MAJOR ARTICLE

Daptomycin Exposure and the Probability of Elevations in the Creatine Phosphokinase Level: Data from a Randomized Trial of Patients with Bacteremia and Endocarditis

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Background. The objective of this analysis was to evaluate the relationship between daptomycin exposure and the probability of an elevation in the creatine phosphokinase (CPK) level (hereafter, "CPK elevation") in patients with *Staphylococcus aureus* bacteremia with or without infective endocarditis.

Methods. Phase 3 data for patients with *S. aureus* bacteremia, with or without infective endocarditis, who received intravenous daptomycin (6 mg/kg daily) and in whom pharmacokinetic data were collected were evaluated. On the basis of univariate logistic regression, the relationship between Bayesian post hoc exposure estimates and the probability of a CPK elevation was evaluated. Time to CPK elevation was examined with Kaplan-Meier analysis and Cox proportional hazards regression.

Results. Significant relationships between the minimum concentration of drug (C_{min}) and area under the plasma concentration time curve and probability of CPK elevation were observed in 108 evaluable patients. Of the 108 patients evaluated, 6 (5.56%) demonstrated a defined CPK elevation, regardless of treatment relationship. C_{min} (breakpoint of 24.3 mg/L) was most significantly associated with CPK elevation ($P = .002$). The probabilities of a CPK elevation with a $C_{min} \geqslant 24.3$ mg/L and <24.3 mg/L were 0.5 and 0.029, respectively. Increases in C_{min}, evaluated as a continuous variable, were also significantly associated with CPK elevation ($P = .01$). Stratified Kaplan-Meier analysis and Cox proportional hazards regression demonstrated C_{min} to be a significant predictor of time to a CPK elevation ($P \leqslant .003$). The probability of a CPK elevation was 0 and 0.01 after 7 days of treatment in patients with a $C_{min} \geqslant 24.3$ mg/L or <24.3 mg/L, respectively. After 14 days, the probabilities were 0.5 and 0.025, respectively.

Conclusions. This analysis demonstrated that a daptomycin $C_{min} \geqslant 24.3$ mg/L was associated with an increased probability of a CPK elevation.

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Daptomycin is a cyclic lipopeptide antibacterial agent with in vitro activity against gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus*. In the early 1990s, clinical trials for this agent [1] used a 12-h dosing interval. After observing a signal of an adverse skeletal muscle effect at a dose level of 4 mg/kg administered every 12 h [2, 3], these trials were voluntarily suspended. Subsequent studies in dogs receiving daptomycin (75 mg/kg daily for 20 days) served to demonstrate decreased skeletal myopathy and creatine phosphokinase (CPK) elevation when the dose was administered once daily compared with 25 mg/kg every 8 h [4], thereby supporting the study of once-daily dosing regimens in clinical trials that followed. Clinical studies of daptomycin administered daily demonstrated a lower incidence of elevations in the creatine phosphokinase (CPK) level (hereafter, "CPK elevations") [5, 6], thus supporting the findings in dogs [4].

After US Food and Drug Administration approval of this agent for the treatment of complicated skin and skin-structure infections attributable to gram-positive

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organisms at a once-daily intravenous dose of 4 mg/kg, daptomycin was studied in a pivotal randomized trial versus a comparator (semisynthetic penicillins or vancomycin) for the treatment of patients with bacteremia and endocarditis caused by *S. aureus* [5]. The favorable results of this clinical trial led to the approval of daptomycin in the United States for therapy of *S. aureus* bacteremia, including right-side infective endocarditis, with 6 mg/kg daily. To better understand the relationship between daptomycin exposure and the probability of CPK elevation, data were evaluated from the described clinical trial [5] in patients with *S. aureus* bacteremia with or without endocarditis.

METHODS

Primary objective. The objective of this analysis was to evaluate the relationship between daptomycin exposure and the probability of CPK elevation in patients with *S. aureus* bacteremia with or without infective endocarditis.

Study design. A subset of data from a phase 3 bacteremia and endocarditis study [5] was analyzed, which included patients who received 6 mg/kg of intravenous daptomycin every 24 h for a minimum of 10 days and a maximum of 42 days and had daptomycin plasma concentration data available. Using population pharmacokinetic modeling, Bayesian daptomycin exposures (day 5) were estimated for each patient. All CPK elevations were evaluated regardless of the causal attribution to daptomycin.

