Pharmacodynamic Analysis of Daptomycin-treated Enterococcal Bacteremia: It Is Time to Change the Breakpoint

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Background. Currently, there is debate over whether the daptomycin susceptibility breakpoint for enterococci (ie, minimum inhibitory concentration [MIC] ≤ 4 mg/L) is appropriate. In bacteremia, observational data support prescription of high doses (>8 mg/kg). However, pharmacodynamic targets associated with positive patient outcomes are undefined.

Methods. Data were pooled from observational studies that assessed outcomes in daptomycin-treated enterococcal bacteremia. Patients who received an additional antienterococcal antibiotic and/or a β -lactam antibiotic at any time during treatment were excluded. Daptomycin exposures were calculated using a published population pharmacokinetic model. The free drug area under the concentration-time curve to MIC ratio ($fAUC/MIC$) threshold predictive of survival at 30 days was identified by classification and regression tree analysis and confirmed with multivariable logistic regression. Monte Carlo simulations determined the probability of target attainment (PTA) at clinically relevant MICs.

Results. Of 114 patients who received daptomycin monotherapy, 67 (58.8%) were alive at 30 days. A $fAUC/MIC >27.43$ was associated with survival in low-acuity ($n = 77$) patients (68.9 vs 37.5%, $P = .006$), which remained significant after adjusting for infection source and immunosuppression ($P = .026$). The PTA for a 6-mg/kg/day (every 24 hours) dose was 1.5%–5.5% when the MIC was 4 mg/L (ie, daptomycin-susceptible) and 91.0%–97.9% when the MIC was 1 mg/L.

Conclusions. For enterococcal bacteremia, a daptomycin $fAUC/MIC >27.43$ was associated with 30-day survival among low-acuity patients. As pharmacodynamics for the approved dose are optimized only when $MIC \leq 1$ mg/L, these data continue to stress the importance of reevaluation of the susceptibility breakpoint.

Keywords. pharmacodynamics; daptomycin; *Enterococcus*; bacteremia.

Daptomycin was approved in the United States in 2003 for the treatment of complicated skin and skin structure infections and in 2006 for *Staphylococcus aureus* bacteremia [1]. Relative to enterococcal infection, the Food and Drug Administration (FDA) susceptibility breakpoint (minimum inhibitory concentration [MIC] ≤ 4 mg/L) pertains only to vancomycin-susceptible *Enterococcus faecalis* for complicated skin and skin structure infections [1]. However, daptomycin is among the few

antibiotics that retain bactericidal activity against vancomycin-resistant *E. faecium* [2], and the susceptibility breakpoint defined by the Clinical and Laboratory Standards Institute (also ≤ 4 mg/L) applies to all *Enterococcus* spp. [3]. Recent reports of failure in daptomycin-treated enterococcal bacteremia suggest reduced efficacy against susceptible isolates with MICs of 3–4 mg/L [4–6], but contrasting findings are also described [7, 8]. At the molecular level, the potential inadequacy of the established breakpoint is evidenced by mutations in genes encoding the LiaFSR regulatory system among daptomycin-susceptible *E. faecium* isolates with MICs >2 mg/L [9, 10].

The FDA-approved dose for *S. aureus* bacteremia is 6 mg/kg (actual body weight) [1]. However, in line with higher reported daptomycin MIC distributions for *Enterococcus* spp. [9], doses prescribed when treating enterococcal bacteremia frequently exceed the approved dose [11]. Observational studies indicate an association between improved survival and doses ≥ 9 mg/kg [7]

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and ≥ 10 mg/kg [12], yet 6 mg/kg remains a commonly-prescribed regimen in clinical practice [13]. Combination therapy with one of many β -lactams is also frequently utilized, a practice supported by favorable clinical [14] and in vitro [15] observations.

