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Simplified Equations Using Two Concentrations To Calculate Area under the Curve for Antimicrobials with Concentration-Dependent Pharmacodynamics: Daptomycin as a Motivating Example

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The effects of several antimicrobial agents are predicted by the ratio of the area under the concentration-time curve (AUC) to the MIC (AUC/MIC). Peak (C_p) and trough (C_t) concentrations are often measured clinically as surrogates of AUC because actual computation of AUC from 1 or 2 samples requires sophisticated mathematical methods. Given that the effects of daptomycin are predicted by AUC/MIC, our objective was to compare simple equation calculated AUC based on C_p and C_t to model integrated AUC. A standard population pharmacokinetic model was used to simulate 5,000 daptomycin concentration-time profiles after 5 doses of 6 mg/kg of body weight/day (0.5-h infusions). The AUC for the 24-h period was computed by integration and by equations with 110 C_p-C_t combination pairs. The C_p time points were in 15-min increments between 0.5 h and 3 h and C_t in 15-min increments within an hour of the end of the dosing interval for each dose. The precision and bias of the calculated AUC relative to the integrated AUC were determined to identify C_p-C_t pairs associated with the lowest bias and highest precision. The equations were further validated using two daptomycin concentration-time data sets from healthy volunteers and critically ill patients. The precision and bias of calculated AUC were based primarily on C_p, and use of a daptomycin C_p 1.5 h to 3 h from the start of infusion was associated with a bias of <10% and an R^2 of >0.95. Data from the healthy volunteers and critically ill patients also demonstrated declining bias with use of C_p ≥1.5 h from the start of infusion with relatively good precision. Simplified equations using a daptomycin C_p approximately 2 h from the start of infusion and a C_t within an hour of the end of the dosing interval should yield precise and unbiased estimates of daptomycin AUC.

The aminoglycosides, vancomycin, and daptomycin are key examples of antimicrobial agents that demonstrate a good correlation between their ratios of area under the concentration-time curve (AUC) to MIC (AUC/MIC) and effects (1). The systemic AUC of a drug is dependent on the dose administered and its systemic clearance (CL). Drug CL is highly variable in certain populations, such as the critically ill, and is not easily predicted on an individual level based solely on clinical parameters (2, 3). Selection of a specific dose in a critically ill patient may or may not achieve the desired AUC for optimal effect (2, 3). Therapeutic drug monitoring (TDM) has been utilized to overcome this fundamental clinical limitation and is used to optimize aminoglycoside and vancomycin dosing (4, 5). As an example, initial aminoglycoside doses are based on weight, while maintenance doses are based on measured concentrations in serum. This TDM practice has contributed to the evolution of empirical aminoglycoside (gentamicin) dosing from 0.5 mg/kg of body weight twice daily to 7 mg/kg once daily for Gram-negative infections over a 40-year period of clinical use (4).

Similar to this experience, the dosing of daptomycin has changed over the past 20 years, from 2- to 3-mg/kg divided daily doses in initial trials to the regulatory approval of a higher single daily dose of 6 mg/kg for methicillin-resistant *Staphylococcus aureus* (MRSA)-related bloodstream infections (BSI) (6). More recently, experts have suggested that higher daptomycin dosages, 8 to 10 mg/kg/day, should be considered to treat MRSA BSI (7). Our group has shown that the use of daptomycin at 6 to 8 mg/kg does not reliably optimize the pharmacokinetic-pharmacodynamic (PK-PD) profile of this agent in critically ill patients (8). Use of an empirical average fixed dose of 750 mg is forecast to achieve comparable probability of target attainment (PTA) as 10 mg/kg for effect but with a lower probability for trough concentrations associated with toxicity (8). However, a fundamental limitation of any population-predicted average dose is that it cannot guarantee with absolute certainty that optimal PK-PD target attainment is achieved on an individual level.

To date, certain clinical groups have utilized TDM to optimize the dose of daptomycin for selected cases (9–12). As with any nascent approach, a clearly defined system to measure and interpret daptomycin concentrations remains to be elucidated. Historically, clinicians have measured peak (C_p) and/or trough (C_t) concentrations of drugs and correlated these point estimates to safety or efficacy related outcomes. Although clinical interpretation of a single point measurement is simple, it is unlikely to accurately reflect the true exposure-response relationship. We recognize the AUC/MIC as the PK-PD index predictive of daptomycin effect, so it would be rational to transform measured daptomycin concentrations into AUC values on an individual basis. The most accurate approach to computation of AUC with a single measurement of concentration in serum includes the use of sophisticated maximum *a priori* probability (MAP) Bayesian methods (13). Alter-

