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Current use of daptomycin and systematic therapeutic drug monitoring: Clinical experience in a tertiary care institution☆

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ABSTRACT

Therapeutic drug monitoring (TDM) could optimise daptomycin use. However, no validated serum target levels have been established. This prospective study at a tertiary centre including hospitalised patients receiving daptomycin aimed to evaluate the adequacy of daptomycin doses in a real-life study, assess interpatient variability in serum levels, identify predictive factors for non-adequate serum levels and assess their clinical impact. Blood samples [trough (C_{min}) and peak (C_{max}) levels] were drawn ≥3 days post-treatment initiation. Serum daptomycin concentrations were determined by HPLC. Outcome was classified as: (i) favourable, if clinical improvement or cure occurred with no adverse events; or (ii) poor, in the case of no clinical response, recurrence, related mortality or if adverse events were detected. Sixty-three patients (63.5% male; median age 63.0 years) were included. The most common indications for daptomycin use were bacteraemia (46.0%), complicated skin and soft-tissue infection (30.2%) and endovascular infection (15.9%). The initial dosage was adequate in 43 patients (68.3%), low in 14 (22.2%) and high in 6 (9.5%). Large interindividual variability in serum levels was observed, with a median C_{min} of 10.6 mg/L (range 1.3–44.7 mg/L) and median C_{max} of 44.0 mg/L (range 3.0–93.7 mg/L). Multivariate analysis showed that C_{min} < 3.18 mg/L was independently related to poor outcome (OR = 6.465, 95% CI 1.032–40.087; $P = 0.046$). High variability in daptomycin use and serum levels was detected. Specific serum targets were identified as risk factors for poor outcome. TDM might be useful to optimise daptomycin doses and to avoid therapeutic failure.

1. Introduction

Daptomycin is a cyclic lipopeptide antibiotic with potent bactericidal activity against most Gram-positive organisms including vancomycin-resistant enterococci, methicillin-resistant staphylococci and 'heterodrug-resistant' glycopeptide-resistant *Staphylococcus aureus* [1]. Daptomycin is indicated for the treatment of complicated skin and soft-tissue infections (cSSTIs) caused by susceptible strains of Gram-positive micro-organisms and is approved for the treatment of *S. aureus* bloodstream infections and right-sided infective endocarditis (IE).

Daptomycin is primarily renally excreted, with the majority of the drug (78%) remaining intact in the urine [2,3]. It has a half-life of 8 h and a prolonged post-antibiotic effect of up to 6.8 h [4]. The safety and efficacy of the dose interval adjustment have not been evaluated in clinical trials. It is recommended to adjust the dose interval from 24 h to 48 h in patients with creatinine clearance (CL_{Cr}) ≤ 30 mL/min, but this recommendation is based on pharmacokinetic studies and modelling results. The same dose

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adjustment is recommended for patients on haemodialysis or continuous ambulatory peritoneal dialysis. Whenever possible, daptomycin should be administered following the completion of dialysis [5]. Some studies have evaluated the use of daptomycin in patients with mild to moderate renal impairment or in patients receiving dialysis, showing that it presents highly variable pharmacokinetics under these circumstances [6–11].

On the basis that daptomycin serum levels are unpredictable [12], several authors have emphasised the importance of routine therapeutic drug monitoring (TDM) to optimise daptomycin use for selected cases [4,6,13–15] and to avoid the development of antimicrobial resistance and/or therapeutic failure [16–18]. Nevertheless, no recommendation for TDM appears in any of the current guidelines for daptomycin and we were not able to find systematic studies analysing the potential clinical impact of daptomycin TDM.

The aims of this study were (i) to evaluate the adequacy of daptomycin doses in an inpatient population, (ii) to assess interpatient variability in daptomycin serum levels, (iii) to identify potential predictive factors for non-adequate serum levels and (iv) to assess their clinical impact.

2. Materials and methods

2.1. Study design

This was a prospective study performed at a tertiary care hospital including hospitalised patients receiving daptomycin for empirical or targeted treatment who accepted to participate, signing an informed consent. Daptomycin treatment and dosage were at the discretion of the attending physicians. Dose was considered adequate according to the drug label sheet that indicates the dose adjustment regarding indication (clinical entity), CL_{Cr} (renal function) and weight. Those doses equal to the doses suggested by the drug label sheet were considered 'adequate' and those doses that were lower or higher than those suggested by the drug label sheet were classified as 'low' or 'high', respectively. For endocarditis, a dosage of 10 mg/kg was considered as adequate following expert opinions [19] and clinical guidelines [20]. Each patient had two blood samples drawn [trough (C_{min}) and peak (C_{max}) levels] ≥3 days post-treatment initiation. C_{min} samples were obtained within 30 min of the next dose, and C_{max} samples were obtained after 1 h of intravenous infusion. A safety threshold for C_{min} was placed at <24.3 mg/L according to the findings of Bhavnani et al. [21]. A previous publication considered a desired C_{max}/minimum inhibitory concentration (MIC) ratio range of 59–94 [6].

Daptomycin serum levels were determined by high-performance liquid chromatography (HPLC) using an absorbance detector of ultraviolet/visible (UV/Vis) light at 220 nm. Extraction and subsequent analysis were based on protocols published in scientific articles with adequate validity and sensitivity [6,22]. Daptomycin levels were determined using a SunFire® C18 5 μm (4.6 × 150 mm) column with ammonium phosphate (0.5%) and acetonitrile as eluents (66%:34%). Calibration curves were constructed.

2.2. Data collection

The following data were retrieved for each patient: demographic characteristics; underlying diseases; type of infection; bacterial isolate with antimicrobial susceptibility (when available); treatment duration; indication; daptomycin daily dosage and serum concentrations; laboratory findings; and concomitant drugs. Laboratory parameters (haemoglobin, red blood cell and platelet counts, serum creatinine and glomerular filtration rate) were collected at baseline and during daptomycin treatment. The estimated glomerular filtration rate (eGFR) was calculated according to the Modification of Diet in Renal Disease (MDRD) equation. Patients were followed for 3 months after discharge.

The occurrence of thrombocytopenia and anaemia during daptomycin treatment were defined as a reduction of >30%, respectively, in platelet count or haemoglobin level from baseline.

Clinical outcome was classified as: (i) favourable, if clinical improvement or cure occurred with no adverse events; or (ii) poor, in the case of no clinical response or recurrence, or related mortality, or if any adverse events were detected [creatine phosphokinase (CPK) elevation of >5 times the upper limit of normal] causing drug discontinuation.

The study was approved by the Ethics Committee of Hospital General Universitario Gregorio Marañón (Madrid, Spain).