Pharmacokinetic sampling. Five serial blood samples were collected on day 5 at predose and 0.25–0.5, 1–1.5, 3–5, and 9–12 h after the infusion ended. Daptomycin plasma concentrations were determined by a validated high-performance liquid chromatography assay.

Population pharmacokinetic modeling. Plasma concentration time data were analyzed using a nonparametric adaptive grid with adaptive γ approach [7]. A 2-compartment, open model with zero-order intravenous input and first-order elimination was used. Weighting was the inverse of the estimated observation variance as determined by an additive plus proportional error model multiplied by the estimated scalar adaptive γ. Bayesian day 5 exposures for maximum concentration of drug (C_{max}), minimum concentration of drug (C_{min}), and area under the plasma concentration time curve (AUC) after 6 doses of daptomycin were estimated for each patient using the population-of-one utility within the nonparametric adaptive grid.

Pharmacodynamic end points evaluated. The occurrence of and time to a CPK elevation during the period that patients received daptomycin treatment to 3 days after therapy represented the pharmacodynamic end points evaluated. Serum CPK activity was measured 3 times during each week of daptomycin treatment. The CPK values were deemed to be elevated in 1 of the following scenarios:

1. No CPK elevations at baseline followed by CPK elevations $\geqslant$3 times the upper limit of normal (ULN) based on 2 sequential measurements during the period from day 4 (after 3 doses) to 3 days after therapy, with 1 of 2 CPK elevations $\geqslant$5 times the ULN.
2. Baseline CPK greater than the ULN followed by CPK elevations $\geqslant$5 times the ULN based on 2 sequential measurements during the period from day 4 (after 3 doses) to 3 days after therapy.

Pharmacodynamic modeling. Univariate logistic regression was used to evaluate the relationship between day 5 exposure measures (C_{max}, C_{min}, and AUC), evaluated as both continuous and categorical variables, and the probability of CPK elevation. Classification and regression tree (CART) analysis was used to identify categorical breakpoints for each of the described exposure measures. Stratified Kaplan-Meier and Cox proportional hazards regression analyses were also used to examine the relationship between exposure and the time to a CPK elevation. Pharmacodynamic modeling was performed using SYSTAT statistical software, version 11.0 [8].

Monte Carlo simulation. By ADAPT II [9], mean parameter estimates and standard deviations from the final population pharmacokinetic model and exposure-response relationships identified by the described pharmacodynamic modeling, Monte Carlo simulations (9999 patients) were conducted. Simulated exposures were assessed at steady-state after 6 daily doses of daptomycin ranging from 4 to 12 mg/kg daily. Normal and log-normal distributions were evaluated. Choices between distributions were made on the basis of the fidelity with which the original population mean parameter values and dispersions were recreated.

RESULTS

Patient population. A total of 120 adult patients receiving 6 mg/kg of daptomycin daily were available for evaluation. Of these, 108 patients had sufficient pharmacokinetic data and comprised the analysis data set. Table 1 shows the patient demographic characteristics.

Population pharmacokinetic model. Mean ($\pm$ standard deviation [SD]) parameter values based on the final population pharmacokinetic model were 6.56 (3.10) L for volume of distribution, 0.957 (0.461) L/h for clearance, and 1.67 (3.04) and 1.34 (3.40) h^{-1} for K_{cp} and K_{pc} (first-order intercompartmental transfer rate constants), respectively. As demonstrated by the observed-predicted daptomycin concentration regression after the Bayesian step, the overall model fit to the data was excellent (observed $= 1.036 \times$ predicted$- 0.808$; $r^2 = 0.991$; $P < .001$).

Table 1. Demographic Characteristics of the 108 Patients Included in the Analysis Data Set

Characteristic	No. of patients	Mean ± SD	Median (range)
Age, years	108	52.1 ± 17.5	50.0 (21.0–87.0)
Baseline weight, kg	108	82.2 ± 18.6	80.5 (52.0–129)
Baseline height, cm	107	170.7 ± 11.0	170 (149–206)
Baseline creatinine clearance, mL/min[a]	108	96.6 ± 44.3	88.6 (28.0–247)
Weight-normalized baseline creatinine clearance, mL/min per 80.5 kg	108	96.2 ± 42.1	88.4 (27.4–242)
Baseline creatinine phosphokinase, IU/L	108	135 ± 186	59.0 (4.0–996)

NOTE. SD, standard deviation.