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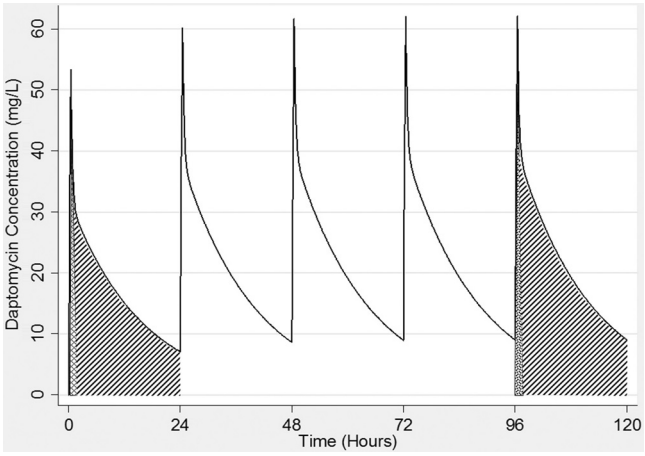

FIG 1 Population model simulated concentration-time curve of daptomycin curve (6 mg/kg every 24 h for 5 doses), with shaded regions illustrating the area under the curve after the first and fifth doses with the area of a triangle (first dose, 0 h) and area of a trapezoid (fifth dose, 96 h).

natively, a simple hand-calculated approach can be used to accurately quantify the AUC using two serum sample measurements (peak and trough) for intravenously administered antimicrobials (4). This simple mathematical approach accurately predicts aminoglycoside AUC (4). As the shape of the aminoglycoside concentration-time profile is similar to that of daptomycin, an analogous approach to daptomycin AUC calculation is plausible.

Our study objective is to define a simple clinically implementable "bedside" approach to aid clinicians who desire to transform measured daptomycin concentrations to AUC values. Measurement and translation of daptomycin concentration-time data may also aid clinical scientists who seek to best define and validate the clinical exposure-response relationships. We show using modeling and simulation that daptomycin AUC can be computed accurately and simply with two concentration measurements based on actual data from healthy and critically ill populations.

MATERIALS AND METHODS

Modeling and simulation approach. This investigation involved a three-step approach to define a simple method to the computation of daptomycin AUC values. The first step included use of a well-described daptomycin population PK model to generate simulated concentration-time profiles. Concentration-time pairs (peak and trough) from each simulated profile were used to compute AUC using a simple mathematical formula and compared to the model integrated AUC value. The model integrated AUC value served as the gold standard. The time point pairs associated with the lowest bias were identified. The second step was to validate this approach using data from a cohort of healthy volunteers based on concentration-time data after administration of a single daptomycin dose. The third step was to also validate this approach using data from critically ill patients with concentration-time data after single and multiple doses. Details for each methodological step are provided as follows.

Step 1: daptomycin population pharmacokinetic model simulations. A standard open 2-compartment population pharmacokinetic model with zero-order input, first-order output, and transfer between compartments was used to generate simulated daptomycin concentration-time profiles (14). The pharmacokinetic parameter estimates for clearance (CL), central compartment volume of distribution (V_c), and intercompartmental transfer rate constants (k_{cp} and k_{pc}) were obtained from a previous study. The mean (standard deviation) values for the PK parameters were as follows: CL, 0.957 (0.461) liter/h; V_c, 6.56 (3.10) liters; k_{cp}, 1.67 (3.04) h^{-1}; and k_{pc}, 1.34 (3.40) h^{-1}. These PK parameters were defined based on data from 108 adult patients who participated in the phase 3 bacteremia and endocarditis study of daptomycin at 6 mg/kg every 24 h (15). A 5,000-subject Monte Carlo simulation was implemented using ADAPT 5 with selection of log normal distributions for these PK parameters (14). The simulation included five daptomycin doses of 6 mg/kg infused over 0.5 h every 24 h based on a mean (standard deviation) body weight of 82.2 (18.6) kg to mimic the original population PK data set (15).

It is difficult to measure the peak concentration exactly at the end of infusion in the clinical setting and the trough concentration exactly prior to the next dose. Due to this clinical limitation, 11 time points in 15-min increments were captured to represent the "peak" concentration (C_p) between the end of infusion and 2.5 h postinfusion after the first (0 h) and fifth (96 h) doses: 0.5 h, 0.75 h, 1 h, 1.25 h, 1.5 h, 1.75 h, 2.0 h, 2.25 h, 2.5 h, 2.75 h, and 3.0 h and 96.5 h, 96.75 h, 97 h, 97.25 h, 97.5 h, 97.75 h, 98 h, 98.25 h, 98.5 h, 98.75 h, and 99 h from the start of infusion. The trough concentrations (C_t) were represented by 5 time points in 15-min increments within 1 h of the end of the dosing interval: 23 h, 23.25 h, 23.5 h, 23.75 h, and 24 h (first dose) and 119 h, 119.25 h, 119.5 h, 119.75 h, and 120 h (fifth dose). Evaluation of these time points permitted generation of 55 possible peak-trough combinations after the first and fifth doses in order to test effects of the sampling time point on hand-calculated AUC estimates. These peak-trough combinations were expected to reflect the potential clinical approach that may be used to measure daptomycin, i.e.,