Antibiotic dosage selection should be supported by pre-clinical pharmacodynamic (PD) data and confirmed in randomized, controlled trials. Against enterococcal species, data from neither methodology are available to justify daptomycin dosing for the treatment of serious enterococcal infection or the optimal susceptibility breakpoint. Nonetheless, pre-clinical data have established a free (unbound) drug area under the concentration-time curve to MIC ratio ($fAUC/MIC$) as the PD parameter most predictive of bacterial killing [16–18]. The precise $fAUC/MIC$ required for successful outcomes in severe enterococcal infections, however, is unknown. Therefore, analyzing human PD exposure is a logical next step for the identification of PD thresholds associated with optimized clinical outcomes. These data may also be useful for establishing dosing regimens and clinical breakpoints. To address this knowledge gap, the primary aim of this study was to determine the daptomycin $fAUC/MIC$ associated with improved 30-day survival rates in enterococcal bacteremia. The secondary aim was to use the identified PD threshold to support clinical breakpoints.

METHODS

Patients

Data were pooled from 7 observational studies assessing outcomes in daptomycin-treated enterococcal bacteremia [4, 7, 8, 12, 19–21]. Institutional Review Board approval and informed consent waivers were obtained at all sites, as only de-identified data were used. Patients were excluded either if the duration of daptomycin treatment was <72 hours or in the setting of concomitant administration of an antibiotic with intrinsic or synergistic activity against enterococci. Specifically, patients administered 1 or more of: (1) any β -lactam, (2) linezolid, (3) tigecycline, (4) any intravenous aminoglycoside, or (5) vancomycin (for vancomycin-susceptible isolates) at any time during daptomycin therapy were considered to have received combination therapy. In addition, patients were excluded if information required for calculation of exposure (outlined below) was unavailable, continuous renal replacement therapy occurred during treatment, or clearance of infection preceded daptomycin therapy. In recurrent bacteremia, only the first episode was included.

Data collected included age, sex, weight, daptomycin regimen (dose and frequency), daptomycin ETEST MIC, source of bacteremia, concomitant antibiotics, concomitant hemodialysis, microbiological response, and survival to 30 days. Patients were considered high acuity if any of the following conditions were met: Acute Physiology and Chronic Health Evaluation (APACHE)-II score ≥ 21 , Charlson comorbidity index ≥ 5 , or Pitt bacteremia score ≥ 4 . These scores were selected because

they have been previously associated with hospital mortality in critically-ill patients with sepsis [22].

Daptomycin Exposure

For each patient, a validated population pharmacokinetic model was used to estimate daptomycin clearance (CL) [23]:

$$CL = y \cdot [CL_R + 0.14 \cdot (TEMP - 37.2)] \quad 1$$

$$CL_R = 0.807 + 0.00514 \cdot (CL_{CR} - 91.2) \quad 2$$

Here, y was 0.8 for females and 1 for males, CL_R (L/h) was renal daptomycin clearance, $TEMP$ was patient temperature ($^{\circ}C$), and CL_{CR} was creatinine clearance, calculated by the Cockcroft-Gault equation [24] using actual body weight (150 mL/min maximum) [23]. In intermittent hemodialysis, CL_R was 0.269 L/h [23]. As temperature data were unavailable and had only marginal contributions to calculated exposure, $37.2^{\circ}C$ was assumed for all patients. The $fAUC$ of daptomycin was calculated as follows [25]:

$$fAUC = (0.1 \cdot Dose) / CL \quad 3$$

Here, 0.1 was the free daptomycin fraction in plasma [1] and the dose was in milligrams. For patients that received daptomycin doses every 48 hours, the dose was divided by 2 to reflect the average 24-hour exposure. The calculated $fAUC$ was divided by the baseline daptomycin ETEST MIC provided by the study site to determine each $fAUC/MIC$.