[a] Estimated using the Cockcroft-Gault method [20].

Pharmacodynamic analyses. Six (5.56%) of 108 patients demonstrated a defined CPK elevation, regardless of treatment relationship. Table 2 provides a summary of relevant clinical information for these patients. According to univariate logistic regression, both C_{min} and AUC, whether evaluated as continuous or categorical variables, were significantly associated with CPK elevation. C_{max} was not significantly associated with CPK elevation. Of these relationships, C_{min} evaluated as a categorical variable, based on a CART-derived breakpoint of 24.3 mg/L, was most significantly associated with CPK elevation ($P < .001$; odds ratio [OR], 33.0; 95% confidence interval [CI], 4.60–237). Three (50%) of 6 patients with a $C_{min} \geqslant 24.3$ mg/L had elevated CPK values compared with 3 (2.9%) of 102 patients with a $C_{min} < 24.3$ mg/L ($P = .002$, by the Fisher exact test). When evaluated as a continuous variable, univariate logistic regression demonstrated that increases in C_{min} were also significantly associated with CPK elevation (OR, 1.11; 95% CI, 1.02–1.20; $P = .01$). By comparison, AUC evaluated either as a categorical ($P = .02$) or a continuous variable ($P = .08$) was less significant. The relationship between C_{min} as a continuous variable and the probability of CPK elevation overlaid on the distribution of C_{min} values estimated for the 108 patients described herein (with open circles representing the C_{min} values corresponding to the 6 cases with CPK elevation) is shown in Figure 1. As shown by the 95% CI around this probability function (dashed lines), the uncertainty around the probability of CPK elevation appears minimal at a $C_{min} < 20$ mg/L. At a $C_{min} \geqslant 20$ mg/L (region representing the upper 10th percentile of the C_{min} distribution), the magnitude of uncertainty around the probability of CPK elevation increased substantially.

Given that C_{min} was most significantly associated with CPK elevation compared with other exposure measures and that this was consistent with the results of a previously described dose-fractionation study in dogs [4], subsequent time-to-event analyses for CPK elevation and Monte Carlo simulations were restricted to the evaluation of daptomycin C_{min} values. By either a stratified Kaplan-Meier analysis or Cox proportional hazards regression, C_{min} was found to be a significant predictor of time to a CPK elevation ($P < .001$ and $P = .003$, respectively). The time course to CPK elevation stratified by C_{min} group is shown in Figure 2. The probability of a CPK elevation was 0 and 0.01 after 7 days of treatment in patients with a $C_{min} \geqslant 24.5$ mg/L or <24.3 mg/L, respectively. After 14 days, these probabilities were 0.5 and 0.025, respectively. Details about the nature of and time course for CPK elevations for the 3 cases in either group are provided in Table 2.

Using the population pharmacokinetic mean parameter values and SDs for daptomycin, 9999-patient Monte Carlo simulations were performed to generate C_{min} values after 6 daily doses of daptomycin, 4–12 mg/kg. Using the CART-derived relationship for C_{min} and the probability of CPK elevation, CPK elevation probabilities were estimated for each simulated C_{min} value. The overall probability of CPK elevation by dose level was calculated by taking the sum of the fractional probabilities associated with a $C_{min} \geqslant 24.3$ mg/L or <24.3 mg/L. The percent probability of CPK elevation associated with musculoskeletal adverse events was also derived for each dose level using the product of the percent probability of CPK elevation and the probability of CPK elevation and musculoskeletal adverse events among those patients with *S. aureus* bacteremia with or without infective endocarditis who received 6 mg/kg daily (2 of 6 patients or 0.33). These percent probabilities are given in Table 3. Because the daptomycin daily dose increased from 4 to 12 mg/kg in 2-mg/kg increments, the percent probability of a CPK elevation and associated musculoskeletal adverse events increased from 3.73 to 19.5% and 1.24 to 6.49%, respectively. These simulations assume the range of renal function evident in the patients with bacteremia with or without infective endocarditis based on the analyses described herein (mean weight-normalized baseline creatinine clearance ± SD, 96.2 ± 42.1 mL/min per 80.5 kg).