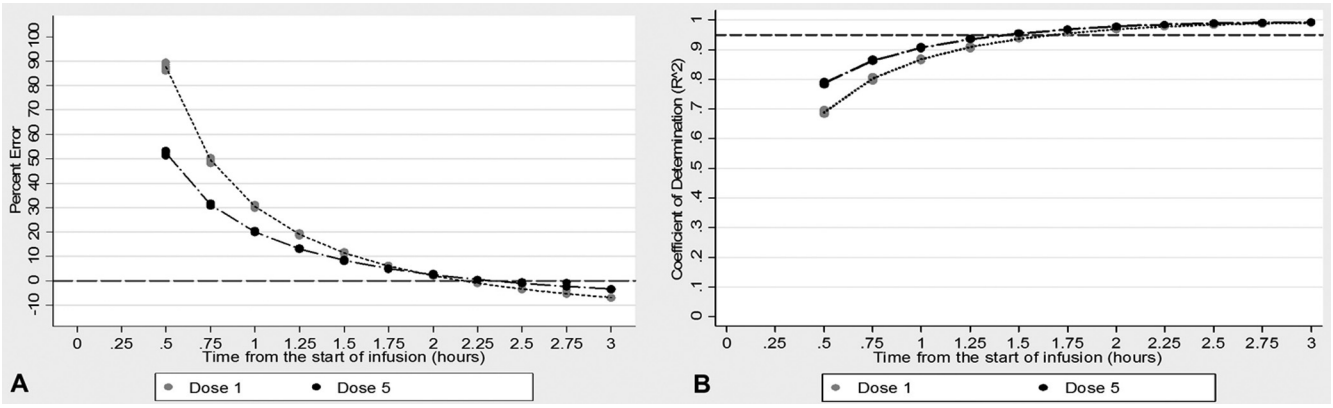

FIG 2 Percent error (A) and coefficient of determination (B) for the AUC_{24} calculation by dose number and time from start of daptomycin infusion compared to the integrated AUC_{24} value.

peak measurement a few hours after the end of infusion and trough before the next dose. We also sought to demonstrate the effects of sample measurement after a single dose and multiple doses on AUC calculation. A differential equation was embedded within the model simulation to generate integrated AUC values for the sampling time points that permitted estimation of AUC for the 24-h period (AUC_{24}) after the first and fifth doses. The integrated AUC_{24} after the specific dose served as the reference standard.

Calculation of area under the curve. The equations to compute AUC_{24} from two samples are based in part on an original approach proposed by Begg et al. for aminoglycosides (16) and modified by Pai and Rodvold (4). We used 55 peak-trough concentration (C_t, where t is time point in hours) pairs after the first and fifth doses as outlined above, e.g., $C_{0.5}$-C_{23}, $C_{0.5}$-$C_{23.25}$, and $C_{0.5}$-$C_{23.5}$, to compute the elimination rate constant (k_{el}) based on the Sawchuk-Zaske method (17).

$$k_{el} = \frac{Ln\left(\frac{C_p}{C_t}\right)}{t} \quad (1)$$

where C_p is the peak concentration, C_t is the trough concentration, and t is the difference in time between these two concentrations. The AUC_{24} can be expressed as the summation of the area of a triangle (after the first dose) or a trapezoid (multiple doses) plus the integral of the concentration-time curve (Fig. 1). The equations for these computations are provided as follows: for single-dose AUC_{24} (first dose as an example),

$$AUC_{0\text{-}24} = 0.5 \cdot t' \cdot C_{max} + \int_{t'}^{infinity} C_{max} \cdot e^{-k_{el} \cdot (t)}\, dt - \int_{24}^{infinity} C_{min} \cdot e^{-k_{el} \cdot (t)}\, dt \quad (2)$$

Equation 2 can be simplified to

$$AUC_{24} = \frac{t' \cdot C_{max}}{2} + \frac{C_{max} - C_{min}}{k_{el}} \quad (3)$$

For multiple-dose AUC_{24} (fifth dose as an example),

$$AUC_{96\text{-}120} = 0.5 \cdot t' \cdot (C_{max} + C_{min}) + \int_{t'}^{infinity} C_{max} \cdot e^{-k_{el} \cdot (t)}\, dt - \int_{120}^{infinity} C_{min} \cdot e^{-k_{el} \cdot (t)}\, dt \quad (4)$$

