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MAJOR ARTICLE

Daptomycin Exposure as a Risk Factor for Daptomycin-Induced Eosinophilic Pneumonia and Muscular Toxicity

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Background. High-dose daptomycin is increasingly used in patients with bone and joint infection (BJI). This raises concerns about a higher risk of adverse events (AEs), including daptomycin-induced eosinophilic pneumonia (DIEP) and myotoxicity. We aimed to examine pharmacokinetic and other potential determinants of DIEP and myotoxicity in patients with BJI receiving daptomycin.

Methods. All patients receiving daptomycin for BJI were identified in a prospective cohort study. Cases were matched at a 1:3 ratio, with controls randomly selected from the same cohort. Bayesian estimation of the daptomycin daily area under the concentration-time curve over 24 hours (AUC_{24h}) was performed with the Monolix software based on therapeutic drug monitoring (TDM) data. Demographic and biological data were also collected. Risk factors of AEs were analyzed using Cox proportional hazards model.

Results. From 1130 patients followed over 7 years, 9 with DIEP, 26 with myotoxicity, and 106 controls were included in the final analysis. Daptomycin AUC_{24h}, C-reactive protein, and serum protein levels were associated with the risk of AEs. The adjusted hazard ratio of DIEP or myotoxicity was 3.1 (95% confidence interval [CI], 1.48–6.5; $P < .001$) for daptomycin $AUC_{24h} > 939$ mg/h/L, 9.8 (95% CI, 3.94–24.5; $P < .001$) for C-reactive protein > 21.6 mg/L, and 2.4 (95% CI, 1.02–5.65; $P = .04$) for serum protein <72 g/L.

Conclusions. We identified common determinants of DIEP and myotoxicity in patients with BJI. Because the risk of AEs was associated with daptomycin exposure, daptomycin TDM and model-informed precision dosing may help optimize the efficacy and safety of daptomycin treatment in this setting. A target AUC_{24h} range of 666 to 939 mg/h/L is suggested.

Keywords. daptomycin; eosinophilic pneumonia; myopathy; pharmacokinetics; therapeutic drug monitoring.

Daptomycin-recommended dosing regimens are 4 mg/kg/24 hours for complicated skin and soft-structure infections and 6 mg/kg/24 hours for bloodstream infections and infectious endocarditis. However, recent studies reported greater efficacy with dosages higher than recommended, up to 8 to 12 mg/kg/24 hours in patients with bone and joint infection (BJI), an off-label indication [1–4]. Pharmacokinetic (PK) and clinical data support higher daptomycin doses for patients with BJI [5–8].

Using daptomycin for BJI treatment raises safety concerns because of high dosages and prolonged treatment duration (from 2 to 12 weeks) [9]. Two major adverse events (AEs) have been reported with daptomycin use: myotoxicity and eosinophilic pneumonia. Myotoxicity has been mainly described as an elevation in serum creatinine phosphate kinase (CPK), but myalgia and rhabdomyolysis have also been reported. Myotoxicity incidence under daptomycin is estimated at 5% to 10% [1, 10–13]. Daptomycin-induced eosinophilic pneumonia (DIEP) estimated incidence is about 2% and was more frequently reported in patients treated for BJI [14]. DIEP is a potentially fatal condition that requires early daptomycin discontinuation. Although myotoxicity and DIEP are reversible on daptomycin discontinuation, preventing those events is clinically relevant.

Little is known about the drug-related risk factors for these 2 events. Bhavnani et al [11] reported an increased risk of CPK elevation when daptomycin trough concentration (C_{min}) was >24.3 mg/L, which was later confirmed by Samura et al, who found $C_{min} > 20$ mg/L to be associated with CPK elevation [15]. The influence of daptomycin exposure on DIEP occurrence remains unclear [14].

To date, the underlying risk factors for DIEP and CPK elevation have yet to be thoroughly studied. This study aimed to

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investigate drug-related and other potential CPK elevation and DIEP determinants in a large cohort of patients treated with high-dose daptomycin for BJI.

METHODS

Inclusion and Exclusion Criteria

We conducted a retrospective collection and analysis of data from patients included in a prospective cohort study (Lyon BJI cohort study) who were treated with daptomycin for a BJI between 2014 and 2021 in our regional reference center for complicated BJI (CRIOAc Lyon; http://www.crioac-lyon.fr/en). The daptomycin initial dose varied between 6 and 12 mg/kg/24 hours.