2.3. Statistical analysis

The median and interquartile range (IQR) was used in the descriptive statistics for continuous variables. Categorical variables were compared by χ^2 test with Yate's correction or Fisher's exact test, as necessary; and continuous variables were compared using the Mann–Whitney test. A P-value of <0.05 was considered statistically significant.

Univariate and multivariate logistic regression analyses were performed to identify independent predictors of poor outcome. Univariate and multivariate linear regression analyses were performed to identify independent predictors of C_{min}, C_{max} and C_{max}/MIC. Multivariate stepwise analysis included all variables significant at $P \leq 0.2$ in the univariate analysis. All statistical analyses were performed using IBM SPSS Statistics v.21 (IBM Corp., Armonk, NY).

3. Results

A total of 63 patients were included in the analysis (63.5% male) with a median age of 63.0 years (IQR 57.0–75.0 years). The median weight was 70.0 kg (IQR 60.0–85.0 kg) and the median body mass index (BMI) was 25.3 kg/m^2 (IQR 22.5–28.1 kg/m^2). Most patients were admitted to a medical department (50.8%). Patient characteristics and the most common underlying diseases are shown in Table 1. The median age-adjusted Charlson comorbidity index was 4.0 (IQR 2.0–5.0). The severity of underlying diseases was classified according to the McCabe criteria as non-fatal in 48 cases (76.2%). The eGFR was normal in 37 patients (58.7%). No patient was receiving extracorporeal membrane oxygenation, but 5 patients (7.9%) were on haemodialysis.

Daptomycin was prescribed as empirical treatment in 24 cases (38.1%) and as targeted therapy in 39 (61.9%) (Table 1). The main indications for daptomycin therapy, accounting for 85.8% of the total, were bacteraemia (46.0%), cSSTI (30.2%) and endocarditis or endovascular infection (15.9%). The infection was confirmed microbiologically (Table 1) and the MIC was determined in 47 (74.6%) of the 63 patients (Table 2). All micro-organisms isolated were susceptible to daptomycin according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints [23]: 1 isolate (1.6%) with an MIC of 0.125 mg/L (*Corynebacterium* sp.), 2 isolates (3.2%) with MICs of <0.15 mg/L (*Staphylococcus* spp.), 33 isolates (52.4%) with MICs of <0.5 mg/L (*Staphylococcus* spp.), 8 isolates (12.7%) with MICs of ≤1 mg/L (3 *Enterococcus* spp. and 5 *Staphylococcus* spp.), 1 isolate (1.6%) with an MIC of 2 mg/L (*Enterococcus* sp.) and 2 isolates (3.2%) with MICs of 4 mg/L (*Enterococcus* spp.).

The median dose of daptomycin was 7.0 mg/kg (IQR 5.0–9.0 mg/kg) and the median duration of daptomycin treatment was 13 days (IQR 6.0–19.0 days). Regarding the daptomycin dosage, 28.6% of subjects in the study were treated with a dose regimen ≥3 mg/kg and <6 mg/kg; 25.4% with ≥6 mg/kg and <8 mg/kg; 22.2%

Table 1
Risk factors for poor outcome: univariate and multivariate analyses.

Characteristic	Global	Univariate analysis[a]		
		Poor clinical outcome ($n = 15$)	Favourable clinical outcome ($n = 48$)	*P*-value
General characteristics				
Age (years) [median (IQR)]	63.0 (57.0–75.0)	67.0 (61.0–73.0)	62.5 (55.5–75.0)	0.479
Sex male [*n* (%)]	40 (63.5)	10 (66.7)	30 (62.5)	1.0
Weight (kg) [median (IQR)]	70.0 (60.0–85.0)	68.2 (55.0–95.0)	70.7 (60.0–84.7)	0.845
BMI (kg/m^2) [median (IQR)]	25.3 (22.5–28.1)	26.8 (22.2–30.1)	24.9 (22.5–28.0)	0.547
Race [*n* (%)]				1.0
White	61 (96.8)	15 (100)	46 (95.8)	
Hispanic	2 (3.2)	0	2 (4.2)	
Department of admission [*n* (%)]				
Medical	32 (50.8)	7 (46.7)	25 (52.1)	0.774
Surgical	24 (38.1)	6 (40.0)	18 (37.5)	1.0
ICU	7 (11.1)	2 (13.3)	5 (10.4)	1.0
ICU stay (days) [median (IQR)]	10.0 (2.0–30.0)	33.5 (30.0–)	10.0 (2.0–12.0)	0.049
Hospital stay [median (IQR)]	30.0 (17.0–63.0)	51.0 (27.0–102.5)	28.0 (16.2–58.5)	0.107
Underlying diseases [*n* (%)]				
Cardiac disease	23 (36.5)	7 (46.7)	16 (33.3)	0.373
Diabetes mellitus	21 (33.3)	7 (46.7)	14 (29.2)	0.347
Solid tumour	17 (27.0)	4 (26.7)	13 (27.1)	1.0
Chronic renal failure	10 (15.9)	2 (13.3)	8 (16.7)	1.0
Liver disease	7 (11.1)	3 (20.0)	4 (8.3)	0.342
HIV infection	5 (7.9)	1 (6.7)	4 (8.3)	1.0
Neurological disease	4 (6.3)	0	4 (8.3)	0.564
COPD	3 (4.8)	1 (6.7)	2 (4.2)	1.0
Solid organ transplantation	2 (3.2)	1 (6.7)	1 (2.1)	0.422
Haematological neoplasia	2 (3.2)	0	2 (4.2)	1.0
Psychiatric disease	2 (3.2)	0	2 (4.2)	1.0
Charlson comorbidity index [median (IQR)]	4.0 (2.0–5.0)	5.0 (3.0–6.0)	3.0 (2.0–5.0)	0.123
McCabe index [*n* (%)]				0.301
Non-fatal	48 (76.2)	11 (73.3)	37 (77.1)	
Ultimately fatal	14 (22.2)	3 (20.0)	11 (22.9)	
Rapidly fatal	1 (1.6)	1 (6.7)	0	
eGFR (MDRD) (mL/min/1.73 m^2) [*n* (%)]				0.370
Normal (≥60)	37 (58.7)	7 (46.7)	30 (62.5)	
Low (<60)	26 (41.3)	8 (53.3)	18 (37.5)	
Hypoalbuminemia [*n* (%)]	39 (61.9)	13 (86.7)	26 (54.2)	0.033
Haemodialysis [*n* (%)]	5 (7.9)	0	5 (10.4)	0.326
ECMO [*n* (%)]	0	0	0	NA
Type of treatment				0.033
Empirical	24 (38.1)	2 (13.3)	22 (45.8)	
Targeted	39 (61.9)	13 (86.7)	26 (54.2)	
Main indication for daptomycin [*n* (%)]				
Bacteraemia	29 (46.0)	8 (53.3)	21 (43.8)	0.516
cSSTI	19 (30.2)	5 (33.3)	14 (29.2)	1.0
Endocarditis or endovascular infection	10 (15.9)	3 (20.0)	7 (14.6)	0.690
Osteoarticular infection	8 (12.7)	2 (13.3)	6 (12.5)	1.0
Intra-abdominal infection	4 (6.3)	1 (6.7)	3 (6.3)	1.0
Prothesis-related infection	3 (4.8)	2 (13.3)	1 (2.1)	0.138
Sepsis of unknown origin	2 (3.2)	0	2 (4.2)	1.0
Urinary tract infection	1 (1.6)	0	1 (2.1)	1.0
Microbiological isolate [*n* (%)]				
Staphylococcus aureus	25 (39.7)	8 (53.3)	17 (35.4)	0.241
MSSA	9 (14.3)	3 (20.0)	6 (12.5)	0.673
MRSA	16 (25.4)	5 (33.3)	11 (22.9)	0.501
Staphylococcus epidermidis	16 (25.4)	3 (20.0)	13 (27.1)	0.740
Other CoNS	3 (4.8)	0	3 (6.3)	0.574
Corynebacterium spp.	6 (9.5)	1 (6.7)	5 (10.4)	1.0
Enterococcus faecalis	7 (11.1)	3 (20.0)	4 (8.3)	0.342
Enterococcus faecium	3 (4.8)	2 (13.3)	1 (2.1)	0.138
Other	15 (23.8)	3 (20.0)	12 (25)	0.747
Daptomycin treatment				
Dose (mg/kg) [median (IQR)]	7.0 (5.0–9.0)	7.0 (5.0–9.0)	7.0 (5.0–9.8)	0.887
Duration of treatment (days) [median (IQR)]	13.0 (6.0–19.0)	14.0 (5.0–19.0)	13.0 (7.0–21.3)	0.876
Dose adequacy				0.717
Adequate dose	43 (68.3)	9 (60.0)	34 (70.8)	
Non-adequate (low)	14 (22.2)	4 (26.7)	10 (20.8)	
Non-adequate (high)	6 (9.5)	2 (13.3)	4 (8.3)	
Daptomycin serum level				
C_{min} (mg/L) [median (IQR)]	10.6 (4.7–17.7)	8.5 (3.2–18.6)	10.7 (4.8–17.4)	0.930
$C_{min} > 24.3$ mg/L [*n* (%)]	6 (9.5)	2 (13.3)	4 (8.3)	0.565
$C_{min} = 3.18$–16.84 mg/L [*n* (%)]	39 (61.9)	6 (40.0)	33 (68.8)	0.045
$C_{min} < 3.18$ mg/L [*n* (%)]	7 (11.1)	4 (26.7)	3 (6.3)	0.028
$C_{min} > 16.84$ mg/L [*n* (%)]	17 (27.0)	5 (33.3)	12 (25.0)	0.526