Equation 4 can be simplified to

$$AUC_{24} = \frac{t \cdot (C_{max} + C_{min})}{2} + \frac{C_{max} - C_{min}}{k_{el}} \quad (5)$$

where t' is the time of infusion (h), C_{max} is the peak concentration at the end of infusion, and C_{min} is the trough concentration at the end of the dosing interval. Given that peak concentrations may be measured up to 2.5 h after the end of infusion in this simulation, concentrations measured between 0.75 h and 3 h were extrapolated to the end of infusion using the Sawchuk-Zaske method. Similarly, trough concentrations sampled before the end of the dosing interval were extrapolated to the expected value at the end of the dosing interval. The percent error for computed AUC_{24} compared to integrated AUC_{24} was calculated for each of the 55 concentration-pairs for the first and fifth doses. Ordinary least-squares regression was also used to define the coefficient of determination for the computed AUC_{24} compared to integrated AUC_{24} values. The partial AUC between 0.5 h (end of infusion) and 2 h from the start of infusion was also calculated and defined as the distribution-phase AUC. The purpose of this calculation was to define the potential AUC not captured by our monoexponential decline assumption relative to the biexponential decline expectation of a 2-compartment system.

Step 2: validation using healthy volunteer data. The raw concentration-time data from a previous study evaluating the single-dose plasma PK of daptomycin at 4 mg/kg in 7 normal-weight and 7 morbidly obese healthy female subjects were used (18). The AUC_{24} (reference standard) was calculated by integration using the aforementioned 2-compartment model and individual maximum *a priori* Bayesian probability procedure in ADAPT 5 (14). The AUC_{24} was also calculated using equation 3 above for a single dose. For this AUC_{24} (calculated by equation), concentrations collected at the end of infusion (0.5 h) and at 1 h, 1.5 h, 2 h, and 4 h served as the peak measurement, while the measurement at 24 h served as the trough. The percent error for calculated AUC_{24} compared to integrated (reference standard) AUC_{24} was computed for each of the 5 peak-trough concentration pairs. Ordinary least-squares regression was used to compare the calculated AUC_{24} to the reference standard AUC_{24} values for each pair.

Validation using data from critically ill patients. The raw concentration-time data from a previous study evaluating the multiple-dose plasma PK of daptomycin at 6 to 8 mg/kg in 50 patients were used (8). The AUC_{24} (reference standard) was calculated using the aforementioned maximum *a priori* Bayesian probability procedure in ADAPT 5 by integration (14). The AUC_{24} was also calculated using equation 3 above for a single dose and using equation 5 for doses 2 to 5. For this AUC_{24} calculation, concentrations collected at approximately 0.5 h, 1 h, 2 h, and 4 h served as the peak measurement, while the measurement at 24 h served as the trough after the first dose. For doses 2 to 5, a peak concentration was measured approximately 1 h from the start of infusion and trough just prior to the dose. The percent error for calculated AUC_{24} compared to integrated AUC_{24} (reference standard) was determined for each of the peak-trough concentration pairs. Ordinary least-squares regression was used to compare the calculated AUC_{24} to the model integrated AUC_{24} values for each pair. Statistical analyses were implemented using STATA SE version 13 (StataCorp, College Station, TX).

RESULTS

Daptomycin population pharmacokinetic model simulations. The mean concentration-time profile generated by the simulations is illustrated in Fig. 1. The mean (standard deviation) values for the simulated PK parameters were as follows: CL, 0.959 (0.451) liter/h; V_c, 6.47 (3.03) liters; k_{cp}, 1.67 (3.11) h^{-1}; and k_{pc}, 1.34 (3.22) h^{-1}. These values matched the population's prior estimates. The mean (standard deviation) weight simulated was 82.0 (18.4) kg, which led to a simulated (6 mg/kg) daptomycin dosage of 492 (110) mg/day. The mean (standard deviation) concentrations at the end of infusion after the first and fifth doses were 69.4 (39.1) mg/liter and 79.6 (39.5) mg/liter, respectively. The mean (standard deviation) concentrations at the end of the dosing interval were 5.81 (4.79) mg/liter and 10.9 (9.67) mg/liter after the first and fifth doses, respectively. The mean (standard deviation) AUC_{24} for the simulated doses were 373 (233) mg · h/liter (dose 1), 462 (276) mg · h/liter (dose 2), 504 (294) mg · h/liter (dose 3), 530 (304) mg · h/liter (dose 4), and 547 (310) mg · h/liter (dose 5). The geometric mean AUC_{24} ratios (90% confidence intervals) of sequential doses were 1.282 (1.278, 1.288) (dose 2/dose 1), 1.113 (1.110, 1.115) (dose 3/dose 2), 1.062 (1.061, 1.064) (dose 4/dose 3), 1.040 (1.039, 1.041) (dose 5/dose 4), and 1.577 (1.563, 1.592) (dose 5/dose 1). The mean (95% confidence interval) distribution-phase AUC represented 5.07% (4.91%, 5.23%) and 3.46% (3.32%, 3.60%) of the AUC_{24} after dose 1 and dose 5, respectively.