Statistical Analysis

The primary outcome was survival at 30 days, assessed from the first day of daptomycin therapy. In a minority of bacteremias, it was not possible to conclusively discriminate survival from the time of diagnosis of enterococcal bacteremia versus from the initiation of daptomycin therapy in the previously-collected data. The former definition was allowed with the assumption that minimal discordance existed between the 2 definitions (i.e., daptomycin therapy was initiated within 1–2 days following diagnosis in all patients). The secondary outcome was microbiological response, which was variably defined by the individual studies as bacteremia clearance prior to day 4 from the first positive blood culture [4, 7, 8, 12, 21], the absence of recurrent infection after initial clearance within 7 days [19], and clearance while receiving daptomycin (Supplementary Table 1) [20].

To transform $fAUC/MIC$ into a binary PD threshold (i.e., exposures achieving or not achieving the threshold), a classification and regression tree (CART) analysis (Salford Systems, San Diego, California) was performed to identify the $fAUC/MIC$ thresholds most predictive of survival to 30 days and of a microbiological response.

Statistical analyses were conducted in Sigma Plot v13.0 (Systat Software Inc., San Jose, California). T-tests or Mann-Whitney Rank Sum tests and χ^2 tests were performed for continuous and categorical variables, respectively. To confirm associations between the CART-derived PD threshold and outcomes, a multivariable logistic regression analysis was performed, with the PD threshold as the exposure of interest and selected covariates with bivariate *P*-values <.2. Covariates that were co-linear with *f*AUC/MIC (e.g., dose) were not included. The Hosmer-Lemeshow statistic was used to assess the model for goodness of fit.

Monte Carlo Simulations

The CART-derived PD threshold was applied in Monte Carlo simulations using Oracle Crystal Ball v11.1 (Oracle, Redwood Shores, California) to determine the probability of target attainment (PTA) of various daptomycin dosing regimens (6, 8, 10, and 12 mg/kg/day). Simulations recapitulated study cohort characteristics, including actual body weight as a log-normal distribution between 37 and 180 kg and CL_{CR} as a uniform distribution between 30 and 150 mL/min, to include the range for once-daily dosing [1]. Assumptions for the unbound daptomycin fraction (uniform distribution, 0.07–0.10) were derived from prescribing information [1]. The *f*AUC/MIC forecasts were performed at doubling MIC dilutions between 0.25 and 16 mg/L, and completed separately for 5000 females and 5000 males to account for gender disparities in daptomycin CL (Equation 1). An *a priori* PTA >90% was defined as optimal.

RESULTS

Cohort Characteristics

A total of 460 patients with enterococcal bacteremia were identified. After applying exclusion criteria, the final cohort included 114 patients, 90 of which were also evaluated for a microbiological response. Patients were excluded primarily for receipt of additional antibiotics (*n* = 240). Other reasons included loss to follow up prior to the 30-day survival assessment (*n* = 2), missing the data required to determine daptomycin exposure (*n* = 48), the clearance of bacteremia prior to daptomycin initiation (*n* = 18), recurrent bacteremia (*n* = 16), a duration of daptomycin therapy <72 hours (*n* = 13), and the receipt of continuous renal replacement therapy (*n* = 9). The number of patients included from each study was 9 [4], 28 [7], 33 [8], 1 [12], 10 [19], 31 [20], and 2 [21]. Vancomycin MICs were not collected; however, an estimated 86% of bacteremias in the final cohort were caused by vancomycin-resistant enterococci (VRE), based upon the proportion of VRE infections included in each original study. Patient characteristics are summarized in Table 1 for the total population and the low-acuity cohort.

Daptomycin Exposure

In the total population (*N* = 114), the mean daptomycin clearance was 0.7 ± 0.2 L/h, translating to a mean *f*AUC equal to

74.3 ± 25.8 mg*h/L and a mean *f*AUC/MIC equal to 35.0 ± 20.2 (range: 10.1–1235.9). In the low-acuity cohort (*n* = 77), the mean daptomycin clearance was 0.8 ± 0.2 L/h and the mean *f*AUC and *f*AUC/MIC were nearly identical to the values in all patients.