(*continued on next page*)

Table 1 (*continued*)

Characteristic	Global	Univariate analysis[a]		
		Poor clinical outcome ($n=15$)	Favourable clinical outcome ($n=48$)	*P*-value
C_{max} (mg/L) [median (IQR)]	44.0 (27.7–63.4)	38.1 (23.5–62.3)	45.6 (27.9–63.9)	0.570
C_{max}/MIC (mg/L) [median (IQR)]	87.7 (46.8–127.1)	63.4 (22.3–119.7)	91.1 (54.9–131.1)	0.152
Concomitant medications [*n* (%)]				
Indinavir	0	0	0	NA
Ritonavir	1 (1.6)	1 (6.7)	0	0.238
Erythromycin	3 (4.8)	1 (6.7)	2 (4.2)	1.0
Clarithromycin	0	0	0	NA
Itraconazole	0	0	0	NA
Rifampicin	9 (14.3)	4 (26.7)	5 (10.4)	0.198
Midazolam	2 (3.2)	1 (6.7)	1 (2.1)	0.422
Statins	23 (36.5)	5 (33.3)	18 (37.5)	1.0

IQR, interquartile range; BMI, body mass index; ICU, intensive care unit; HIV, human immunodeficiency virus; COPD, chronic obstructive pulmonary disease; eGFR (MDRD), estimated glomerular filtration rate (Modification of Diet in Renal Disease equation); ECMO, extracorporeal membrane oxygenation; NA, not available; cSSTI, complicated skin and soft-tissue infection; MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; CoNS, coagulase-negative staphylococci; C_{min}, trough level; C_{max}, peak level; MIC, minimum inhibitory concentration.

[a] Multivariate analysis: C_{min} < 3.18 mg/L, *n* (%); odds ratio = 6.465, 95% confidence interval 1.032–40.087 ($P=0.046$).

Table 2
Distribution of minimum inhibitory concentrations (MICs) to daptomycin among the micro-organisms isolated in this study

Micro-organism (*n*)	No. of isolates at an MIC (mg/L) of:					
	0.125	<0.15	≤0.5	≤1	2	4
CoNS (16)			14	2		
Corynebacterium striatum (1)	1					
Enterococcus faecalis (3)				3		
Enterococcus faecium (3)					1	2
MRSA (15)		2	12	1		
MSSA (9)			7	2		
Total (47)	1	2	33	8	1	2

CoNS, coagulase-negative staphylococci; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*.

with ≥8 mg/kg and <10 mg/kg; and 23.8% with ≥10 mg/kg. The initial daptomycin dosage was adequate in 43 cases (68.3%), lower than recommended in 14 (22.2%) and higher in 6 (9.5%). Moreover, 23 patients (36.5%) were treated with statins (Table 1).

The median C_{min} and C_{max} for daptomycin are shown in Table 1 and Fig. 1. The median C_{min} was 10.6 mg/L, with a wide range of distribution (1.3–44.7 mg/L; IQR 4.7–17.7 mg/L). C_{min} values >24.3 mg/L were found in 6 patients (9.5%), of which only 3 were accompanied by a mild CPK elevation, and 2 of these 3 patients were taking a statin concomitantly. In these 3 patients, the highest CPK values were 32, 68 and 256 U/L, and maximum C_{min} values were 30.0, 34.1 and 44.7 mg/L. The median C_{max} was 44.0 mg/L, also with a wide distribution range (3.0–93.7 mg/L; IQR 27.7–63.4 mg/L). The median C_{max} was 53.2 mg/L (IQR 29.4–62.8 mg/L) at 8 mg/kg, 41.0 mg/L (IQR 27.6–66.0 mg/L) at 6 mg/kg and 23.5 mg/L (IQR 14.7–27.8 mg/L) at 4 mg/kg dosage intravenously.