On data collection, a team of physicians reviewed all patients who experienced pneumonia or presented signs of muscular toxicity. DIEP cases were identified by a new algorithm proposed by our group that includes chest computed tomography scans and blood eosinophilia [16]. Myotoxicity cases were defined based on any of the following criteria:

1. CPK elevation >3 times the upper limit of normal (192 U/L), with normal CPK levels at baseline
2. Normal CPK levels at baseline followed by CPK elevation >3 times the baseline value and return to normal after daptomycin discontinuation
3. Clinical signs of muscular toxicity (eg, pain) during daptomycin treatment with resolution after daptomycin discontinuation

Serum CPK analysis was performed on a weekly basis in all patients, as recommended in daptomycin summary of product characteristics. Eosinophil counts were routinely monitored during follow-up visits at the hospital, with a frequency depending on the type of BJI (eg, 2 weeks, 6 weeks, 3 months after surgery). Eosinophilic count was promptly performed in patients with clinical signs of eosinophilic pneumonia. Control patients were randomly selected from the Lyon BJI cohort study: they were treated with daptomycin but did not experience any AEs. Cases were matched at a 1:3 ratio with controls. All controls were selected within the same timeline as the cases. After selection, controls were excluded if: (1) they had no measured daptomycin concentrations, (2) they were initially diagnosed with an infection other than BJI, and (3) they were younger than age 18 years.

Data Collection

Therapeutic drug monitoring (TDM) was performed on at least one occasion for each patient. On each occasion, a typical PK profile was obtained with 3 daptomycin samples: predose or C_{min}, 30 minutes (C_{max}), and 5 to 6 hours after the end of the infusion. A limited number of patients had only 1 or 2 samples available. Sampling times were recorded precisely for each patient. Daptomycin concentrations were measured by a high-performance liquid chromatography ultraviolet assay, as described in previous publications [5, 6].

Other variables collected from the patient's files were age, sex, weight, serum creatinine, blood urea nitrogen, CPK, C-reactive protein (CRP), serum protein, serum albumin, white blood cell count, absolute eosinophil count, daptomycin dosing history, and daptomycin cumulative dose. All the variables were collected over the full course of treatment. Renal function was estimated using Cockcroft-Gault formula to calculate creatinine clearance [17]. Chest computed tomography scans were collected in patients with suspected eosinophilic pneumonia.

Ethics

This study was part of the prospective Lyon BJI cohort study (NCT02817711). Patients' consent was obtained for retrospective collection of the data needed for the present study, which was authorized by the appropriate committee for individual data protection (number 17-057) and registered on ClinicalTrials.gov (number NCT04933344).

Pharmacokinetic Profile Estimation

The steady-state area under the concentration-time curve over 24 hours (AUC_{24h}) and cumulative AUC were estimated by a Bayesian approach based on a previously published population PK model of daptomycin specifically built for patients with BJI [7]. The steady-state AUC_{24h} was estimated based on concentrations measured on the first TDM occasion in all patients. Individual AUC_{24h} values were computed based on a 2-compartment model including covariates (creatinine clearance, body weight, sex) and measured concentrations. The original population PK parameters were not reestimated but used as the prior distribution to estimate individual PK parameters in the cohort. All PK analyses were performed with Monolix 2021R1 (Lixoft, Anthony, France).

Statistical Analysis

Continuous variables were described using arithmetic mean ± standard deviation or median and interquartile range, as appropriate, and categorical variables were described as proportions.

Missing values were investigated before starting the analysis. Among patients included in the survival analysis, 138 (97.8%) had a complete dataset. Missing data were inferred using Little's test and a regression-based approach [18, 19] and were categorized as missing completely at random. Imputation was performed using recursive partitioning and regression trees. The distribution of all covariates remained unchanged after missing data imputation (data not shown).

In univariate analysis, the Wilcoxon-Mann-Whitney test was used for 2-group comparisons and the Kruskal-Wallis test was

used for multiple group comparisons of continuous variables. A Fisher exact test was used for categorical variables. All variables with P value < 0.2 in univariate analysis were retained for multivariate analysis. Correlation analysis was performed to avoid collinearity. In the case of substantial correlation (>0.6), the variable with the lowest P value was included in the multivariate analysis. The analysis was first carried out with the whole dataset. Then, a subgroup analysis was also conducted in patients with DIEP only and myotoxicity only to identify risk factors specific to each AE.