Calculation of area under the curve. The bias and precision of the AUC_{24} were primarily influenced by the peak concentration time point and not by the trough concentration time point. Figure 2A illustrates a clear reduction in the mean percent error from 50 to 90% to approximately −10% between 0.5 h and 3 h, with convergence of the error to near 0% between 2 h and 2.25 h. Use of a simulated peak concentration-time point between 1.5 h and 3 h was associated with approximately a ±10% bias in the estimate of AUC_{24} after doses 1 and 5 using the stated equations. Similarly, the precision of calculated AUC_{24} increased with use of a peak con-

TABLE 1 Comparison of bias and precision of bedside models compared to integration computed AUC_{24} values based on single-dose data from healthy volunteers[a]

Model	Time points	AUC_{24} (mg · h/liter), mean (95% CI)	Percent error, mean (95% CI)	R^2
Ref	All	463 (371, 555)	Ref	Ref
1	0.5 h, 24 h	499 (393, 606)	13.0 (1.47, 24.0)	0.874
2	1 h, 24 h	476 (396, 555)	3.03 (−7.54, 13.6)	0.780
3	1.5 h, 24 h	424 (358, 490)	−5.61 (−13.7, 2.47)	0.888
4	2 h, 24 h	398 (333, 463)	−11.4 (−19.0, −3.74)	0.828
5	4 h, 24 h	373 (304, 442)	−17.2 (−24.5, −9.87)	0.858

[a] Ref, referent; CI, confidence interval.

centration time point above 0.5 h with convergence to an R^2 of >0.95 between 1.5 h and 1.75 h.

Validation using data from healthy volunteers. As suggested by the population model simulations, use of a peak concentration-time point at the end of infusion was associated with the greatest positive bias in the calculated AUC_{24}. Table 1 includes the mean (95% confidence interval) AUC_{24}, percent error, and precision (R^2) for each of the concentration-time pairs that were tested. The R^2 was highest with use of the 1.5-h peak concentration-time point, which was also associated with an unbiased estimate of the AUC_{24} value. Use of the 4-h time point as a peak value was associated with underestimation of AUC_{24} by ≥9.87%.

Validation using data from critically ill patients. Uses of concentrations after 0.5 h as the peak measurement were associated with declining bias. The mean (95% confidence interval) AUC_{24}, percent error, and R^2 for each of the concentration-time pairs that were tested are provided in Table 2. As shown, use of the 0.5-h time point after the first dose was associated with a mean (95% confidence interval) error of 46.2% (30.1%, 62.3%) and was unbiased with the use of the 2-h (lowest mean bias) or 4-h time point as the peak measurement. Use of the 1-h time point as the peak was associated with a mean (95% confidence interval) error of 12.1% (1.71%, 22.6%). As stated in Materials and Methods, only single time points approximately 1 h from the start of infusion were available after doses 2 to 5. Fewer observations were available for doses 2 to 5 than for dose 1. Although good precision was observed ($R^2 > 0.7$) for calculated AUC_{24} values, use of the single peak concentration measurement was associated with a mean bias of 6.14% to 37.2%. Linear regression of all calculated AUC_{24} values using the data from 1 h from the start of infusion only demonstrated good overall precision ($R^2 = 0.806$). However, as illustrated in Fig. 3, use of the data from 1 h after start of infusion from the single and multiple doses was associated with significant positive bias.

DISCUSSION

Selection of the optimal individual antimicrobial dosage regimen is problematic in clinical practice due to interindividual PK variability. Population pharmacokinetic analysis has emerged as a science to identify sources of this interindividual variability and mitigate them through the design of regimens that increase the PTA (13). Body weight and kidney function estimates have often been identified as sources of this interindividual variability and have been used to aid antimicrobial dosing. Unfortunately, critically ill patients experience dynamic shifts in physiologic function that can reduce the predictability of interindividual antimicrobial PK (2, 3). As a consequence, TDM is applied in clinical practice to overcome this problem. Unfortunately, the application of TDM is hindered by the lack of availability of assays to expedite analysis and technical knowhow on the interpretation of these data. However, the delivery of optimal antimicrobial pharmacotherapy is predicated on overcoming these fundamental challenges.

