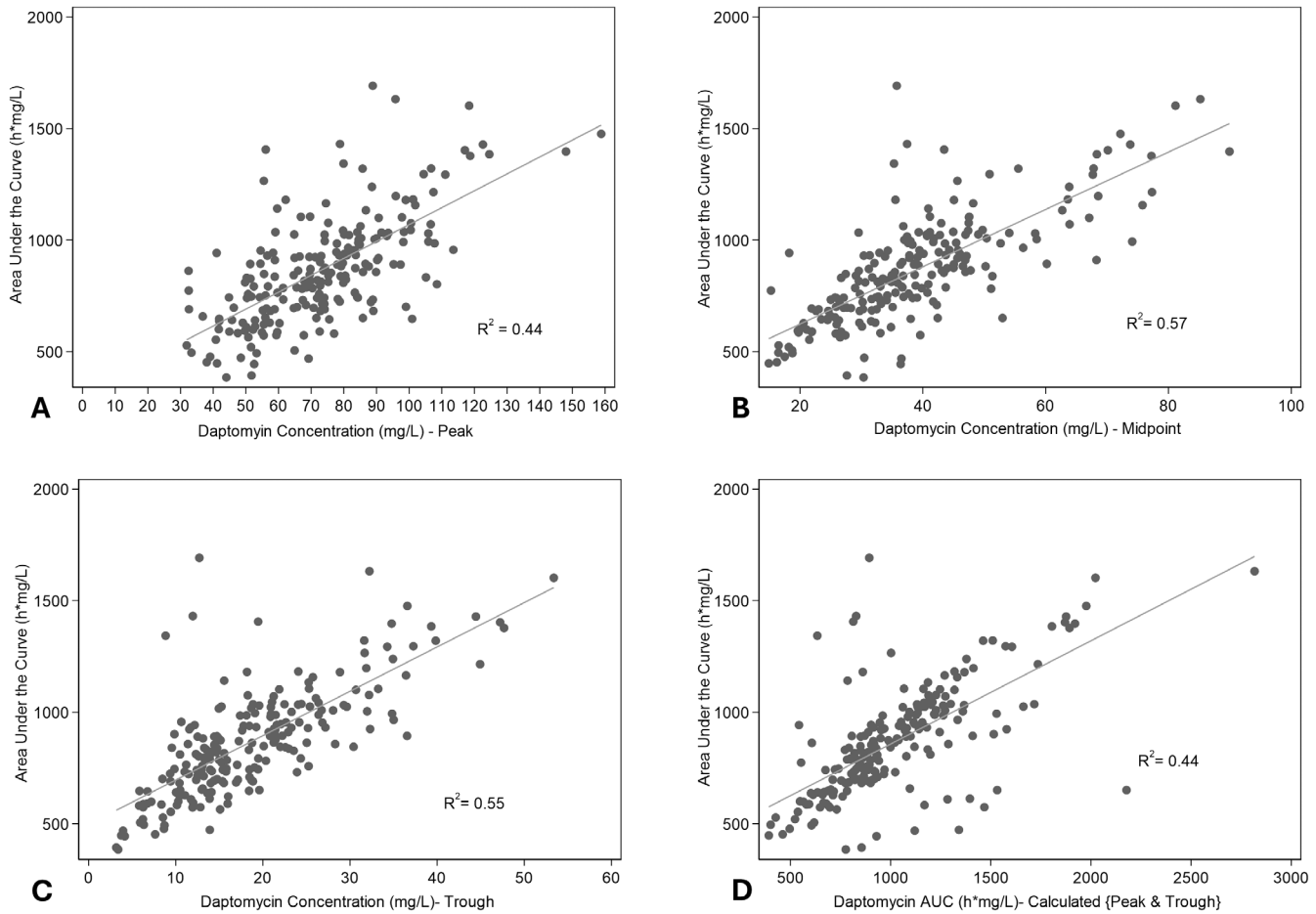

FIGURE 3 | Scatter plot with linear fit of the reference area under the curve versus (A) peak concentration; (B) mid-point concentration; (C) trough concentration; and (D) peak and trough concentration calculated.