DISCUSSION

Daptomycin has been shown to be of value for the treatment of *S. aureus* bacteremia and endocarditis. It is associated with

Table 2. Summary of Relevant Clinical Information for Patients with Elevated Creatine Phosphokinase (CPK) Levels

Patient	Age, years	Weight, kg	Duration of treatment, days	Day of first CPK elevation	Peak CPK level, U/L	Ratio of peak CPK level to ULN	Day of peak CPK level	Baseline CrCL, mL/min	Muscle AE	Disposition	C_{min}, mg/L	Clinical factor(s)
1	63	111	28	20	1934	9.9	20	132.1	No	Completed treatment	3.8	Obesity, gout, swollen elbow
2	43	71	10	5	5548	30.0	10	106.7	Yes	DC	7.5	Steroid-dependent asthmatic patient with osteoporosis, baseline CPK level of 833 U/L, spinal cord compression requiring surgery day 10 after treatment
3	36	121	28	14	895	5.1	14	194.2	No	Completed treatment	8.6	Obesity
4	63	80	14	13	3171	21.1	2 days after treatment	65.6	No	Completed treatment	24.3	None
5	55	115	15	15	2977	22.1	3 days after treatment	105.0	Yes	DC	25.6	Obesity, simvastatin use
6	86	112	16	14	3140	13.5	1 day after treatment	39.7	No	DC	45.4	Obesity, abdominal ecchymoses at insulin and heparin injection sites

NOTE. AE, adverse event; C_{min}, minimum concentration of drug (based on Bayesian post hoc estimate from population pharmacokinetic model for each patient); CrCL, creatinine clearance (calculated using the Cockcroft-Gault method [20]); DC, discontinued treatment because of CPK elevation; ULN, upper limit of normal.

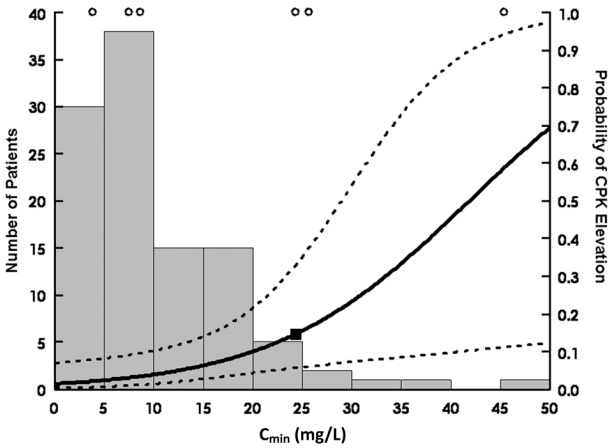

Figure 1. Relationship between minimum concentration of drug (C_{min}) evaluated as a continuous variable and the probability of creatine phosphokinase (CPK) elevation (*solid line*) with the 95% confidence interval around this probability function shown by the dashed lines ($P = .01$) overlaid on the distribution of steady-state C_{min} values estimated for the 108 patients who received daptomycin (6 mg/kg) as a once-daily regimen (*shaded bars*). The box represents the categorical C_{min} breakpoint of 24.3 mg/L. The open circles represent the C_{min} values corresponding to the 6 cases with CPK elevation.

a low incidence of adverse musculoskeletal effects in treated patients. These effects are manifested as muscle weakness and pain, generally preceded by elevations in serum CPK concentrations, and are fully reversible on therapy cessation. Although CPK elevation does not always correlate with musculoskeletal symptoms, it may serve as an early warning signal.

We demonstrated an association between daptomycin C_{min} values and the occurrence of a CPK elevation. At a C_{min} ⩾24.3 mg/L, the probability of CPK elevation was significantly higher compared with a C_{min} <24.3 mg/L (50% vs 2.9%; $P = .002$). This observation is consistent with preclinical dog studies in which myopathy was minimized by time between doses and a C_{min} <27 mg/L for ~12 h [4]. Through time-to-event analyses, duration of therapy was also found to influence the probability of CPK elevation among patients with higher C_{min} values. Although the risk of CPK elevation was similar among patients with low and high C_{min} values after 1 week of therapy, patients with a C_{min} ⩾24.3 mg/L had a higher probability of CPK elevation (50%) compared with those with a C_{min} <24.3 mg/L (2.50%) after 2 weeks of therapy. For both the low and high C_{min} groups, CPK increased after day 5, with 5 of 6 elevations occurring within the first 2 treatment weeks and the last at 20 days. Of the 6 patients with CPK elevation, CPK levels returned to the normal range during treatment or within the posttreatment follow-up period for all patients. Daptomycin therapy was stopped for 3 patients (1 with a C_{min} <24.3 mg/L and 2 with a C_{min} ⩾24.3 mg/L), 2 of whom (1 with a C_{min} <24.3 mg/L and 1 with a C_{min} ⩾24.3 mg/L) had musculoskeletal effects.