A multivariate time-to-event (TTE) analysis was performed using Cox proportional hazards model to describe the relationship between the primary endpoint (occurrence of an AE, either myotoxicity or DIEP) and baseline variables. A P value < 0.05 was considered statistically significant. In the case of statistical significance for continuous covariates, a log-rank test was used to determine the best cutoff to inform clinical decisions, as described elsewhere [20]. All statistical analyses were performed using R software (version 4.1).

Finally, simulations were performed to estimate the probability to achieve a target AUC_{24h} interval of 666 to 939 mg/h/L (see Results section) for daptomycin doses of 4, 6, and 8 mg/kg/24 hours. Probabilities were computed based on the patients' parameters and by bootstrapping.

RESULTS

Patients' Characteristics

A flow diagram of patients included in the study is provided as Supplementary Figure 1. A total of 1130 patients received daptomycin for BJI between 2014 and 2021 in our center. Among them, 16 (1.4%) had confirmed eosinophilic pneumonia and 42 (3.7%) had confirmed myotoxicity. Daptomycin concentrations were available in 9 patients with DIEP and 26 patients with myotoxicity. From the 120 patients randomized in the control group, 14 were excluded from the analysis (1 was younger than age 18 years, 1 did not have any daptomycin concentrations measured, and 12 were primarily diagnosed with an infection other than BJI).

Univariate Analysis

Baseline characteristics in patients with DIEP, myotoxicity, and control subjects are shown in Table 1. White blood cell count was significantly higher in DIEP and myotoxicity groups than in the control group ($P < 0.01$). When compared with controls, median serum protein and serum albumin levels were significantly lower in patients with DIEP and myotoxicity.

Pharmacokinetic Analysis

Regarding daptomycin TDM, 659 concentrations were measured in 141 patients on 247 occasions (with 50, 90, and 519 measures in patients with DIEP, myotoxicity, and controls, respectively). Multiple group comparisons did not show a significant difference for initial dose across groups (ie, patients with DIEP, patients with myotoxicity, and controls). Median trough concentrations were significantly different across groups. They were higher in patients with DIEP (21.8 vs 16.2 mg/L; $P = .045$) and in patients with myotoxicity (23 vs 16.2 mg/L; $P < .001$) compared with controls. Baseline AUC_{24h} values were lower in control patients than in patients experiencing AEs (DIEP or myotoxicity), as shown in Table 1. A comparison of AUC_{24h} and trough concentration is displayed in Figure 1. Pharmacokinetic parameters are reported in Table 2. Model diagnostic plots are shown in Supplementary Figures 2 and 3 in the supplementary material.

Joint Survival Analysis

Fifty-eight patients developed an AE during daptomycin treatment. Among them, 35 had a TDM history (9 DIEP and 26 myotoxicity). In the multivariate analysis, daptomycin AUC_{24h}, serum protein, and CRP remained significantly associated with the risk of AEs. The adjusted hazard ratios estimated by the Cox model for pooled and subgroup analysis are reported in Table 3.

As shown in Figure 2, 2 variables influenced the probability of an AE (either DIEP or myotoxicity), CRP, and daptomycin AUC_{24h}. Overall, in patients with low baseline CRP (<21.6 mg/L), 1 patient (2.3%) with $AUC_{24h} < 939$ mg/h/L and 6 patients (13.9%) with $AUC_{24h} > 939$ mg/h/L experienced an AE. In patients with high baseline CRP (>21.6 mg/L), 11 (42.3%) patients with low AUC_{24h} (<939 mg/h/L) and 17 patients (62.9%) with high AUC_{24h} (>939 mg/h/L) presented an AE. The latter group had the highest risk of DIEP or myotoxicity and a median TTE of 23 days. High baseline CRP and daptomycin AUC_{24h} remained predictive of AEs in the subgroup analysis in patients with DIEP or myotoxicity only, as shown in Figure 3. Probabilities to achieve the target AUC_{24h} interval of 666 to 939 mg/h/L are shown in Table 4. Probabilities were <40%, whatever the dosage, with a maximum of 35.8% for a daily dose of 6 mg/kg.

DISCUSSION

High-dose daptomycin is an effective treatment for staphylococcal BJI. However, prolonged treatment and high drug exposure may result in an increased risk of serious AEs. Elevated trough concentration has already been identified as a myotoxicity risk factor [11, 15]. However, little is known about other myopathy or DIEP risk factors.