Our group has demonstrated through the use of TDM that the current daptomycin dosing recommendations on body weight and kidney function are no better than fixed dosing at achieving the AUC target for effect in critically ill patients (8). Specifically, use of 750 mg/day in patients with sepsis and 500 mg/day in patients not in sepsis is expected to achieve PTA comparable to those

TABLE 2 Comparison of bias and precision of bedside models compared to integration computed AUC_{24} values based on single- and multiple-dose daptomycin data from critically ill patients[a]

Dose	Model	No. of observations	Time points	AUC_{24} (mg · h/liter), mean (95% CI)	Percent error, mean (95% CI)	R^2
1	0	50	Ref	488 (427, 549)	Ref	Ref
1	1	50	0.5 h, 24 h	696 (593, 799)	46.2 (30.1, 62.3)	0.619
1	2	50	1 h, 24 h	535 (468, 602)	12.1 (1.71, 22.6)	0.725
1	3	50	2 h, 24 h	493 (431, 555)	3.67 (−7.41, 14.8)	0.689
1	4	49	4 h, 24 h	453 (392, 513)	−4.87 (−14.7, 4.95)	0.712
2	0	36	Ref	691 (619, 764)	Ref	Ref
2	1	36	25 h, 48 h	700 (603, 797)	6.14 (−9.07, 21.35)	0.854
3	0	26	Ref	723 (642, 805	Ref	Ref
3	1	26	49 h, 72 h	859 (667, 1,051)	31.8 (13.7, 50.0)	0.868
4	0	21	Ref	716 (621, 812)	Ref	Ref
4	1	21	73 h, 96 h	746 (555, 938)	19.3 (3.60, 35.0)	0.870
5	0	25	Ref	717 (610, 824)	Ref	Ref
5	1	25	97 h, 120 h[b]	834 (667, 1,000)	37.2 (11.7, 62.7)	0.742

[a] Ref, referent; CI, confidence interval.
[b] Value for 120 h defined by superposition of the value for 96 h.

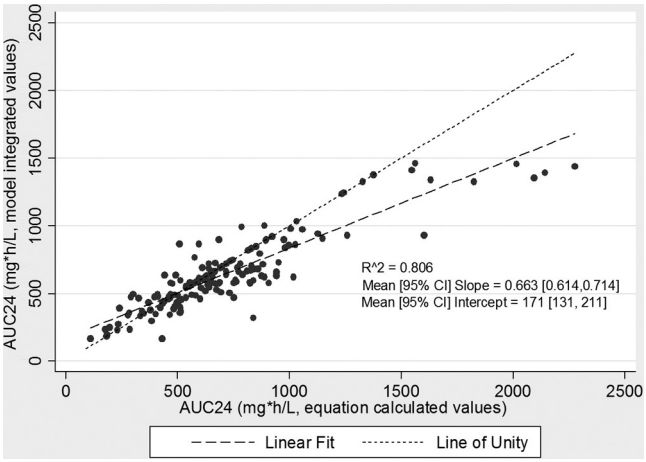

FIG 3 Scatter and linear fit plot with regression of AUC_{24} computed by the equations compared to model integrated values using the time points of 1 h after the start of infusion and end of dosing interval.

of dosages of 8 to 10 mg/kg/day but with a lower probability of toxicity (8). An important caveat of these prior findings is that they should be validated by other clinical groups to increase generalizability. As stated, major limitations to validation of this approach by other groups are accessibility to TDM and the technical knowhow on the execution of MAP-Bayesian analyses. We sought to define a simple clinically implementable "bedside" approach to aid clinicians who desire to transform measured daptomycin concentrations to AUC values and perhaps aid in these validations.

We used modeling and simulation with a standard daptomycin PK model and parameters defined through an MRSA BSI study to demonstrate that collection of two samples can permit unbiased estimation of daptomycin AUC_{24}. Collection of the peak sample between 2 h and 2.25 h was associated with almost no bias. For more practical consideration, collection of a peak sample 1.5 h to 3 h from the start of the daptomycin infusion and trough within an hour of the end of the dosing interval was associated with a bias of no more than ±10%. As illustrated in Fig. 1, the concentration-time profile for the 2-compartment model declines rapidly after the end of infusion and transitions from the alpha-phase (distribution) to the beta-phase (elimination) around 1.5 to 3 h from the start of infusion. The AUC of the alpha-phase potentially not captured by our equation-based assumptions represented a mean of ≤5.07% of the AUC_{24}. Hence, our observations of low mean percent error in the AUC_{24} and high precision (>0.95) with selection of time points in this range are consistent with this expected profile.

Validation of this approach was undertaken using data from our prior studies with healthy volunteers and critically ill patients (8, 18). Consistent with our population model approach above, we observed a trend for positive bias and negative bias around the time point of 1.5 h as the peak sample point. A similar observation was noted around the 2-h peak sample point with the data set from critically ill patients. The level of precision was lower with these validation data sets due to the lower number of observations and limited sampling time points relative to the simulation data set. Despite this limitation, the consistent trend across these three data sets speaks to the potential generalizability of equations 3 and 5 defined in this investigation. We did not conduct a prospective validation of these equations, so this limitation affects generalizability. Evaluation of this equation-based AUC calculation approach by other groups in other patient populations is necessary to overcome this limitation.