Survival Pharmacodynamic Threshold

In patients treated with daptomycin monotherapy, 67 (58.8%) were alive at 30 days. The CART-derived PD threshold associated with survival to 30 days is depicted in Figure 1. Although a greater proportion of total patients survived when daptomycin *f*AUC/MIC was greater than 27.43, compared with patients that did not achieve the threshold, the difference was not significant (Figure 1, *P* = .051). However, in low-acuity patients (*n* = 77), the CART-derived *f*AUC/MIC threshold was identical and was associated with survival (Figure 1, *P* = .006). Controlling for catheter source and immunosuppression, the *f*AUC/MIC >27.43 was independently associated with survival (*P* = .026, Table 2). In low-acuity patients alive at 30 days, the median *f*AUC/MIC was higher (32.9 versus 26.0, *P* = .085), and significantly higher daptomycin doses were prescribed (7.7 versus 6.3 mg/kg/dose, *P* = .023). The median daptomycin MIC was 2 mg/L, and did not differ between those alive and deceased at 30 days (*P* = .607). Significant relationships with *f*AUC/MIC thresholds were not identified when assessed in high-acuity patients only (data not shown).

Microbiologic Response Pharmacodynamic Threshold

In total, 66 (73.3%) patients achieved a microbiological response. However, despite higher observed microbiological response rates in patients with exposures exceeding the CART-derived thresholds both in all patients (*f*AUC/MIC >19.94) and low-acuity patients (*f*AUC/MIC >20.01), neither threshold was statistically significant in bivariate analyses (Figure 2).

Monte Carlo Simulations

Using the approved daptomycin dose (6 mg/kg/day), the PTA of the PD threshold associated with survival (*f*AUC/MIC >27.43) remained >90% when exposures were simulated for susceptible isolates with MICs of 0.25, 0.5, and 1 mg/L (Figure 3). At MICs of 2 mg/L, the PTA dropped precipitously, to 32.4% for males and 54.4% for females (Supplementary Table 2). As the relationship between dose and AUC is directly proportional, an identical pronounced decline was present between MICs of 2 and 4 mg/L with 12 mg/kg/day.

DISCUSSION

The appropriateness of the daptomycin susceptibility breakpoint for enterococcal infection is uncertain [4, 9, 13, 15], and the controversy has been propagated by conflicting reports of the effect of MIC on patient outcomes [4, 5, 7, 8]. PD relationships that may explain these observations were previously

Table 1. Cohort Characteristics

Characteristic	All Patients (n = 114)	Low-acuity Cohort (n = 77)
Age in y	55.0 (18.6), 59.0	53.8 (17.6), 58.5
Female sex, n (%)	48 (42.1)	36 (46.8)
Weight in kg	76.2 (21.2), 74.1	79.1 (22.1), 76.7
Serum creatinine in mg/dL	1.2 (0.9), 0.9	1.0 (0.6), 0.8
Low-acuity, n (%) ^a	77 (67.5)	77 (100.0)
APACHE-II score ^a	14.4 (7.0), 14.0	11.5 (4.9), 13.0
Charlson co-morbidity index ^a	3.3 (2.5), 3.0	1.5 (1.4), 2.0
Pitt bacteremia score ^a	2.1 (2.5), 3.0	0.8 (1.0), 0.0
Infection source	...	...
Catheter, n (%)	54 (47.4)	36 (46.8)
Endocarditis, n (%)	0 (0.0)	0 (0.0)
Gastrointestinal, n (%)	20 (17.5)	17 (22.1)
Urinary tract, n (%)	8 (7.0)	5 (6.5)
Other or unknown, n (%)	32 (28.1)	19 (24.7)
Intermittent hemodialysis, n (%)	5 (4.4)	0 (0.0)
Immunosuppressed, n (%) ^b	91 (79.8)	64 (83.1)
<i>Enterococcus faecium</i> bacteremia, n (%)	103 (90.4)	68 (88.3)
ETEST daptomycin MIC, mg/L, median (range)	2 (0.5–4)	2 (0.5–4)
Daptomycin dose, mg/dose	553 (169), 500	575 (176), 500
Daptomycin dose, mg/kg/dose	7.4 (1.5), 7.2	7.4 (1.8), 7.0
Survived at 30 days, n (%)	67 (58.8)	43 (55.8)

Data are presented as mean (standard deviation), median unless otherwise noted.

