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BRIEF REPORT

# Experience with daptomycin daily dosing in ICU patients undergoing continuous renal replacement therapy

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**Abstract**
*Purpose* For critically ill patients undergoing continuous renal replacement therapy (CRRT), daptomycin dosing recommendations are scarce. We, therefore, retrospectively assessed routinely measured daptomycin plasma concentrations, daptomycin dose administered and microbiological data in 11 critically ill patients with Gram-positive infections that had received daptomycin once daily.
*Methods* The retrospective analysis included critically ill patients treated at the intensive care unit (ICU) who had daptomycin plasma concentrations measured.
*Results* Daptomycin dose ranged from 3 to 8 mg/kg/q24 h in patients undergoing CRRT ($n = 7$) and 6 to 10 mg/kg/q24 h in patients without CRRT ($n = 4$). Peak and trough concentrations showed a high intra- and inter-patient variability in both groups, independent of the dosage per kg body weight. No drug accumulation was detected in CRRT patients with once-daily daptomycin dosing. Causative pathogens were *Enterococcus faecium* ($n = 6$), coagulase-negative *Staphylococcus* ($n = 2$), *Staphylococcus aureus* ($n = 2$) and unknown in one patient. Microbiological eradication was successful in 8 of 11 patients. Two of three patients with unsuccessful microbiological eradication and fatal outcome had an *Enterococcus faecium* infection.
*Conclusion* In critically ill patients undergoing CRRT, daptomycin exposure with once-daily dosing was similar to ICU patients with normal renal function, but lower compared to healthy volunteers. Our data suggest that daptomycin once-daily dosing is appropriate in patients undergoing CRRT.

**Keywords** Antibiotics · Dosing · Gram-positive infection · Continuous renal replacement therapy · Intensive care

## Introduction

Gram-positive bacteria frequently cause severe infections in patients hospitalised in the intensive care unit (ICU). Optimal antibiotic dosing ensuring therapeutic concentrations is essential to reduce the risks of therapeutic failure and the development of antibiotic resistance. Considering that sepsis has a high mortality in critically ill patients with acute kidney injury [1], optimising antibiotic dosing is crucial in this patient population. On the other hand, drug accumulation and excessive antibiotic concentrations can result in an increased risk of adverse events. In our ICU, daptomycin is used in patients with contraindication to standard antibiotic therapy with glycopeptides due to its low nephrotoxic potential. Although very rare cases of acute eosinophilic pneumonia have been reported [2], its dose-dependent toxicity is limited to creatine kinase elevation with rare cases of rhabdomyolysis [3]. Daptomycin is a lipopeptide antibiotic active against Gram-positive organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA) or vancomycin-resistant pathogens.

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Daptomycin resistance has only rarely been reported in *Staphylococcus aureus* [4, 5] and enterococcal strains [6, 7]. Factors like high bacterial load at the infection site and suboptimal daptomycin exposure have been associated with treatment failure and loss of daptomycin susceptibility; therefore, high-dose daptomycin treatment has been proposed for complicated Gram-positive and enteroccocal infections [8, 9].

Daptomycin is approved at a dose of 6 mg/kg once daily for bacteraemia and at 4 mg/kg once daily for soft tissue infections in adults with normal or mildly impaired renal function (creatinine clearance >30 ml/min). Twice-daily dosing has been reported in children [10]. Sepsis often leads to acute kidney injury and the need for continuous renal replacement therapy (CRRT) [11]. As daptomycin is mostly eliminated by the kidneys, dose adjustments are required in patients with renal insufficiency. However, official daptomycin dosing recommendations for patients undergoing CRRT are currently not available [3]. The high plasma protein binding (90–96 %) of daptomycin suggests that the drug may not be extensively removed by CRRT. However, in a CRRT model with bovine plasma enriched with daptomycin using filtration rates of 35 ml/kg/h or higher, daptomycin CRRT clearance was comparable or even higher (>10 ml/min) than the clearance in patients with normal renal function (7–10 ml/min) [12]. In a recent study by Vilay et al. [13], a single daptomycin dose of 8 mg/kg in critically ill patients under CRRT resulted in a similar transmembrane clearance [mean 6.3 ml/min ± 2.9 standard deviation (SD)], indicating a good elimination by CRRT. The authors suggest a dose of 8 mg/kg once every 48 h, but we worry that exposure to daptomycin will be insufficient beyond 24 h with a q48 h dosing regimen [14]. Khadzhynov et al. determined daptomycin steady-state pharmacokinetics after the administration of 4 mg/kg q48 h in eight patients undergoing continuous haemodialysis. They, likewise, conclude that a once every 48 h dosing might be inappropriate, because of very low daptomycin exposure during the second half of the dosing interval [15]. Daptomycin plasma concentrations in our ICU patients undergoing CRRT and receiving daptomycin q48 h showed low peak and very low trough concentrations (data not shown) compared to values found in healthy volunteers with the equivalent doses [16]. We, therefore, started to administer daptomycin q24 h along with regular monitoring of peak and trough plasma concentrations in clinical routine. In this case series, we present the daptomycin plasma concentrations of critically ill patients receiving daptomycin once daily.