Our demonstration of a clinically feasible approach to compute daptomycin AUC_{24} after single and multiples doses creates an opportunity to individually optimize the dose of daptomycin. Specifically, computation of the AUC_{24} value based on the administered dose can be used to calculate a new dose by a proportionate method, i.e., new dose = target AUC_{24} × (current dose/calculated AUC_{24}). Although a target daptomycin AUC_{24} value is not well established to empirically treat MRSA-related BSI, it is expected to be between 579 and 753 mg · h/liter and should be selected based on the clinical judgment of the prescriber (19). Alternatively, clinical scientists who seek to identify the optimal daptomycin target AUC_{24} or AUC_{24}/MIC (once the pathogen is identified and MIC defined) could use this approach to aid in such investigation. It is, however, disingenuous to simply accept that 8- to 10-mg/kg/day dosages of daptomycin should be used in patients without simultaneously accepting that the purpose of this higher dose is to reliably increase the AUC_{24} to a higher threshold value than with standard doses (7). Identification of daptomycin AUC_{24} target values for different MRSA-related infections and patient populations will contribute to improve dosing strategies, as has been the case for aminoglycosides and vancomycin (4, 5).

Our suggested approach of two sample measurements is comparable to the practice applied to the dosing of aminoglycosides. As should be expected, use of sparse sample measurements and a MAP-Bayesian approach will yield the best results (13). In the absence of software or the technical knowhow on the execution of this approach, our simpler approaches may be feasible. Although limited availability of clinical assays to measure daptomycin concentrations hinders the application of this approach, it may be applicable to other agents. Novel techniques to simultaneously measure vancomycin, telavancin, daptomycin, and colistin have been developed that may become routine in some institutions (20). Evaluation of our approach should be undertaken with these agents, as their effects are also predicted by their AUC (1). Furthermore, novel techniques such as dried plasma spot sample collections have recently been validated for the assay of daptomycin (21). Improved sample collection and analysis techniques by centralized reference laboratories, for example, could extend TDM to institutions that do not routinely offer this service (22). As should be predicted, the AUC values computed by these methods will vary based on the exact sample time point measurements and analytical approaches. Although one would expect the bias and precision of these AUC_{24} estimates to fall within the range identified through our evaluation, empirical confirmation of this expectation is needed. Despite these limitations, clinical translation of the principles outlined in this work will serve as a key step forward for physicians to individualizing the dose of daptomycin and improving clinical outcomes.

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REFERENCES

1. **Martinez MN, Papich MG, Drusano GL.** 2012. Dosing regimen matters: the importance of early intervention and rapid attainment of the pharma-

cokinetic/pharmacodynamic target. Antimicrob. Agents Chemother. **56:** 2795–2805. http://dx.doi.org/10.1128/AAC.05360-11.