Larger drug doses are believed to provide a higher likelihood of a good therapeutic outcome. However, little information is usually available to clinicians about attendant risks. Table 3 summarizes probabilities for CPK elevation and CPK elevation associated with musculoskeletal adverse events as a function of daptomycin dose. For instance, it is predicted that a patient receiving a 4- or 6-mg/kg once-daily daptomycin dose will have, respectively, a 3.73% or 6.92% probability of a CPK elevation. Only daptomycin doses of 4 and 6 mg/kg daily are currently approved by the Food and Drug Administration [10]. Extensive clinical data are not available to assess the potential for musculoskeletal effects and CPK elevations after once-daily daptomycin doses of ⩾8 mg/kg. Two ascending-dose, phase 1 trials with a small number of healthy volunteers (6–9 per dose group) demonstrated no clinically significant CPK elevations or adverse musculoskeletal effects after 14 days of once-daily doses of daptomycin of 8, 10, and 12 mg/kg [10, 11]. A recent evaluation by Katz et al [12] of high-dose, short-duration therapy with daptomycin (10 mg/kg daily) for 4 days in 48 patients with complicated skin and skin structure infections demonstrated a CPK elevation rate of 8.3% (4 of 48). Of the 4 reported cases, 3 (6.25%) had elevations >500 IU/L occurring during therapy and that were associated with musculoskeletal symptoms. In the present evaluation, which was based on a longer treatment period for a more seriously ill patient population, a musculoskeletal adverse event rate of 6.49% would have been predicted.

There is a background rate of CPK elevation in clinical trials, and these elevations may be related to other causes, such as surgical procedures, other procedures, or other conditions or therapies (e.g., diabetes mellitus or statins). Consequently, some portion of the CPK elevation events may not be associated with daptomycin per se, particularly in patients with low

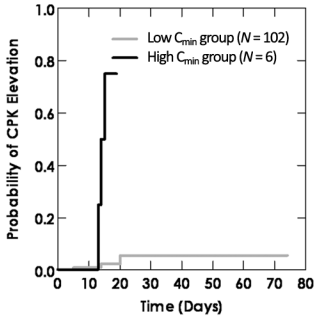

Figure 2. Kaplan-Meier plot showing time to creatine phosphokinase (CPK) elevation stratified by the classification and regression tree–derived breakpoint for minimum concentration of drug (C_{min}; $P < .0001$); 102 patients were in the low C_{min} (<24.3 mg/L) group, and 6 patients were in the high C_{min} (⩾24.3 mg/L) group.

Table 3. Probability of Elevated Creatine Phosphokinase (CPK) Level ("Elevated CPK"), Stratified by Dose, as Predicted from Monte Carlo Simulations

Daily dose, mg/kg	Probability of CPK elevation, %	Probability of CPK elevations associated with musculoskeletal adverse events, %[a]
4	3.73	1.24
6	6.92	2.31
8	10.7	3.57
10	15.3	5.11
12	19.5	6.49

[a] Derived using the product of the percent probability of CPK elevation and the probability of CPK elevation and musculoskeletal adverse events among those patients with *Staphylococcus aureus* bacteremia, with or without infective endocarditis, who received daptomycin (6 mg/kg daily; 2 of 6 patients or 0.33).

daptomycin C_{min} values. Although the focus of the analyses described herein was to evaluate the relationship between daptomycin exposure and probability of CPK elevation, relationships between other factors and CPK elevation were also examined. Of these, the relationship between total body weight ⩾111 kg and CPK elevation was most impressive ($P = .001$). Indeed, 4 of the patients with CPK elevation and a history of obesity listed in Table 2 had total body weights ⩾111 kg.