## Materials and methods

In this chart review, we retrospectively gathered data from critically ill patients with and without CRRT exposed to a once-daily daptomycin regimen in which daptomycin peak ($C_{max}$) and trough ($C_{min}$) concentrations had been determined. Continuous veno-venous haemodiafiltration (CVVHDF) or continuous veno-venous haemodialysis (CVVHD) is used at our ICU and is performed with multiFiltrate (Fresenius Medical Care, Homburg, Germany) using the capillary haemofilter AV 1000S (polysulphon, surface area 1.8 $m^2$) or Prismaflex ST150 (Gambro AB, Lund, Sweden) using the capillary haemofilter AN69 ST (acrylonitrile-natrium-methylsulphonate, surface area 1.5 $m^2$). The total combined filtration/dialysate rates are usually maintained between 30 and 40 ml/kg/h. Samples were taken at the end of a 30-min daptomycin infusion for the determination of $C_{max}$ and before the next dose for $C_{min}$. They were immediately transported to the laboratory, centrifuged and analysed by liquid chromatography/mass spectrometry/mass spectrometry (LC–MS/MS) using a C18 reversed-phase analytical column, 0.1 % formic acid and methanol as the mobile phase, and electrospray ionisation. Heparinised plasma samples were extracted by protein precipitation after the addition of the internal standard (CB 183253). The concentration of daptomycin was calculated by linear regression analysis of the calibration curve ranging from 0.1 to 150 mg/l. The lower limit of the quantification of the method was 0.03 mg/l, the precision 3.1 % and the accuracy 101 %.

Patient characteristics and microbiological data, including minimum inhibitory concentrations (MICs), if available, were collected from the patient charts. Microbiological eradication was defined as the absence of the original pathogen in a culture specimen obtained in the same anatomical site. Data are represented in a descriptive way. Plasma concentrations measured in our patients and previously published mean values from healthy volunteers at steady state [17, 18] were represented graphically. A linear regression analysis was performed between the total daily dose and plasma concentrations measured.

## Results

Between May 2008 and December 2010, 11 adult patients admitted to our ICU receiving once-daily daptomycin treatment were retrospectively analysed. Seven of them had oliguric renal failure requiring CRRT (daily urine output <200 ml) and four had normal or mildly impaired renal function without undergoing CRRT. The daptomycin dose ranged from 3 to 8 mg/kg/h in patients undergoing CRRT and 6 to 10 mg/kg/h in patients without CRRT. The patient characteristics and microbiological data are presented in Table 1. Peak and trough daptomycin plasma concentrations are shown in Fig. 1a, b, respectively. Peak and trough concentrations showed high intra- and inter-patient

**Table 1** Patient characteristics and microbiological data

| Age (years) | Weight (kg) | Daptomycin dose mg/kg/d (total dose) | Renal function | Haemodiafiltration flow rates (ml/h) | Diagnosis | Microorganism | Daptomycin MIC | Microbiological eradication | SAPS | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|
| 43 | 140 | 3–4 (400–600) | CRRT | 4,000 | H1N1, MOF | *Enterococcus faecium* (VRE) | 2 | No | 60 | Died |
| 74 | 58 | 3–6 (175–350) | CRRT | 2,600–4,400 | Endocarditis | *Enterococcus faecium* (VSE) | n.a. | Yes | 69 | Survived |
| 57 | 56 | 4 (250) | CRRT | 2,100 | Septic shock | Coagulase-negative *Staphylococcus* | 0.125 | No | 65 | Died |
| 78 | 104 | 5 (500) | CRRT | 4,050 | Septic shock | *Enterococcus faecium* (VSE) | n.a. | Yes | 42 | Survived |
| 80 | 80 | 6 (500) | CRRT | n.a. | Sepsis | *Staphylococcus aureus* (MSSA) | n.a. | Yes | 50 | Survived |
| 66 | 112 | 5–7 (850–500) | CRRT | 3,600 | Sepsis | *Enterococcus faecium* (VSE) | 3 | No | 57 | Died |
| 42 | 70 | 5 (350) | CRRT | 4,050 | Endocarditis | Coagulase-negative *Staphylococcus* | n.a. | Yes | 33 | Survived |
| 38 | 85 | 6 (500) | Normal | – | H1N1, ARDS | n.a. | n.a. | Yes | 28 | Survived |
| 33 | 70 | 10 (700) | Normal | – | Sepsis | *Enterococcus faecium* (VSE) | 1.5 | Yes | 15 | Survived |
| 42 | 76 | 6 (500) | Normal | – | Sepsis | *Staphylococcus aureus* (MSSA) | n.a. | Yes | 36 | Survived |
| 72 | 100 | 6 (650) | Mildly impaired | – | Sepsis | *Enterococcus faecium* (VSE) | n.a. | Yes | 41 | Survived |