The median C_{min} and C_{max} in intensive care unit (ICU) patients ($n=7$) were 3.4 mg/L (IQR 2.4–8.9 mg/L) and 31.7 mg/L (IQR 22.4–53.0 mg/L), respectively (Fig. 2). Fig. 3 shows the median decrease in daptomycin C_{min} levels (59.8%) before–after haemodialysis among the five patients included in this study under this condition. The median C_{min} pre-dialysis was 11.7 mg/L (IQR 3.7–21.2 mg/L) and the median C_{min} post-dialysis was 4.7 mg/L (IQR 2.1–9.7 mg/L). Excluding patients in the ICU and on haemodialysis, the global median C_{min} and C_{max} in the study cohort ($n=52$) were 11.6 mg/L (IQR 6.9–18.6 mg/L) and 44.9 mg/L (IQR 27.2–63.9 mg/L), respectively (Fig. 4).

The daptomycin dose was adjusted after C_{min} measurements in 11 patients (17.5%). However, this was done in an unsystematic way only dependent on the decision of the attending physician because no clinically validated guidelines on target levels were available.

Fig. 5 shows how C_{min} values varied widely despite the administration of 4, 6 or 8 mg/kg of daptomycin and the correlation

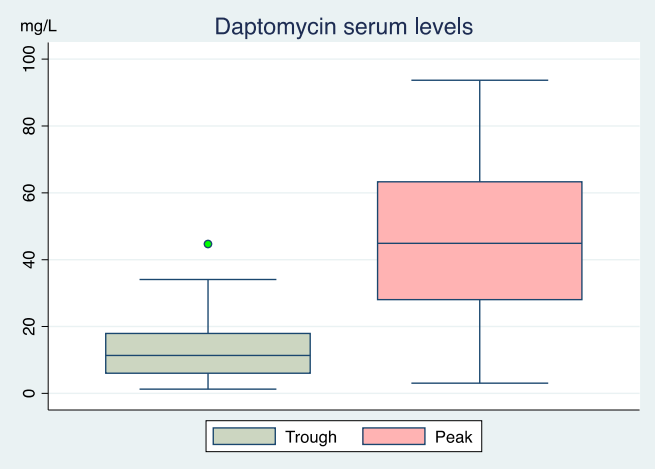

Fig. 1. Variability in daptomycin trough (C_{min}) and peak (C_{max}) serum levels ($n=63$ patients).

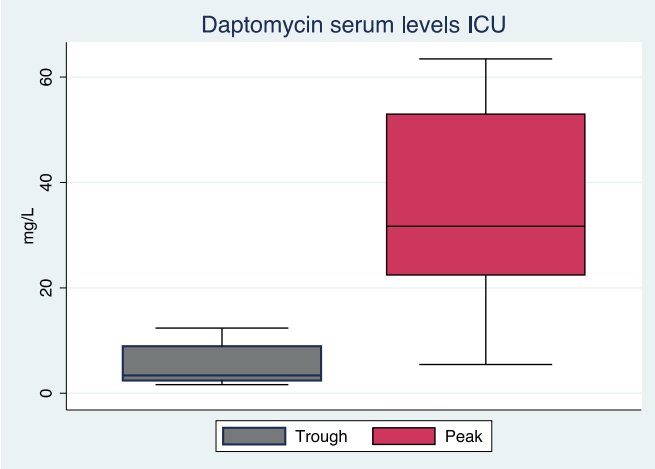

Fig. 2. Variability in daptomycin trough (C_{min}) and peak (C_{max}) serum levels in intensive care unit (ICU) patients ($n=7$).

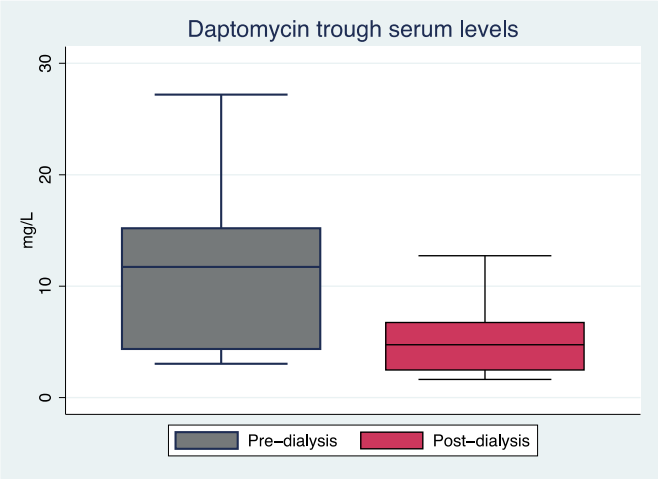

Fig. 3. Variability in daptomycin trough (C_{min}) serum levels in patients pre- and post-haemodialysis ($n = 5$; 1 of these patients had an intensive care unit stay).

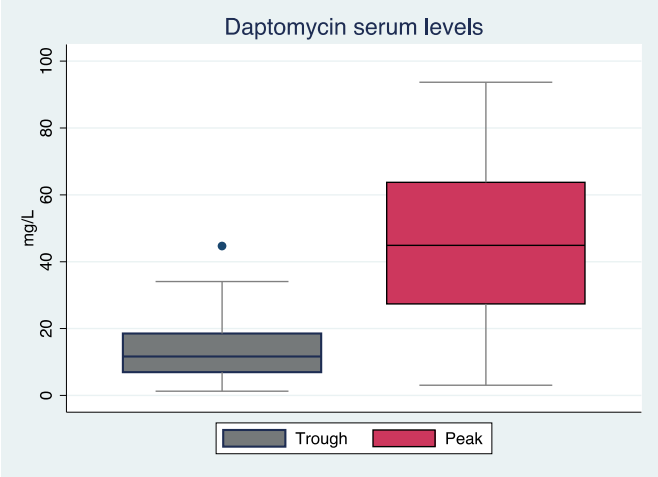

Fig. 4. Variability in daptomycin trough (C_{min}) and peak (C_{max}) serum levels in all patients except intensive care unit (ICU) patients and those on haemodialysis ($n = 52$).

with clinical outcome. Overall, 48 patients (76.2%) achieved a favourable outcome and 15 (23.8%) a poor outcome. Nineteen patients (30.2%) died; related mortality was 12.7% (8 patients). Regarding adverse events, 9 (14.3%) of 63 patients experienced anaemia and 16 (25.4%) experienced a decrease in platelet count (considered as >30% decrease from the platelet baseline count) but they could not be clearly attributable to daptomycin use. Only 2 patients (3.2%) developed a relevant increase of CPK during treatment according to the study criteria. The mean ± standard deviation C_{min} and C_{max} in these 2 patients were 2.3 ± 1.2 mg/L and 9.3 ± 5.4 mg/L, respectively. Discontinuation of daptomycin was deemed necessary in both cases. Both patients had cardiac disease as an underlying condition. One of them received daptomycin as empirical treatment, which was discontinued because the patient was asymptomatic and with clinical improvement. Of note, it was observed that the patient was receiving a dose of daptomycin lower than required and that CPK was already elevated before beginning daptomycin, so administration of this drug might not be the cause of the CPK elevation. The other patient had daptomycin as targeted treatment and suffered rhabdomyolysis with daptomycin as the suspected cause. The treatment was then changed to vancomycin and CPK values decreased. However, the patient suffered renal insufficiency and the drug was then changed to linezolid, which was also switched to tedizolid because of linezolid-related thrombocytopenia.