TABLE 2 | Comparison of the mean bias (95% confidence interval) and coefficient of determination (R^2) of the area under the curve estimation based on regression analyses.

AUC_{24} estimation method	Mean bias [95% CI]	Precision [R^2]
Dose (mg/kg)	24.4 [−7.35, 56.2]	0.06
Dose (mg)	18.5 [−12.1, 49.1]	0.13
Calculated		
Peak	11.9 [−12.8, 36.7]	0.44
Mid-point	0 [−21.7, 21.7]	0.57
Trough	12.2 [−9.83, 34.3]	0.55
Peak & Trough[a]	−158.3 [194, −122]	0.44
Bayesian		
Peak	0 [−23.0, 23.0]	0.67
Mid-point	0 [−23.0, 23.0]	0.67
Trough	0 [−24.8, 24.8]	0.62
Peak & Trough	0 [−14.6, 14.6]	0.87

[a]This is formula-based for the peak and trough measurement as noted in the text while the single concentration measurements (peak, trough, or mid-point) are based on ordinary least squares based determination.

simulation by Yamada et al. (2024) demonstrated that adding an extra mid-interval sample to trough-based monitoring markedly improves daptomycin target attainment; the probability of achieving the desired AUC increased from roughly 60% with trough-only to approximately 74% with trough plus 7-h sampling [13].

These concordant findings underscore that two-point Bayesian TDM is superior to simpler one-point methods for individualizing daptomycin doses. By leveraging prior pharmacokinetic knowledge and patient-specific concentrations, Bayesian dose optimization can reliably reach AUC targets while minimizing bias. Clinically, the implications of these results are significant. They highlight that relying on fixed regimens without monitoring may jeopardize patient care by failing to ensure adequate drug exposure or by inadvertently causing toxicity.

Our work suggests that simple adjustments, such as preferring a mid-interval sample if only one level is obtainable, can meaningfully improve the precision of daptomycin dosing. More importantly, embracing a model-informed dosing approach with peak and trough measurements can refine therapy to each patient's pharmacokinetics. Although routine daptomycin TDM is not yet standard practice in all centers, our data contribute to the mounting evidence that it enables more predictable attainment of pharmacodynamic targets. Future work should