We analyzed data from a large cohort of patients who received high-dose daptomycin for BJI and identified common risk factors associated with DIEP and myotoxicity incidence. To our knowledge, this is the first study providing such findings.

Table 1. Summary of Patients' Characteristics at Baseline

	DIEP, N = 16	Myotoxicity, N = 42	Control, N = 106	*P* Value[a]
Demographic				
Female sex	6 (38%)	19 (45%)	41 (38%)	.5
Age, y	76 (71–79)	65 (57–78)	62 (52–73)	.033
Weight, kg	72 (66–81)	82 (75–90)	79 (68–94)	.8
Height, cm	168 (164–174)	170 (163–175)	170 (163–176)	.4
BMI, kg/m²	28 (23–30)	28 (25–33)	27 (24–31)	.3
Biology				
CPK, U/L	30 (18–68)	63 (42–132)	54 (33–94)	.9
CRP, mg/L	80 (51–168)	54 (12–134)	11 (5–26)	<.001
Blood urea Nitrogen, mmol/L	6.4 (5.4–13.8)	7.5 (4.3–10.0)	5.3 (4.1–7.6)	.032
Serum creatinine, µmol/L	93 (74–116)	87 (62–118)	68 (53–90)	<.001
Creatinine clearance, mL/min[b]	54 (38–67)	84 (46–126)	100 (69–148)	<.001
White blood cells, 10^9 cells/L	9.4 (7.2–14.0)	8.3 (6.7–10.3)	6.9 (5.4–8.5)	<.001
Percentage of eosinophils in white blood cells	3.1 (1.5–4.6)	2.4 (1.4–4.1)	3.6 (2.5–6.1)	.002
Eosinophil count, 10^9 cells/L	0.30 (0.18–0.38)	0.20 (0.10–0.37)	0.27 (0.16–0.44)	.078
Serum albumin, g/L	18 (17–19)	28 (27–29)	32 (26–35)	.024
Serum protein, g/L	72 (65–74)	66 (62–69)	74 (68–78)	<.001
Pharmacology				
Coadministration of rifampicin	3 (19%)	5 (12%)	16 (15%)	
Daptomycin cumulative dose, g	12.8 (10.5–14.7)	12.5 (9.6–23.6)	23.8 (11.6–44.1)	NS
Initial daptomycin dose, mg/kg	7.5 (7.1–7.9)	8.5 (7.4–9.1)	8 (7.1–9.1)	NS
AUC_{24h}, mg/h/L	1009 (816–1199)	1027 (838–1438)	876 (730–1067)	.015
C_{max}, mg/L	81.1 (67.8–103.3)	87.7 (77.2–100.7)	75.8 (64–91)	NS
C_{min}, mg/L	21.8 (15.6–30.1)	23 (13–46)	16.2 (11.3–25.5)	.013

Data are presented as n (%) and median (interquartile range).

Abbreviations: AUC_{24h}, daily area under the concentration-time curve; BMI, body mass index; C_{max}, peak concentration; C_{min}, trough concentration, CPK, creatine phosphokinase; CRP, C-reactive protein; DIEP, daptomycin-induced eosinophilic pneumonia.

[a]Kruskal-Wallis rank sum test or Fisher exact test for the multiple group comparison (DIEP, myotoxicity, and control).

[b]Creatinine clearance was calculated using the Cockcroft and Gault formula.

We identified daptomycin AUC_{24h}, CRP, and serum protein levels as significant determinants for these 2 AEs in a joint survival analysis. We identified cutoff values for the variables associated with an increased risk of either DIEP or myotoxicity: $AUC_{24h} > 939$ mg/h/L, CRP > 21.6 mg/L, and serum protein <72 g/L. These 3 variables and cutoff values were remarkably consistent in the subgroup analysis in patients with DIEP or myotoxicity only.

Regarding DIEP, the median TTE was 19.5 days, which is consistent with previous studies reporting the median TTE ranging from 14.8 to 23 days [14, 21, 22]. We found high daptomycin exposure to be significantly associated with DIEP occurrence. By contrast, Hirai et al reported that DIEP was neither associated with daptomycin dose nor with treatment duration [22]. However, they only investigated daptomycin dose as an exposure variable and did not use drug concentration. Indeed, dose is a raw descriptor of drug exposure and AUC may greatly vary between patients for the same dosage regimen [5, 7]. In our analysis, daptomycin exposure, but not dose, was significantly associated with the probability of DIEP, suggesting that this event is concentration driven. Interestingly, most DIEP cases reported in the literature were observed in patients treated for BJI who received higher doses of daptomycin and longer courses of treatment compared with other indications [14].