Clinical outcome and the potential consequences of reaching trough levels >24.3 mg/L were evaluated and it was observed that there were no differences with respect to adverse events (3.5% vs. 0%; $P = 0.641$), related mortality (12.3% vs. 16.7%; $P = 0.759$) and overall poor outcome (22.8% vs. 33.3%; $P = 0.565$). Similarly, when patients receiving targeted therapy were analysed, we were unable to demonstrate differences between both groups. No patient receiving daptomycin as empirical treatment and having C_{min} values >24.3 mg/L was found. However, it was observed that C_{min} values in the range of 3.18–16.84 mg/L had a correlation with favourable outcome (84.6% vs. 62.5%; $P = 0.045$), less adverse events (0% vs. 8.3%; $P = 0.067$) and less related mortality (5.1% vs. 25.0%; $P = 0.021$). C_{max} values in the range of 63.45–76.29 mg/L also had a correlation with favourable outcome (100% vs. 69.4%; $P = 0.018$). More favourable outcome cases were found in the range of C_{max}/MIC values between 72.7 and 128.7 (82.1% vs. 17.9%; $P = 0.068$).

At univariate analysis, risk factors associated with poor outcome were a longer stay in the ICU ($P = 0.049$), presence of hypoalbuminemia ($P = 0.033$), targeted treatment ($P = 0.033$) and $C_{min} < 3.18$ mg/L ($P = 0.028$). Multivariate analysis showed that $C_{min} < 3.18$ mg/L (odds ratio = 6.465, 95% confidence interval 1.032–40.087; $P = 0.046$) were independently related to poor outcome (Table 1).

Variables that could potentially influence daptomycin serum levels (C_{min} and C_{max}) were analysed (Table 3). Multivariate analysis confirmed that patients who were in the ICU at the beginning of daptomycin treatment or on haemodialysis had lower C_{min} values, and that those patients receiving higher daptomycin doses or with a higher McCabe score (rapidly fatal) or were treated with midazolam as concomitant medication had higher C_{min} values (Table 3). The adjusted R^2 of 0.412 proved that 41.2% of the variability in C_{min} was explained by these variables.

Multivariate analysis confirmed that patients with ICU-onset infection also had lower C_{max} values, and that those patients receiving higher daptomycin doses or midazolam as concomitant medication had also higher C_{max} values (Table 3). The adjusted R^2 of 0.456 proved that 45.6% of the variability in C_{max} of daptomycin among the study population was explained by these variables. In addition, C_{max}/MIC values were also positively related to daptomycin doses administered (Table 3).

Conversely, we were not able to identify a significant correlation between other concomitant medications (indinavir, ritonavir, erythromycin, clarithromycin, itraconazole, rifampicin and statins) or other variables and the C_{min}, C_{max} and/or C_{max}/MIC (Table 3). Of note, among 63 patients included in this study, 23 (36.5%) were receiving statins but only 3 patients had a $C_{min} > 24.3$ mg/L. As such, we cannot conclude any association between the administration of statins and an increase in daptomycin levels.

4. Discussion

In this study, serum levels of daptomycin were prospectively determined in hospitalised adult patients treated with different doses of the antimicrobial agent. The results, collected systematically in a non-selected population, confirm the variability of daptomycin serum levels and that this variability occurs even in different patients receiving the same dosage. High interindividual variability in daptomycin serum levels has been previously associated with drug underexposure. Pea et al. described a case of a patient with life-threatening *S. aureus* bacteraemic cSSTI who required high daptomycin dosages to reach plasma exposures similar to those observed in healthy volunteers receiving the standard dosage of 6 mg/kg [15]. Therefore, we question the need for daptomycin TDM, as suggested by other authors [6,11,12,14].