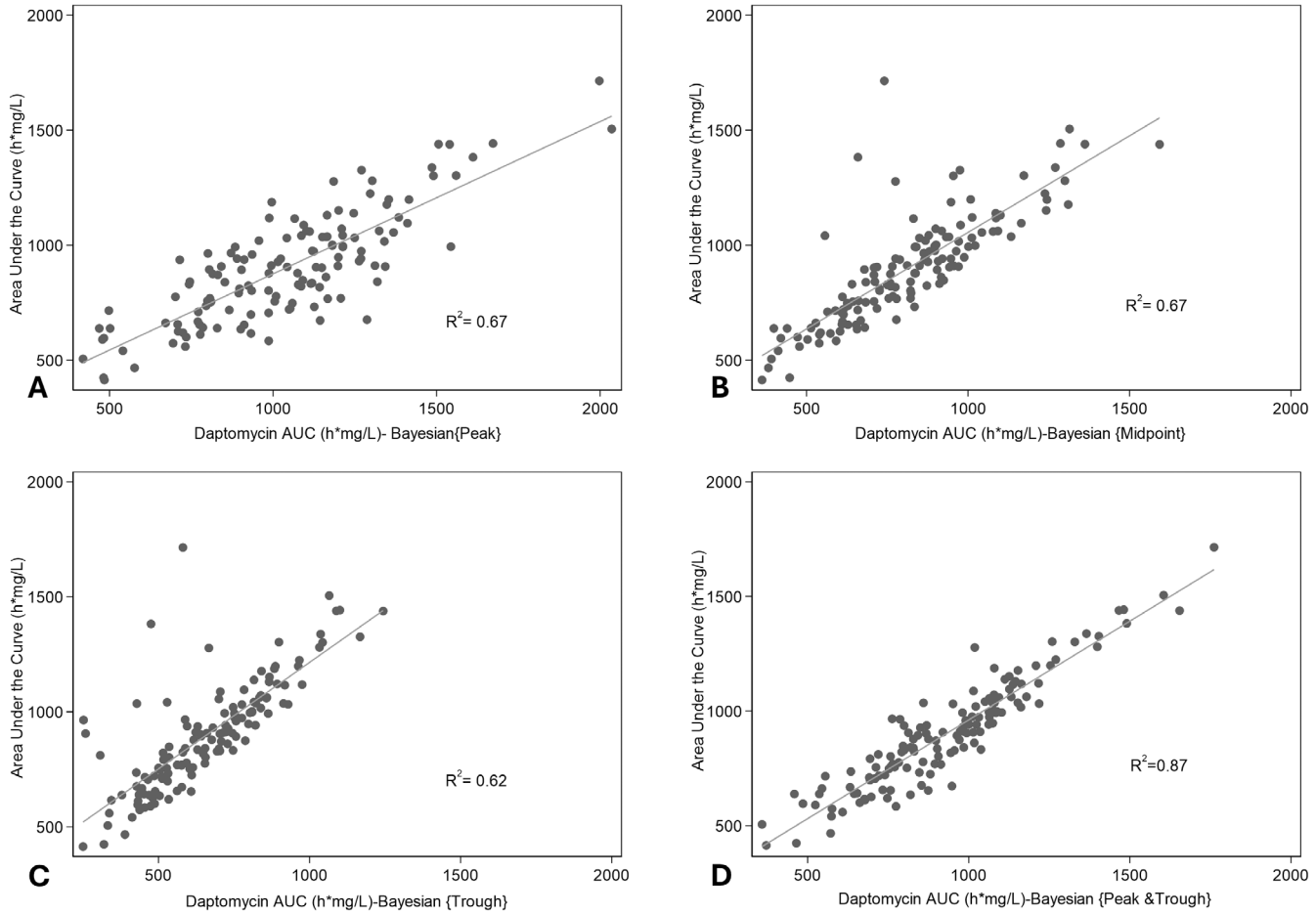

FIGURE 4 | Scatter plot with linear fit of the reference area under the curve versus Bayesian computed area under the curve using (A) peak concentration; (B) mid-point concentration; (C) trough concentration; and (D) peak and trough concentration.

explore the feasibility and impact of integrating Bayesian dose–individualization for daptomycin in various clinical contexts, including patients with altered pharmacokinetics (e.g., critical illness, obesity, or renal insufficiency). Additionally, cost–benefit analyses would be valuable, as precision dosing might reduce downstream costs by preventing therapeutic failures or toxicity. Overall, our discussion reinforces that a shift from conventional weight-based dosing to a personalized, exposure-guided dosing strategy could substantially enhance the safety and efficacy of daptomycin therapy.

5 | Conclusion

This study underscores the importance of precision dosing for daptomycin. Dosing based solely on body weight, without TDM, was associated with the poorest precision in AUC estimation, confirming that unguided regimens often fail to account for interpatient pharmacokinetic variability. We found that a single optimally timed plasma concentration (around 7–11 h post dose) yields a more accurate and less biased AUC estimate than traditional peak or trough measurements alone. Furthermore, the most reliable AUC predictions were achieved through a Bayesian two-sample approach using both peak and trough levels, which outperformed all one-sample methods in accuracy and bias. These findings highlight that model-informed precision dosing can improve the consistency of daptomycin exposure, which should translate to improved safety and efficacy with further investigations.

Author Contributions

Simone Giuliano: resources, investigation, writing – review and editing, data curation. **Manjunath P. Pai:** writing – original draft, writing – review and editing, formal analysis, methodology, software, conceptualization. **Jacopo Angelini:** project administration, resources, writing – review and editing, investigation, data curation, validation, visualization, methodology. **Sarah Flammini:** investigation, resources, writing – review and editing. **Luca Martini:** writing – review and editing, investigation, resources. **Massimo Baraldo:** writing – review and editing, resources, validation. **Carlo Tascini:** resources, writing – review and editing, supervision, investigation.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available upon reasonable request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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