Another recent study examined DIEP risk factors and reported age ≥70 years, treatment duration >14 days, and total cumulative dose ≥10 g as risk factors [21]. Age might be a surrogate for impaired renal function (not examined in that study), which is known to influence daptomycin clearance. Daptomycin drug concentrations were not examined in this analysis, but we hypothesize that older patients with high cumulative doses also had higher daptomycin AUCs. Although not thoroughly investigated, CRP levels were significantly higher in patients who experienced DIEP in Boixader et al's study [21]. Overall, our results and previously published data indicate that there are drug-related DIEP risk factors, including drug exposure and treatment duration.

Regarding myotoxicity, AUC_{24h} was found to be significantly associated with an increased AE risk, which is consistent with previous studies [11, 15]. Bhavnani et al analyzed data from a clinical trial in patients with bacteremia and endocarditis and reported that daptomycin $C_{min} \geq 24.3$ mg/L was associated with an increased probability of CPK elevation. Indeed,

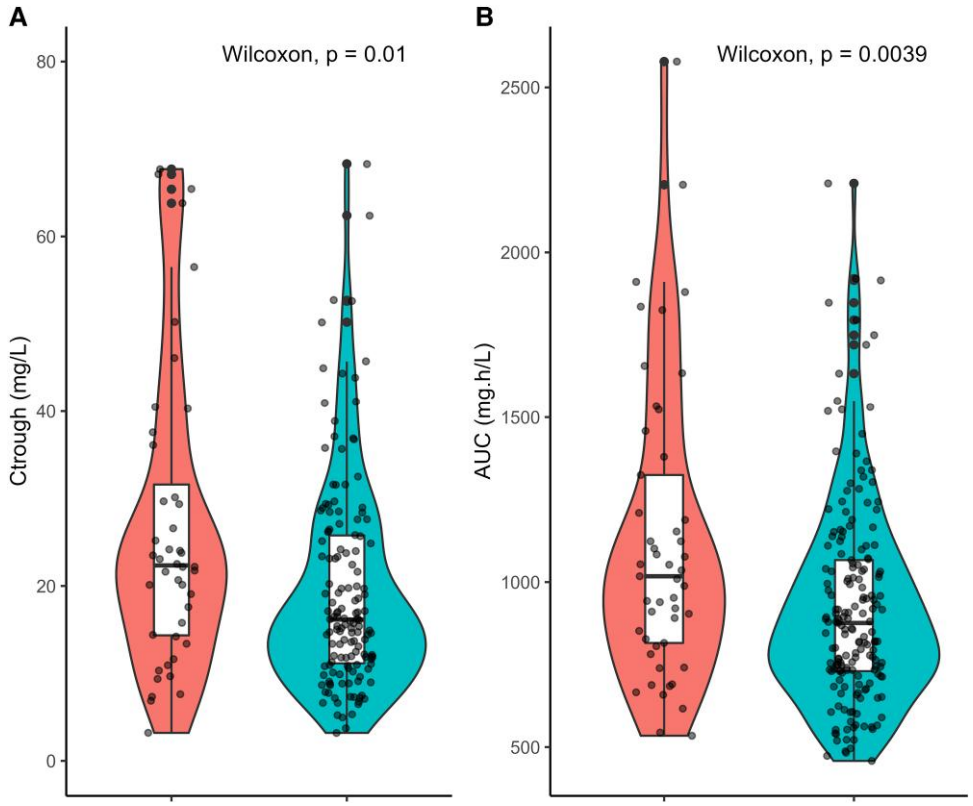

Figure 1. Violin plot of AUC_{24h} and C_{min} in case (left, red violin) and control (right, blue violin) patients. *P* values of the comparison with the Wilcoxon-Mann-Whitney test are indicated. Abbreviations: AUC_{24h}, area under the concentration-time curve over 24 hours; C_{min}, trough concentration.