*ARDS* acute respiratory distress syndrome, *CRRT* continuous renal replacement therapy, *n.a.* not available, *MIC* minimal inhibitory concentration, *MOF* multiple organ failure, *MSSA* methicillin-susceptible *Staphylococcus aureus*, *SAPS* Simplified Acute Physiology Score, *VRE* vancomycin-resistant *Enterococcus*, *VSE* vancomycin-susceptible *Enterococcus*

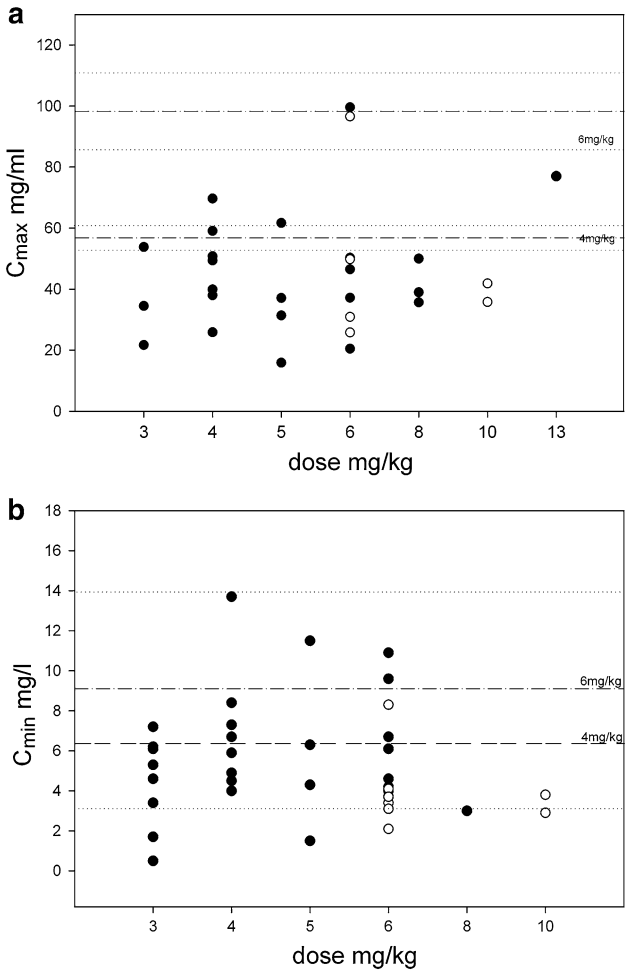


**Fig. 1** **a** Daptomycin $C_{max}$ concentrations in intensive care unit (ICU) patients with once-daily daptomycin dosing. **b** Daptomycin $C_{min}$ concentrations in ICU patients with once-daily daptomycin dosing. *Filled circles* patients undergoing continuous renal replacement therapy (CRRT), *open circles* no CRRT. **a** *Lines* mean daptomycin plasma concentration and standard deviation (*dotted lines*) after 4 mg/kg and 6 mg/kg in healthy volunteers, as published in Dvorchik et al. [16]. **b** *Lines* median daptomycin plasma concentration and range (*dotted lines*) after 4 mg/kg and 6 mg/kg in healthy volunteers, as published in Dvorchik et al. [16]

variability in both groups. In CRRT patients, daptomycin plasma concentrations were in the range of those patients without CRRT. Interestingly, there was no clear correlation between dosing per kg body weight and daptomycin plasma concentration ($R^2 = 0.06$). Errors in the estimation of body weight and some variability in sampling times for peak values might explain the inconsistency. Considerable differences in haemodiafiltration rates (HDFRs) were found, ranging from 29 to 76 ml/kg/h, corresponding to 2,600–4,400 ml/h, depending on body weight. High-volume haemodiafiltration of $\geq$50 ml/kg/h was used in some patients with septic shock or severe metabolic disturbances. Although the HDFR is the main determinant of daptomycin

clearance in CRRT, no correlation was found between plasma concentrations and the HDFR. Trough concentrations (Fig. 1b) were in the range of values measured in healthy volunteers [16], independent of daily dose given. However, when doses of 4 mg/kg were used, $C_{max}$ (Fig. 1a) was in the lower range of values measured in healthy volunteers at the equivalent dose and were substantially lower at daptomycin doses >6 mg/kg compared to equivalent doses in healthy volunteers.