Given that daptomycin dosing is based on total body weight, we examined the percentage of patients who weighed <111 kg and ⩾111 kg receiving daptomycin, 6 mg/kg daily, who would be expected to have a C_{min} ⩾24.3 mg/L in a separate analysis using Monte Carlo simulation. A C_{min} ⩾24.3 mg/L would be expected in 6.5% and 19.4% of simulated patients, respectively. Such findings are not unexpected given the results of the study by Pai et al [13], which demonstrated that daptomycin C_{max} and AUC values were ~60% higher in morbidly obese patients compared with normal weight patients ($P < .05$) after daptomycin (4 mg/kg daily, on the basis of total body weight). In the simulations herein, when daptomycin was administered as 6 mg/kg daily on the basis of lean body weight [14] rather than total body weight in simulated patients weighing ⩾111 kg, only 7.4% of such patients would be expected to have a C_{min} ⩾24.3 mg/L. Dosing based on lean body weight for simulated patients weighing ⩾111 kg and on total body weight for simulated patients weighing <111 kg produced AUC distributions that were not significantly different. Because the ratio of AUC to minimum inhibitory concentration is the pharmacokinetic-pharmacodynamic measure most predictive of outcome [15, 16], maintaining similar AUC values in both groups is of interest to ensure similar efficacy. When treating obese patients, should a clinician choose to administer daptomycin dosed on lean body weight, the risk-benefit of lower AUC values relative to potentially reduced efficacy and a lower probability of CPK elevation needs to be explicitly assessed. Given the weight range on which pharmacokinetic parameter estimates were based for the simulations, further examination of the pharmacokinetics of daptomycin in obese patients with consideration of the exposure-response relationship for CPK elevation described herein and pharmacokinetic-pharmacodynamic relationships for efficacy may be warranted.

Although CPK elevation is a sensitive marker for potential adverse musculoskeletal effects, low-level increases of <5 to 10 times the ULN are often not accompanied by symptoms of skeletal myopathy (pain and weakness). Furthermore, although values as high as 35,000–40,000 IU/L have been reported after strenuous exercise, individuals with normal renal function recover rapidly to normal resting values, usually within 7–10 days, and demonstrate no permanent detrimental effects [17, 18].

Symptoms of musculoskeletal effects, which have been shown to be reversible on cessation of daptomycin treatment and not associated with any alteration in function, are generally preceded by CPK elevation. Thus, in patients receiving standard daptomycin dosing (4 or 6 mg/kg daily), weekly monitoring of CPK is recommended. More frequent monitoring is also recommended in the product label for daptomycin for patients receiving prior or concomitant therapy with a β-hydroxy-β-methylglutaryl–coenzyme A reductase inhibitor or those with renal insufficiency [19]. The results of the analyses described herein and those of Katz et al. [12] support more frequent monitoring of serum CPK in all patients receiving daptomycin, starting 3–5 days after initiation of therapy.

Although the results of these analyses would suggest that monitoring daptomycin C_{min} may be beneficial, this would require the use of expensive chemical assays. Given the wide availability and low cost associated with the serum CPK assay, the implementation of therapeutic drug monitoring for daptomycin seems unwarranted for patients receiving approved dosing regimens. However, one exception in which periodic monitoring of daptomycin C_{min} may be indicated is when a CPK elevation of >1000 IU/L (~5 times the ULN) with clinical signs of adverse muscle effects or >2000 IU/L (⩾10 times the ULN) without any clinical signs of adverse muscle effects has occurred and the clinician thinks that continuing daptomycin therapy is imperative. These data from Katz et al [12], in which 3 cases of CPK elevation occurred during a 4-day course of therapy with daptomycin (10 mg/kg daily), followed by concurrent musculoskeletal symptoms, suggest that patients receiving higher-than-approved doses may also benefit from early and frequent monitoring of daptomycin C_{min}. In each of these situations, an assay result demonstrating a low daptomycin C_{min} would represent a reduced probability that the CPK elevation was daptomycin related.

In summary, patients with *S. aureus* bacteremia, with or without infective endocarditis, receiving daptomycin had a significantly increased probability of CPK elevations when C_{min}

values were ⩾24.3 mg/L, with this elevation in CPK becoming apparent when therapy approximated 2 weeks. The uncertainty about the probability of CPK elevation increased as C_{min} values exceeded the threshold of 24.3 mg/L, but the lower bound of the probability function still approached ~10%. Lastly, CPK elevation during daptomycin therapy was an infrequent event and not always associated with symptoms of adverse musculoskeletal effects. These data are important for clinicians evaluating the risk and benefit of increased daptomycin dosing regimens in the case of high medical need.

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