Abbreviations: APACHE-II, Acute Physiology and Chronic Health Evaluation II; MIC, minimum inhibitory concentration.

^aLow acuity indicates that none of following conditions were met: APACHE-II score ≥ 21 (available for 32 patients in the total population and 24 in the low-acuity cohort), Charlson comorbidity index ≥ 5 (available for 41 patients in the total population and 24 in the low-acuity cohort), or Pitt bacteremia score ≥ 4 (available for 60 patients in the total population and 41 in the low-acuity cohort).

^bImmunosuppressed patients were those with active malignancy, a history of solid organ/bone marrow transplantation, neutropenia (absolute neutrophil count <500), human immunodeficiency virus infection, or those receiving chemotherapy, mycophenolate, tacrolimus, cyclosporine, biological therapy, or corticosteroids.

unexplored. Therefore, we conducted a human PD analysis utilizing global data generated from diverse populations (Supplementary Table 1), and demonstrated an association between a daptomycin $fAUC/MIC > 27.43$ and improved 30-day survival rates in enterococcal bacteremia. Among low-acuity patients administered monotherapy, the odds of survival for those that achieved the optimal PD threshold were 3.1-fold higher than those with sub-threshold exposures.

No other human PD studies are available for comparison. However, the PD threshold of $fAUC/MIC > 27.43$ is higher than the target for 2-log₁₀ kill reported in 2003 by Alder and colleagues following an assessment of daptomycin PD in a murine renal infection model [16]. Given that daptomycin is primarily excreted as an intact drug in the urine, the authors cautioned that their results may not be applicable to other infection sites [16]. Indeed, Kidd and colleagues recently reassessed the in vivo pharmacodynamics utilizing human-simulated doses in a murine thigh infection model, and reported a 1-log₁₀ kill target of $fAUC/MIC > 12.9$ for *E. faecium* isolates [26], which is 3-fold higher than the murine target reported by Alder and colleagues [16]. Thus, our human PD analysis and the new murine PD target suggest that higher exposures are associated with survival and antibacterial

efficacy, respectively. Moreover, our data were also supportive of higher doses and a higher $fAUC/MIC$ (when analyzed as a continuous variable, data not shown) being associated with survival, albeit the relationship with $fAUC/MIC$ was not statistically significant, which was likely due to lack of power. Notably, the median MIC was the same regardless of survival, thereby suggesting that it is the PD exposure (i.e., $fAUC/MIC$) that is most important for daptomycin in predicting survival in patients with enterococcal bacteremia.

The exclusion of patients that received an active combination therapy for enterococcal bacteremia was imperative in order to conduct an analysis that appropriately informs daptomycin breakpoint decisions. However, many have extensively described the observed enhancement of daptomycin in the presence of β -lactams [27–31], as well as the increased activity of β -lactams after the cell envelope changes induced by daptomycin [32] in some enterococcal strains. Thus, future analyses that define the PD effect of combination therapy on daptomycin-treated enterococcal bacteremia are needed, especially in light of a recent finding of improved end-of-treatment survival rates with high-dose daptomycin (≥ 9 mg/kg/day) plus a β -lactam, compared with high-dose daptomycin monotherapy [14].

Figure 1. CART-derived pharmacodynamic thresholds in (A) all patients and (B) the low-acuity cohort for the 30-day survival outcome. Survival thresholds were identified in low-acuity patients to control for unknown confounding variables, which may contribute to overall mortality risk. Low acuity was defined as the absence of any of the following conditions: APACHE-II score ≥ 21 , Charlson comorbidity index ≥ 5 , and Pitt bacteremia score ≥ 4 . Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; CART, classification and regression tree analysis; fAUC/MIC, area under the free drug concentration-time curve to minimum inhibitory concentration ratio.