Table 2. Distribution of daptomycin PK Parameters

Cohort	Patients with DIEP	Patients with myotoxicity	Control patients
Clearance, L/h	0.52 (0.38–0.79)	0.53 (0.39–0.66)	0.64 (0.49–0.87)
V_1, L	10.6 (6.9–11.8)	7.8 (6.8–8.7)	8.1 (6.48–10.1)
Q, L/h	0.98 (0.88–1.10)	0.91 (0.83–1.09)	0.89 (0.77–1.01)
V_2, L	3.2 (2.9–3.3)	3.0 (2.7–3.3)	3.1 (2.7–3.3)

All results are given as median (interquartile range).

Abbreviations: DIEP, daptomycin-induced eosinophilic pneumonia; PK, phosphate kinase; Q, intercompartmental clearance; V_1, central volume of distribution; V_2, peripheral volume of distribution.

Table 3. Adjusted Hazard Ratios for Risk Factors of Adverse Events

	Patients with DIEP	Patients with myotoxicity	Patients with either DIEP or myotoxicity
AUC_{24h} > 939 mg.h/L	4.02 (1.09-16.2)*	4.05 (1.6-10.15)	3.1 (1.48-6.5)
CRP > 21.6 mg.L	39.5 (4.8-326)	8.43 (3.2-22)	9.8 (3.94-24.5)
Serum protein <72 g/L	/	3.16 (1.3-7.7)	2.4 (1.02-5.65)

Results are presented as point estimate (95% confidence intervals) of odds ratios.

Abbreviations: AUC_{24h}, area under the concentration-time curve of daptomycin over 24 hours; CPK, creatinine phosphate kinase; CRP, C-reactive protein; DIEP, daptomycin-induced eosinophilic pneumonia.

both C_{min} and AUC_{24h} were significantly associated with an AE in that study, whereas C_{max} was not. C_{min} was retained in the final model because of higher statistical significance compared with AUC_{24h}. The authors acknowledged uncertainty in the results because of the low number of CPK elevation cases (6 of 108 patients). In addition, only PK variables were examined in the analysis. Samura et al analyzed data from 17 and 189 patients with and without CPK elevation, respectively. $C_{min} \geq$ 20 mg/L was 1 of the risk factors for CPK elevation. A major limitation of the study was that C_{min} was not measured but estimated based on a PK model (population prediction of C_{min}). Again, daptomycin AUC_{24h} was not investigated in that study. Of note, this study evaluated only the impact of daptomycin concentration at a single time point, which does not reflect the overall exposure.

By contrast, we used a richer PK dataset and were able to estimate the AUC_{24h} in addition to concentration measurements. Both AUC_{24h} and C_{min} values were significantly different in case and control patients. We select AUC_{24h} in the final model based on higher statistical significance and clinical relevance

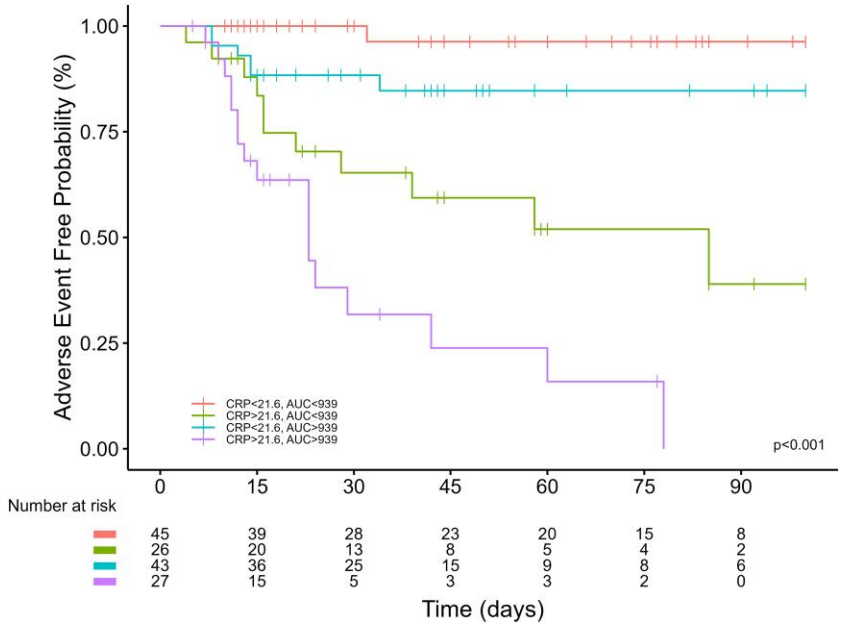

Figure 2. Survival analysis of daptomycin adverse events (DIEP and myotoxicity). Survival curve differences were tested using a log-rank test. Abbreviations: AUC, daptomycin daily area under the concentration-time curve; CRP, C-reactive protein; DIEP, daptomycin-induced eosinophilic pneumonia.

because AUC_{24h} is also the pharmacodynamically linked variable to daptomycin antimicrobial effect.