## Discussion

In our retrospective analysis of critically ill patients undergoing CRRT and receiving daptomycin once daily, we found highly variable daptomycin exposure and relatively low daptomycin peak concentrations, despite high per body weight dosage in some patients compared to healthy volunteers. No evidence of excessively high daptomycin plasma concentrations was found with once-daily dosing, indicating that once-daily daptomycin dosing might be more appropriate. Our findings are consistent with those of Vilay et al. [13], who determined daptomycin pharmacokinetics after a single dose of daptomycin 8 mg/kg in critically ill patients undergoing CRRT and concluded that 8 mg/kg is necessary to reach sufficient plasma peak levels. Daptomycin exhibits a concentration-dependent antibacterial activity. In an animal model, the area under the curve (AUC)/minimal inhibitory concentration (MIC) ratio and the $C_{max}$/MIC ratio were the main determinants of its efficacy [19]. A daptomycin $C_{max}$/MIC ratio of 100–400 was found to exhibit a log2 killing in *Staphylococcus aureus* with a daptomycin MIC of 0.5 mg/l. Peak concentrations of 50–200 mg/l would be necessary to reach those ratios. The peak concentrations in our patient population reached a mean of 46 mg/l, with about two-thirds of the values being below 50 mg/l at steady state. MIC values were determined in a patient with coagulase-negative *Staphylococcus* (MIC 0.125 mg/ml) and in 3 of 6 patients with *Enterococcus faecium* (MIC 1.5–3 mg/ml) infection. The higher MICs for *Enterococcus* spp. correspond to epidemiological MIC distributions published by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) in 2005 [20]. As daptomycin exhibits lower potency against *Enterococcus* spp., the drug concentrations measured in our study could, therefore, theoretically be insufficient to treat *Enterococcus* ssp. In in vitro models, higher doses were required in order to achieve the same effect (80 % of $E_{max}$) against *Enterococcus faecium* (6.8 mg/kg) compared to *Staphylococcus aureus* (3.1 mg/kg) [21]. In an in vitro model with endocardial vegetations of vancomycin-resistant *Enterococcus* exposed to daptomycin at concentrations corresponding to 6, 8, 10 and 12 mg/kg daily in vivo, bactericidal activity was not sustained at doses of 6 mg/kg and 8 mg/kg, and the development of reduced susceptibility was observed at doses 6–10 mg/kg, but not at 12 mg/kg [22]. Clinical experience is limited to retrospective observational studies though. In one study, daptomycin doses of >6 mg/kg were associated with higher clinical success in enterococcal infections [23]. However, prospective data in humans with enterococcal infections comparing daptomycin plasma concentrations and outcome are lacking. Nevertheless, based on the available data and as daptomycin was generally well tolerated at doses >8 mg/kg [24, 25], doses higher than 6 mg/kg daily should be considered in complicated enterococcal infections As the peak levels were relatively low in critically ill patients undergoing CRRT with HDFR of 30–40 ml/kg/h, high-dose regimens must be considered in this patient population.

In two of the patients with enterococcal infection, microbiological eradication failed, and both patients died in the ICU. Both patients were obese and had received doses ranging from 400 to 850 mg daily, which corresponded to 3–4 and 5–7 mg/kg, respectively. A third patient with septic shock and fatal outcome had a coagulase-negative *Staphylococcus* isolated and was treated with a low total daily daptomycin dose of 250 mg (4 mg/kg). All other patients had successful microbiological eradication and all of them survived until ICU discharge. As daptomycin was never given as a single antibiotic agent, and because ICU severity scores were substantially higher in non-survivors than in survivors, it is not possible to make a definite conclusion on daptomycin exposure and outcome.

The retrospective character of this work and the small patient number may certainly limit the conclusions drawn from the present data; however, the data represent real-life situations, underlining the difficulty in interpreting routinely performed therapeutic drug monitoring.

In order to prevent under dosing of daptomycin in critically ill patients, especially those undergoing CRRT, we suggest a dose of at least 6 mg/kg body weight every 24 h and recommend regular monitoring of daptomycin concentrations. To further elucidate the optimal daptomycin dose in critically ill patients undergoing CRRT, a prospective dose-finding study is ongoing at our institution (http://clinicaltrials.gov/ct2/show/NCT01171547).

**Conflict of interest** Dr. Corti was on the advisory board for Novartis, Basel, Switzerland. Drs. Preiswerk, Rudiger and Fehr have not disclosed any potential conflicts of interest.

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