When the survival PD threshold was explored in Monte Carlo simulations, the FDA-approved dose produced a poor PTA when corresponding isolate MICs exceeded 1 mg/L. When exposures for 8 and 10 mg/kg/day regimens were simulated, PTAs remained $<90\%$ for MICs ≥ 2 mg/L. Even when the dose was maximized at 12 mg/kg/day, the PTA was suboptimal for

MICs of 4 mg/L. Thus, an optimal PTA was only achievable at an MIC of 2 mg/L using a 12 mg/kg/day regimen. Overall, the PTA estimations best support a susceptibility breakpoint of an MIC ≤ 1 mg/L for daptomycin monotherapy with the licensed dose (6 mg/kg/day) and the susceptible-dose dependent designation at an MIC of 2 mg/L for daptomycin 12 mg/kg/day.

Although most bacteremias were caused by *E. faecium* in this analysis, breakpoint modifications should apply to all enterococcal species to avoid reporting errors and misinterpretation. Even if vancomycin-resistant, *E. faecalis* are rarely ampicillin-non-susceptible [11], and the reduction of daptomycin breakpoints is therefore unlikely to impact overall prescribing trends. Nonetheless, it should be recognized that there are important biological differences between pathogenic enterococcal species [11]. For example, the emerging data reported by Kidd and colleagues supported a bacteriostatic target for *E. faecalis* (fAUC/MIC >7.2), as 1- $\log_{10}$ kill was not achieved [26]. This observation may indicate differing responses to daptomycin between the 2 enterococcal species in this murine model, though further studies are required to ultimately determine whether separate PD targets exist in humans.

While our analysis reveals that revised breakpoints are warranted to optimize PD exposures, hypotheses regarding the safety of such changes cannot be gleaned from these data. Clinicians may fear that high-dose daptomycin translates to an increased frequency of adverse effects; however, the literature does not support dose-dependent toxicities related to creatine phosphokinase elevation [12] or eosinophilic interstitial pneumonia [33, 34]. In fact, recently-updated treatment guidelines for enterococcal endocarditis recommend doses up to 12 mg/kg [35]. Moreover, a prospective review of high-dose daptomycin in the treatment of endocarditis captured only 15 (15%) patients with creatine phosphokinase elevation, while 11 (73%) continued treatment without any alteration of muscle function. There were 3 cases of eosinophilic interstitial pneumonia, and no patient discontinued due to renal toxicity, leading the authors to conclude that high-dose daptomycin was well tolerated in patients with multiple comorbidities [36].

Table 2. Effect of Characteristics on 30-Day Survival in the Low-acuity Cohort (n = 77)

Characteristic	Survived (n = 43), n (%)	Deceased (n = 34), n (%)	Bivariate OR (95% CI)	Bivariate P Value	Multivariable OR (95% CI)	Multivariable P Value
Immunosuppressed	32 (74.4)	32 (94.1)	0.18 (0.04–0.89)	.022	0.24 (0.05–1.21)	.084
Bacteremia source						
Gastrointestinal	11 (25.6)	6 (17.6)	1.60 (0.53–4.90)	.405	...	...
Urinary tract ^a	4 (9.3)	1 (2.9)	3.38 (0.36–31.79)	.376	...	...
Catheter-related	16 (37.2)	20 (58.8)	0.42 (0.17–1.04)	.059	0.51 (0.19–1.38)	.185
Other or unknown	12 (27.9)	7 (20.6)	1.49 (0.51–4.33)	.459	...	...
fAUC/MIC >27.43	31 (72.1)	14 (41.2)	3.69 (1.42–9.58)	.006	3.10 (1.14–8.38)	.026

Abbreviations: CI, confidence interval; fAUC/MIC, area under the free drug concentration-time curve to minimum inhibitory concentration ratio; OR, odds ratio

^aBivariate statistical analysis performed with Fisher's exact test.