2. **Varghese JM, Roberts JA, Lipman J.** 2011. Antimicrobial pharmacokinetic and pharmacodynamic issues in the critically ill with severe sepsis and septic shock. Crit. Care Clin. **27:**19–34. http://dx.doi.org/10.1016/j.ccc.2010.09.006.
3. **Udy AA, Roberts JA, Lipman J.** 2013. Clinical implications of antibiotic pharmacokinetic principles in the critically ill. Intensive Care Med. **39:** 2070–2082. http://dx.doi.org/10.1007/s00134-013-3088-4.
4. **Pai MP, Rodvold KA.** 22 November 2013. Aminoglycoside dosing in patients by kidney function and area under the curve: the Sawchuk-Zaske dosing method revisited in the era of obesity. Diagn. Microbiol. Infect. Dis. http://dx.doi.org/10.1016/j.diagmicrobio.2013.10.011.
5. **Rybak M, Lomaestro B, Rotschafer JC, Moellering R, Jr, Craig W, Billeter M, Dalovisio JR, Levine DP.** 2009. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. Am. J. Health Syst. Pharm. **66:**82–98. http://dx.doi.org/10.2146/ajhp080434.
6. **Eisenstein BI, Oleson FB, Jr, Baltz RH.** 2010. Daptomycin: from the mountain to the clinic, with essential help from Francis Tally, MD. Clin. Infect. Dis. **50**(Suppl 1)**:**S10–S15. http://dx.doi.org/10.1086/647938.
7. **Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, Kaplan SL, Karchmer AW, Levine DP, Murray BE, Rybak JM, Talan DA, Chambers HF.** 2011. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children: executive summary. Clin. Infect. Dis. **52:**285–292. http://dx.doi.org/10.1093/cid/cir034.
8. **Falcone M, Russo A, Venditti M, Novelli A, Pai MP.** 2013. Considerations for higher doses of daptomycin in critically ill patients with methicillin-resistant Staphylococcus aureus bacteremia. Clin. Infect. Dis. **57:** 1568–1576. http://dx.doi.org/10.1093/cid/cit582.
9. **Di Paolo A, Tascini C, Polillo M, Gemignani G, Nielsen EI, Bocci G, Karlsson MO, Menichetti F, Danesi R.** 2013. Population pharmacokinetics of daptomycin in patients affected by severe Gram-positive infections. Int. J. Antimicrob. Agents **42:**250–255. http://dx.doi.org/10.1016/j.ijantimicag.2013.06.006.
10. **Pea F, Crapis M, Cojutti P, Bassetti M.** 25 July 2013. Daptomycin underexposure in a young intravenous drug user who was affected by life-threatening Staphylococcus aureus-complicated skin and soft tissue infection associated with bacteraemia. Infection http://dx.doi.org/10.1007/s15010-013-0511-2.
11. **Falcone M, Russo A, Cassetta MI, Lappa A, Tritapepe L, d'Ettorre G, Fallani S, Novelli A, Venditti M.** 2013. Variability of pharmacokinetic parameters in patients receiving different dosages of daptomycin: is therapeutic drug monitoring necessary? J. Infect. Chemother. **19:**732–739. http://dx.doi.org/10.1007/s10156-013-0559-z.
12. **Pea F, Cojutti P, Sbrojavacca R, Cadeo B, Cristini F, Bulfoni A, Furlanut M.** 2011. TDM-guided therapy with daptomycin and meropenem in a morbidly obese, critically ill patient. Ann. Pharmacother. **45:** e37. http://dx.doi.org/10.1345/aph.1P745.
13. **Jelliffe RW, Schumitzky A.** 1990. Modeling, adaptive control, and optimal drug therapy. Med. Prog. Technol. **16:**95–110.
14. **D'Argenio DZ, Schumitzky A, Wang X.** 2009. ADAPT 5 user's guide: pharmacokinetic/pharmacodynamic systems analysis software. Biomedical Simulations Resource, Los Angeles, CA.
15. **Bhavnani SM, Rubino CM, Ambrose PG, Drusano GL.** 2010. Daptomycin exposure and the probability of elevations in the creatine phosphokinase level: data from a randomized trial of patients with bacteremia and endocarditis. Clin. Infect. Dis. **50:**1568–1574. http://dx.doi.org/10.1086/652767.
16. **Begg EJ, Barclay ML, Duffull SB.** 1995. A suggested approach to once-daily aminoglycoside dosing. Br. J. Clin. Pharmacol. **39:**605–609. http://dx.doi.org/10.1111/j.1365-2125.1995.tb05719.x.
17. **Sawchuk RJ, Zaske DE.** 1976. Pharmacokinetics of dosing regimens which utilize multiple intravenous infusions: gentamicin in burn patients. J. Pharmacokinet. Biopharm. **4:**183–195.
18. **Pai MP, Norenberg JP, Anderson T, Goade DW, Rodvold KA, Telepak RA, Mercier RC.** 2007. Influence of morbid obesity on the single-dose pharmacokinetics of daptomycin. Antimicrob. Agents Chemother. **51:** 2741–2747. http://dx.doi.org/10.1128/AAC.00059-07.
19. **EUCAST.** 13 September 2005. Daptomycin: rationale for the EUCAST clinical breakpoints, version 1.0. http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Rationale_documents/Daptomycinrationale1.0.pdf. Accessed 10 October 2013.
20. **Tsai IL, Sun HY, Chen GY, Lin SW, Kuo CH.** 2013. Simultaneous quantification of antimicrobial agents for multidrug-resistant bacterial infections in human plasma by ultra-high-pressure liquid chromatography-tandem mass spectrometry. Talanta **116:**593–603. http://dx.doi.org/10.1016/j.talanta.2013.07.043.
21. **Baietto L, D'Avolio A, Pace S, Simiele M, Marra C, Ariaudo A, Di Perri G, Rosa FG.** 2013. Development and validation of an UPLC-PDA method to quantify daptomycin in human plasma and in dried plasma spots. J. Pharm. Biomed. Anal. **88C:**66–70. http://dx.doi.org/10.1016/j.jpba.2013.08.022.
22. **Meesters RJ, Hooff GP.** 2013. State-of-the-art dried blood spot analysis: an overview of recent advances and future trends. Bioanalysis **5:**2187–2208. http://dx.doi.org/10.4155/bio.13.175.