Although the underlying physiological mechanisms of daptomycin myotoxicity and DIEP are supposed to be different, we hypothesize that the situations leading to this toxicity may be similar. It has been suggested that daptomycin may bind to the pulmonary surfactant and accumulate in the alveolar space [23]. This could trigger an inflammatory response with eosinophil migration to the lungs [24]. Yamada et al confirmed that daptomycin-induced muscle toxicity was concentration dependent. They showed that the concentration threshold appeared to be lower in anoxic conditions [25]. It has been shown that hypoxia and inflammation are intertwined at a molecular level, which could explain the increased susceptibility of developing daptomycin AEs in patients having an inflammatory syndrome at treatment initiation [26].

Our finding may have important implications for daptomycin use and TDM. Considering that a target AUC_{24h}/MIC ratio ≥666 is required for *Staphylococcus aureus* infections [27, 28], and that an $AUC_{24h} > 939$ mg/h/L is associated with greater risk of DIEP and CPK elevation, an AUC_{24h} target range from 666 to 939 mg/h/L is suggested for empirical therapy. Because the AUC_{24h} interval is narrow and PK variability is large, no standard dosage can ensure a high probability of achieving this target range, as shown in Table 4. Daptomycin TDM may be relevant for achieving the target AUC_{24h} interval and optimize efficacy and safety. TDM may be especially relevant in subpopulations with a lower daptomycin clearance and higher risk of overexposure (women, patients with impaired renal function). As for vancomycin, daptomycin AUC_{24h} can be estimated using Bayesian PK software programs [29, 30]. Such a model-informed precision dosing (MIPD) should be performed early, especially for patients with elevated CRP, to prevent AEs [31]. However, clinical studies are necessary to confirm the benefits of MIPD applied to daptomycin.

This study has several limitations. First, the data required to perform this study were collected retrospectively, so missing or erroneous data may have occurred. Because the main clinical outcomes of this study were infrequent AEs, a prospective design was virtually impossible. However, controls were randomly selected from the same cohort as cases, and population baseline characteristics were not significantly different across groups.

Second, although this is the largest study reporting DIEP and myotoxic events, the number of DIEP cases was still low, which may alter the power to identify other risk factors of AE. However, our results are consistent with the drug-related risk factors reported in the literature. Third, although our PK model has shown good performance in predicting drug concentration (see Supplementary material), the AUC estimation has not been thoroughly validated versus a gold standard.

Finally, we could not examine all potential determinants of AEs. Samura et al reported that some coadministered drugs were risk factors for CPK elevation, namely antihistamines and statins. Although several studies reported statins to be an independent risk factor for CPK elevation during daptomycin treatment [15, 32], others did not report this association [10, 12, 13, 33]. Statins were not examined in our analysis because