Figure 2. CART-derived pharmacodynamic thresholds in (A) all patients and (B) the low-acuity cohort for the microbiological response outcome. Low acuity was defined as the absence of any of the following conditions: APACHE-II score ≥ 21 , Charlson comorbidity index ≥ 5 , and Pitt bacteremia score ≥ 4 . Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; CART, classification and regression tree analysis; fAUC/MIC, area under the free drug concentration-time curve to minimum inhibitory concentration ratio. ^aDifference assessed by Fisher's exact test.

In line with the existing literature, we observed mortality rates $>40\%$ [37] and daptomycin cure rates $<80\%$ [9] in enterococcal bacteremia. However, we were unable to detect the PD thresholds associated with microbiological eradication. A contributory factor may be the variability in microbiological response definitions used by the original studies, as well as the wide range of response rates among data sets (47% to 94%, [Supplementary Table 1](#)). Others have failed to observe associations between daptomycin doses and microbiological outcomes [7, 38], though Britt and colleagues reported a significant dose-dependent relationship via the investigation of response as a continuous variable of time to microbiologic clearance [12]. Furthermore, Shukla and colleagues reported a clear influence of MIC in microbiological eradication [4]. Data are conflicting, but with robust in vitro evidence of enterococcal activity [39], the observed effect of optimized daptomycin exposure on survival is likely mediated by microbiological clearance.

The current body of literature includes multiple reports of daptomycin failures in susceptible enterococcal infections, as

Figure 3. Monte Carlo simulation results for (A) males and (B) females. The probability of target attainment (PTA) was higher in simulations for female patients ([Supplementary Table 2](#)); however, both PTAs were either above or below 90% at each dose simulated, except for 10 mg/kg/day (males: 80.4%, females: 92.9%). Abbreviations: DAP, daptomycin; fAUC/MIC, area under the free drug concentration-time curve to minimum inhibitory concentration ratio; MIC, minimum inhibitory concentration.

well as the presence of mutations that confer resistance in isolates with MICs ≤ 4 mg/L. Thus, we believe that the human PD relationships presented here indicate that the time has come to revise daptomycin breakpoints for enterococcal infections. Our identification of the thresholds predictive of survival is consistent with previous observations of improved survival with high-dose daptomycin for enterococcal bacteremia [7, 12] as patients administered higher doses achieve higher fAUC and are more likely to attain optimized fAUC/MIC exposures. However, several limitations should be noted. First, the measured daptomycin concentrations were unavailable. However, the mean calculated fAUCs for patients that received 6 mg/kg/day were within the range of measured values in small pharmacokinetic analyses conducted in other patient populations [40, 41]. Second, as patient data originated from individually-published

studies, different acuity scoring systems were utilized; thus, we applied cut-offs that had been previously identified in critically-ill patients to partition the high-acuity from low-acuity patients. Third, our results are only generalizable to adult populations. In addition, as our findings were subject to the inherent limitations of a retrospective observational study design, the results signify the presence of an association between PD exposure and 30-day survival, rather than a causal relationship. It is also important to recognize that we were unable to control for time to adequate therapy or source control, which may impact mortality in cases of enterococcal bacteremia.

CONCLUSIONS

This study identified a daptomycin *fAUC*/MIC >27.43 to be associated with improved 30-day survival rates in low-acuity patients with enterococcal bacteremia. The probability of a 6 mg/kg/day daptomycin regimen achieving this PD threshold is negligible for isolates with MICs ≥2 mg/L; thus, clinicians may be misguided by susceptibility reports. Our results support reduced daptomycin susceptibility breakpoints to optimize patient outcomes. Furthermore, strategies that employ higher daptomycin doses to maximize *fAUC*/MIC should be seriously considered in deep-seated enterococcal infections.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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