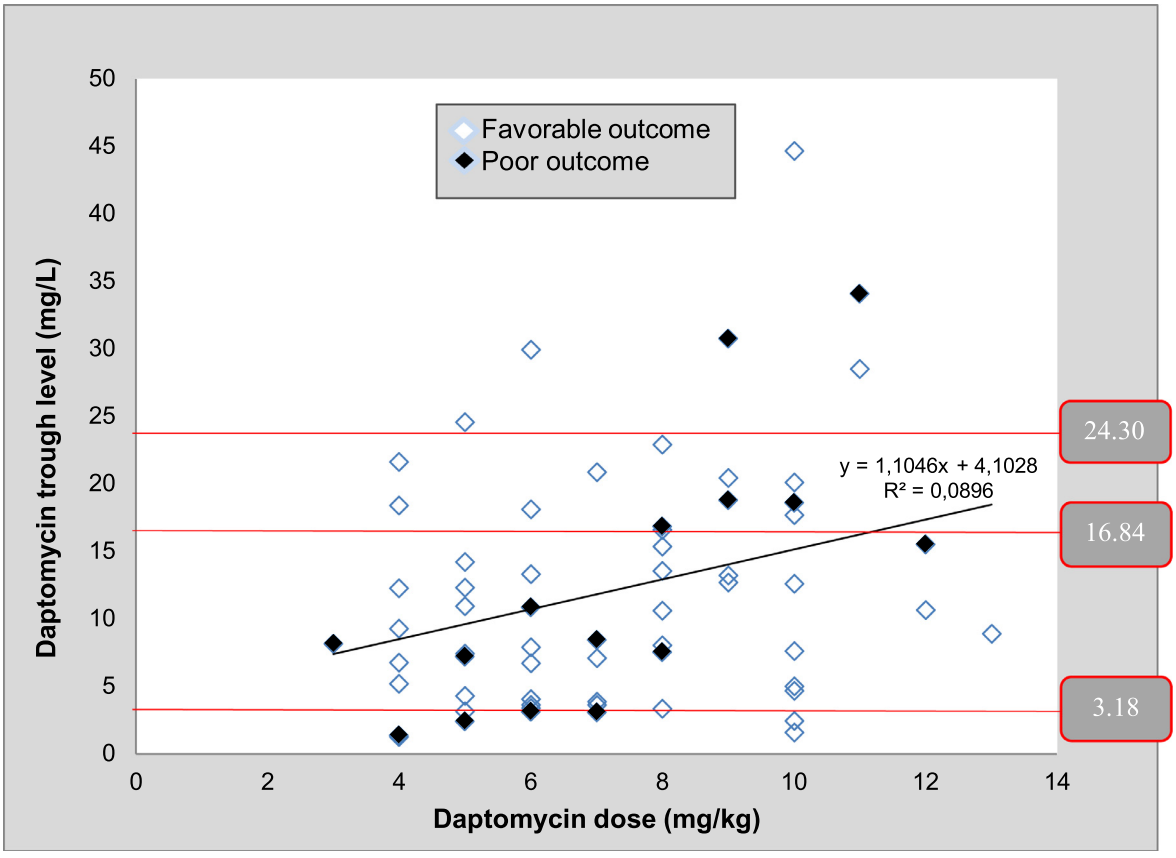

Fig. 5. Correlation of daptomycin dose, trough serum level (C_{min}) and clinical outcome (adverse events and mortality).

Daptomycin TDM-guided therapy has been shown to be useful in ensuring rapid clinical response and preventing drug-related toxicity in patients with morbid obesity, hypoalbuminemia or rapidly changing renal function [14]. Reiber et al. found that C_{min} and C_{max} values were associated with total dose administered and that C_{min} was additionally positively related to CL_{Cr} and albumin concentration and negatively related to dose interval [12]. The current multivariate study showed significant correlations between daptomycin serum levels and ICU-onset infection, daptomycin dosage, midazolam as concomitant medication, haemodialysis and McCabe score. Ulldemolins et al. observed that the volume of distribution (V_d) and clearance of highly protein-bound antibacterials such as daptomycin were significantly increased in critically ill patients with hypoalbuminaemia compared with healthy subjects [24]. In the current study, no relationship was detected in daptomycin serum levels among critically ill patients with hypoalbuminemia, probably due to the small sample size (7 patients in the ICU). Only two patients were receiving midazolam and, given the scarcity of data in the literature supporting this finding, we are cautious about this observation and a possible interaction with daptomycin pharmacokinetics.

The actual labelled dose for daptomycin is 4 mg/kg once daily for the treatment of cSSTIs and 6 mg/kg for *S. aureus* bloodstream infections. Approximately one-half of the patients in this study were treated with a high-dose regimen of ≥8 mg/kg. High-dose daptomycin regimens (8–10 mg/kg) have been suggested for difficult-to-treat infections such as complicated or persistent methicillin-resistant *S. aureus* (MRSA) bacteraemia, MRSA native-valve IE, MRSA foreign-body infections when bacteraemia is cleared, coagulase-negative staphylococci infections, and complicated enterococcal bacteraemia and IE [19]. The maximum licensed dose in Europe is 6 mg/kg for the treatment of non-complicated *S. aureus* bacteraemia and right-sided IE or cSSTIs. The variability in each individual dose might represent the physician prescribing variability for off-label treatments for which no prospective controlled studies have been developed and no clear doses have been indicated. One-third of the daptomycin initial doses prescribed in our institution during the study period were considered non-adequate. Dosing intervals were not always chosen according to the drug label sheet, which indicates a prolongation of the dosing interval to 48 h in patients with CL_{Cr} < 30 mL/min. In particular, the highest heterogeneity of dosing intervals was noticed in patients with CL_{Cr} of 15–30 mL/min. In one-third of these patients doses were not adjusted to every 48 h and this generated higher C_{min} values. In contrast, in 15.4% of patients with CL_{Cr} of 30–60 mL/min, dose intervals were adjusted to 48 h.

Bhavnani et al. associated daptomycin C_{min} levels >24.3 mg/L with a higher risk of CPK elevation [21]. In the current study, C_{min} levels were above this threshold in 6 patients (9.5%) receiving a median dose of 9.5 mg/kg (IQR 5.75–11.0 mg/kg) ($P = 0.007$). Nevertheless, no significant CPK elevations were observed in these patients. Conversely, two cases with a significant CPK elevation that was not accompanied by higher C_{min} daptomycin values were detected. Clinical trials show a background rate of CPK elevation related to several causes, including concomitant medications (statins, fibrates, colchicine, hydroxychloroquine, zidovudine), comorbidities (e.g. diabetes mellitus), and surgical or other procedures, other than higher C_{min} daptomycin plasma values [25] that might explain this situation. Recently, Dare et al. found a strong association between daptomycin and statin co-administration and myopathy and rhabdomyolysis [26], which would be the only evidence suggesting frequent CPK monitoring or withholding statins.

The median C_{max} values observed in this study were slightly lower than those previously published in the literature [25,27–29].

Table 3
Univariate and multivariate analyses of variables associated with C_{min}, C_{max} and C_{max}/MIC of daptomycin ($n = 63$)