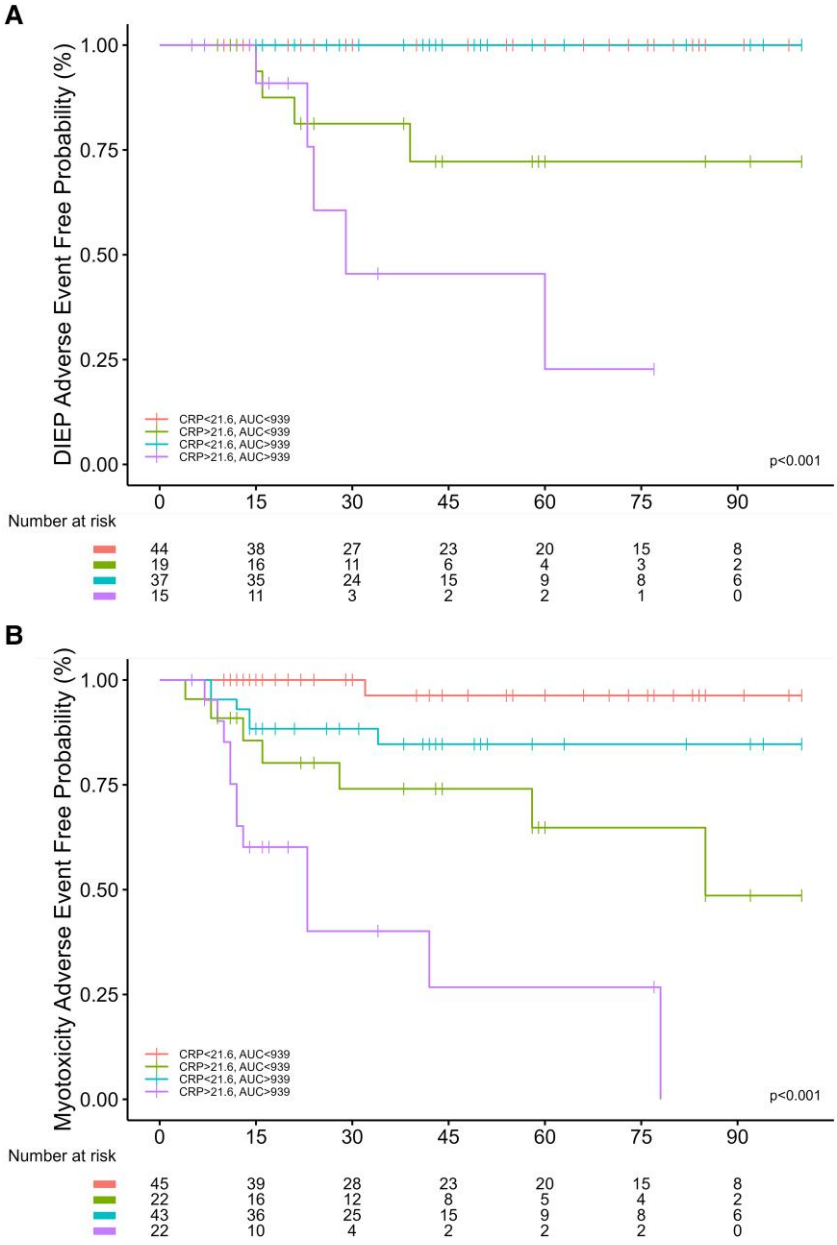

Figure 3. Survival analysis of daptomycin in adverse event subgroups. Panel A, DIEP; panel B, myotoxicity. Survival curve differences were tested using a log-rank test. Abbreviations: AUC, daptomycin daily area under the concentration-time curve; CRP, C-reactive protein; DIEP, daptomycin-induced eosinophilic pneumonia.

Table 4. Probability to Achieve the Daptomycin Target AUC_{24h} Interval

	Daily Dosage					
	4 mg/kg		6 mg/kg		8 mg/kg	
	Estimate From Population	Bootstrap Estimate (95% CI)	Estimate From Population	Bootstrap Estimate (95% CI)	Estimate From Population	Bootstrap Estimate (95% CI)
$AUC_{24h} > 666$, %	27.6	29.0 (21–38)	66.4	66.9 (58–77)	90.3	90.8 (.85–.96)
$AUC_{24h} > 939$, %	6.6	8.6 (4–14)	30.6	31.9 (23–41)	59	58.6 (49 .0–69)
$666 \leq AUC_{24h} \geq 939$, %	21	20.4 (12–29)	35.8	35.2 (26–45)	31.3	32.2 (.23–.42)

Abbreviation: AUC_{24h}, daptomycin area under the concentration-time curve over 24 hours; CI, confidence interval.

they were discontinued at daptomycin initiation in almost all patients (fewer than 3% of patients were prescribed statins). The use of antihistamine agents was also infrequent (8 in control and 0 in case patients).

CONCLUSION

In this case-control analysis of a large cohort of patients who received high-dose daptomycin for BJI, daptomycin $AUC_{24h} > 939$ mg/h/L, CRP > 21.6 mg/L, and serum protein <72 g/L were associated with an increased risk of DIEP or myotoxicity. Based on these results, we recommend performing daptomycin TDM and MIPD and targeting an AUC_{24h} range of 666 to 939 mg/h/L to maximize efficacy and minimize the risk of AEs.

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

Author Contributions. All authors contributed to the study conception and design. T. F. designed the Lyon BJI cohort study and participated in the clinical management of the patients. Material preparation and data collection were carried out by R. G., T. P., D. B., M. D., and V. F. Analysis was performed by R. G. and verified by S. G. and L. B. The first draft of the manuscript was written by R. G., and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability. The datasets generated and analyzed during the current study are available on reasonable request from the authors.

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