Variable	Univariate analysis		Multivariate analysis	
	Unstandardised β-coefficient (95% CI)	*P*-value	Unstandardised β-coefficient (95% CI)	*P*-value
C_{min} ($n = 63$)				
Age (years)	0.170 (0.013 to 0.326)	0.034		
Sex	3.567 (−1.075 to 8.210)	0.130		
Weight (kg)	−0.095 (−0.225 to 0.035)	0.150		
BMI (kg/m^2)	−0.111 (−0.527 to 0.305)	0.596		
eGFR (MDRD)	−0.535 (−5.160 to 4.090)	0.818		
Dose (mg/kg)	1.105 (0.203 to 2.006)	0.017	1.386 (0.642 to 2.129)	<0.01
Dose interval	−0.235 (−0.469 to −0.001)	0.049		
Days of treatment	0.111 (−0.077 to 0.299)	0.242		
Haemodialysis	−7.027 (−15.260 to 1.206)	0.093	−10.669 (−17.362 to −3.977)	<0.01
Beginning in ICU	−7.297 (−14.301 to −0.293)	0.041	−14.146 (−20.292 to −8.000)	<0.01
Hypoalbuminemia	−0.280 (−4.850 to 4.290)	0.903		
Co-treatment with				
Indinavir	NA			
Ritonavir	−1.253 (−19.477 to 16.971)	0.891		
Erythromycin	−3.836 (−14.488 to 6.816)	0.474		
Clarithromycin	NA			
Itraconazole	NA			
Rifampicin	5.776 (−0.564 to 12.116)	0.073		
Midazolam	9.751 (−3.000 to 22.502)	0.131	17.032 (6.676 to 27.388)	<0.01
Statins	1.0 (−3.725 to 5.725)	0.674		
CCI	0.528 (−0.402 to 1.459)	0.261		
McCabe score	3.805 (−0.940 to 8.549)	0.114	7.959 (3.868 to 12.049)	<0.01
C_{max} ($n = 63$)				
Age (years)	0.341 (−0.030 to 0.712)	0.071		
Sex	12.888 (2.284 to 23.491)	0.018		
Weight (kg)	−0.386 (−0.680 to −0.092)	0.011		
BMI (kg/m^2)	−0.628 (−1.595 to 0.338)	0.199		
eGFR (MDRD)	−0.764 (−11.622 to 10.094)	0.889		
Dose (mg/kg)	5.086 (3.292 to 6.881)	<0.01	5.485 (3.846 to 7.124)	<0.01
Dose interval	−0.119 (−0.686 to 0.447)	0.675		
Days of treatment	0.611 (0.193 to 1.029)	0.005		
Haemodialysis	7.758 (−11.921 to 27.438)	0.434		
Beginning in ICU	−11.305 (−28.070 to 5.459)	0.183	−20.905 (−33.808 to 8.003)	<0.01
Hypoalbuminemia	−2.832 (−13.534 to 7.871)	0.599		
Co-treatment with				
Indinavir	NA			
Ritonavir	−0.038 (−42.816 to 42.740)	0.999		
Erythromycin	0.615 (−24.491 to 25.721)	0.961		
Clarithromycin	NA			
Itraconazole	NA			
Rifampicin	16.149 (1.440 to 30.858)	0.032		
Midazolam	23.782 (−6.099 to 53.664)	0.117	33.707 (10.765 to 56.650)	<0.01
Statins	5.820 (−5.184 to 16.825)	0.294		
CCI	0.424 (−1.780 to 2.628)	0.702		
McCabe score	5.864 (−5.404 to 17.132)	0.302		
C_{max}/MIC ($n = 47$)				
Age (years)	0.142 (−2.666 to 2.949)	0.920		
Sex	63.183 (−3.705 to 130.070)	0.064		
Weight (kg)	−1.779 (−3.546 to −0.012)	0.048		
BMI (kg/m^2)	−4.299 (−9.922 to 1.323)	0.131		
eGFR (MDRD)	0.099 (−67.468 to 67.665)	0.998		
Dose (mg/kg)	21.097 (8.954 to 33.241)	0.001	21.097 (8.954 to 33.241)	<0.01
Dose interval	−0.928 (−4.318 to 2.462)	0.584		
Days of treatment	1.984 (−0.695 to 4.664)	0.143		
Haemodialysis	−5.905 (−125.612 to 113.802)	0.921		
Beginning in ICU	41.736 (−65.885 to 149.357)	0.439		
Hypoalbuminemia	−8.837 (−75.979 to 58.305)	0.792		
Co-treatment with				
Indinavir	NA			
Ritonavir	−62.543 (−293.281 to 168.194)	0.588		
Erythromycin	−15.142 (−151.727 to 121.443)	0.824		
Clarithromycin	NA			
Itraconazole	NA			
Rifampicin	−3.017 (−91.903 to 85.868)	0.946		
Midazolam	−16.855 (−182.281 to 148.572)	0.838		
Statins	14.403 (−54.182 to 82.989)	0.674		
CCI	−2.751 (−20.731 to 15.228)	0.759		
McCabe score	39.207 (−26.332 to 104.746)	0.235		

C_{min}, trough serum level of daptomycin; C_{max}, peak serum level of daptomycin; MIC, minimum inhibitory concentration; CI, confidence interval; BMI, body mass index; eGFR (MDRD), estimated glomerular filtration rate (Modification of Diet in Renal Disease equation); ICU, intensive care unit; NA, not available; CCI, Charlson comorbidity index.

Di Paolo et al. demonstrated that daptomycin pharmacokinetics might be altered in patients affected by severe Gram-positive infections [13], which was also characterised by plasma concentrations lower than those previously described in healthy volunteers and patients [30], even after accounting for the estimated increase in V_d in patients with an active infection. Accordingly, higher daptomycin doses (up to 8–10 mg/kg) should be considered depending on the severity of the infection and the patient's clinical condition. In this study, we considered as adequate a dosage of 10 mg/kg for endocarditis treatment.

A pilot pharmacokinetic study in haemodialysis patients with infected medical devices demonstrated that high-dose daptomycin (10 mg/kg after every session) fulfils pharmacokinetic/pharmacodynamic (PK/PD) targets better than standard doses (4–6 mg/kg) [31]. The five haemodialysis patients included in the current study received a median dose of 10 mg/kg (IQR 7.5–10.0 mg/kg), that was adjusted to intervals of 48 h and considered adequate in all the cases. Of note, a decrease of 42.1% in daptomycin dose through haemodialysis was observed, but the C_{max}/MIC target was reached and all outcomes were favourable.

Antibiotic underdosing and a high frequency of low daptomycin exposure might lead to the emergence of antimicrobial resistance, without adequate dosing adjustments. Bassetti et al. showed three risk factors for the emergence of daptomycin-non-susceptible strains: a daptomycin dose of <6 mg/kg/day; a longer therapy duration; and previous use of teicoplanin [32]. We were not able to identify any potential role of risk factors as all of the micro-organisms isolated in the current study were susceptible to daptomycin.

This study is based on real-life data obtained using HPLC in a large tertiary hospital. Nevertheless, it has some limitations. The facts that a high number of patients were receiving daptomycin as empirical therapy and the small sample size are probably the most relevant. In addition, dose adjustments were only dependent on the decision of the attending physician, and we did not intervene directly in that decision.

In conclusion, this study allowed us to identify the pattern of daptomycin use in our institution and the need for implementing new strategies to reduce the percentage of non-adequate use and the marked variability of dosing for the same indication among different attending physicians. In the absence of clinically validated serum level targets, the results can only suggest, not confirm, an effective treatment; even so, these data provide a basis for designing a pharmacokinetic study in a large population with several measurements per patient that could allow calculation of the area under the concentration –time curve (AUC) and different PK/PD parameters needed to create a more accurate model for daptomycin exposure.

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Competing interests

None declared.

Ethical approval

This study was approved by the Ethics Committee of the Hospital General Universitario Gregorio Marañón (Madrid, Spain) [study no. MICRO.HGUGM.2016-017].

References

[1] Wise R, Gee T, Andrews JM, Dvorchik B, Marshall G. Pharmacokinetics and inflammatory fluid penetration of intravenous daptomycin in volunteers. Antimicrob Agents Chemother 2002;46:31–3.

[2] Steenbergen JN, Alder J, Thorne GM, Tally FP. Daptomycin: a lipopeptide antibiotic for the treatment of serious Gram-positive infections. J Antimicrob Chemother 2005;55:283–8.

[3] Shoemaker DM, Simou J, Roland WE. A review of daptomycin for injection (Cubicin) in the treatment of complicated skin and skin structure infections. Ther Clin Risk Manag 2006;2:169–74.

[4] Safdar N, Andes D, Craig WA. In vivo pharmacodynamic activity of daptomycin. Antimicrob Agents Chemother 2004;48:63–8.

[5] European Medicines Agency (EMA). *European public assessment report: Cubicin*. London, UK: EMA. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000637/human_med_000730.jsp&mid=WC0b01ac058001d124 [accessed 19 January 2018].

[6] Falcone M, Russo A, Cassetta MI, Lappa A, Tritapepe L, d'Ettorre G, et al. Variability of pharmacokinetic parameters in patients receiving different dosages of daptomycin: is therapeutic drug monitoring necessary? J Infect Chemother 2013;19:732–9.

[7] Falcone M, Russo A, Cassetta MI, Lappa A, Tritapepe L, Fallani S, et al. Daptomycin serum levels in critical patients undergoing continuous renal replacement. J Chemother 2012;24:253–6.

[8] Kielstein JT, Eugbers C, Bode-Boeger SM, Martens-Lobenhoffer J, Haller H, Joukhadar C, et al. Dosing of daptomycin in intensive care unit patients with acute kidney injury undergoing extended dialysis—a pharmacokinetic study. Nephrol Dial Transplant 2010;25:1537–41.

[9] Kullar R, McClellan I, Geriak M, Sakoulas G. Efficacy and safety of daptomycin in patients with renal impairment: a multicenter retrospective analysis. Pharmacotherapy 2014;34:582–9.

[10] Vilay AM, Grio M, Depestel DD, Sowinski KM, Gao L, Heung M, et al. Daptomycin pharmacokinetics in critically ill patients receiving continuous venovenous hemodialysis. Crit Care Med 2011;39:19–25.

[11] Cojutti PG, Candoni A, Ramos-Martin V, Lazzarotto D, Zannier ME, Fanin R, et al. Population pharmacokinetics and dosing considerations for the use of daptomycin in adult patients with haematological malignancies. J Antimicrob Chemother 2017;72:2342–50.

[12] Reiber C, Senn O, Muller D, Kullak-Ublick GA, Corti N. Therapeutic drug monitoring of daptomycin: a retrospective monocentric analysis. Ther Drug Monit 2015;37:634–40.

[13] Di Paolo A, Tascini C, Polillo M, Gemignani G, Nielsen EI, Bocci G, et al. Population pharmacokinetics of daptomycin in patients affected by severe Gram-positive infections. Int J Antimicrob Agents 2013;42:250–255.

[14] Pea F, Cojutti P, Sbrojavacca R, Cadeo B, Cristini F, Bulfoni A, et al. TDM-guided therapy with daptomycin and meropenem in a morbidly obese, critically ill patient. Ann Pharmacother 2011;45:e37.

[15] Pea F, Crapis M, Cojutti P, Bassetti M. 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 2014;42:207–10.

[16] Barreau S, Benaboud S, Kerneis S, Moachon L, Blanche P, Groh M, et al. *Staphylococcus aureus* osteo-articular infection: usefulness of the determination of daptomycin serum concentration to explain a treatment failure. Int J Clin Pharmacol Ther 2016;54:923–7.

[17] Skiest DJ. Treatment failure resulting from resistance of *Staphylococcus aureus* to daptomycin. J Clin Microbiol 2006;44:655–6.

[18] Cavalcante FS, Ferreira Dde C, Chamon RC, da Costa TM, Maia F, Barros EM, et al. Daptomycin and methicillin-resistant *Staphylococcus aureus* isolated from a catheter-related bloodstream infection: a case report. BMC Res Notes 2014;7:759.

[19] Gould IM, Miro JM, Rybak MJ. Daptomycin: the role of high-dose and combination therapy for Gram-positive infections. Int J Antimicrob Agents 2013;42:202–10.

[20] Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, et al. 2015 ESC guidelines for the management of infective endocarditis: the Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J 2015;36:3075–128.

[21] Bhavnani SM, Rubino CM, Ambrose PG, Drusano GL. 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 2010;50:1568–74.

[22] Martens-Lobenhoffer J, Kielstein JT, Oye C, Bode-Boger SM. Validated high performance liquid chromatography–UV detection method for the determination of daptomycin in human plasma. J Chromatogr B Analyt Technol Biomed Life Sci 2008;875:546–50.

[23] European Committee on Antimicrobial Susceptibility Testing. Clinical breakpoints v.8.1. [accessed 1 January 2018] http://www.eucast.org/clinical_breakpoints.

[24] Ulldemolins M, Roberts JA, Rello J, Paterson DL, Lipman J. The effects of hypoalbuminaemia on optimizing antibacterial dosing in critically ill patients. Clin Pharmacokinet 2011;50:99–110.

[25] D'Avolio A, Pensi D, Baietto L, Pacini G, Di Perri G, De Rosa FG. Daptomycin pharmacokinetics and pharmacodynamics in septic and critically ill patients. Drugs 2016;76:1161–74.

[26] Dare RK, Tewell C, Harris B, Wright PW, Van Driest SL, Farber-Eger E, et al. Effect of statin coadministration on the risk of daptomycin-associated myopathy. Clin Infect Dis 2018;67:1356–63.

[27] Benvenuto M, Benziger DP, Yankelev S, Vigliani G. Pharmacokinetics and tolerability of daptomycin at doses up to 12 milligrams per kilogram of body weight once daily in healthy volunteers. Antimicrob Agents Chemother 2006;50:3245–9.
[28] Dvorchik BH, Brazier D, DeBruin MF, Arbeit RD. Daptomycin pharmacokinetics and safety following administration of escalating doses once daily to healthy subjects. Antimicrob Agents Chemother 2003;47:1318–23.
[29] Woodworth JR, Nyhart EH Jr, Brier GL, Wolny JD, Black HR. Single-dose pharmacokinetics and antibacterial activity of daptomycin, a new lipopeptide antibiotic, in healthy volunteers. Antimicrob Agents Chemother 1992;36:318–25.
[30] Dvorchik B, Arbeit RD, Chung J, Liu S, Knebel W, Kastrissios H. Population pharmacokinetics of daptomycin. Antimicrob Agents Chemother 2004;48:2799–807.
[31] Diolez J, Venisse N, Belmouaz S, Bauwens MA, Bridoux F, Beraud G. Pilot pharmacokinetic study of high-dose daptomycin in hemodialysis patients with infected medical devices. Am J Kidney Dis 2017;70:732–4.
[32] Bassetti M, Villa G, Ansaldi F, De Florentiis D, Tascini C, Cojutti P, et al. Risk factors associated with the onset of daptomycin non-susceptibility in *Staphylococcus aureus* infections in critically ill patients. Intensive Care Med 2015;41:366–8.