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## **Bone penetration of Daptomycin in diabetic patients with bacterial foot infections**

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## Abstract

**Objectives:** Daptomycin has shown clinical efficacy in diabetic foot infections (DFI). However, few data are available about its bone penetration in this particular population. We aimed to determine daptomycin bone concentrations in patients with diabetic foot infection that underwent surgery after multiple daptomycin infusions and determine bone daptomycin inhibitory quotients (IQs) for predominant Gram-positive species involved in DFI.

**Patients and methods:** Fourteen adult patients hospitalized with DFI treated by daptomycin and requiring surgical bone debridement and amputation were included in this monocentric prospective study. Daptomycin concentrations in serum and bone were determined by HPLC at steady state. Bones IQs were then calculated according to different MICs (range 0.25 to 4 mg/L) that are representatives of main MICs for *S. aureus*, coagulase negative staphylococci and *Enterococcus* sp. populations

**Results:** Residual and peak concentrations varied from 4.5-to 39.9 mg/L and from 31.8 to 110.9 mg/L, respectively. Bone daptomycin concentrations at the moment of surgery varied from 1.2 to 17 mg/L. Up to a MIC of 1 mg/L, which is the E-COFF and breakpoint (BP) values for *S. aureus* and CNS, all bone daptomycin IQs were positive. Highest bones IQs were observed with *Staphylococcus* species. Calculated bones IQs for *Enterococcus* species were often weak at MIC values near the E-coff.

**Conclusions:** Daptomycin well penetrates bone in patients treated for DFI. At an initially recommended dosage of 6 mg/Kg, bone concentrations are likely to be effective against staphylococcal infections and infections due to low-MIC *Enterococcus*.

Key words: Daptomycin, Bone concentration, bacterial foot infection

## Introduction

Daptomycin is a cyclic lipopeptide antibiotic with rapid and concentration-dependent bactericidal activity against Gram-positive bacteria, including methicillin-resistant *S. aureus* (with or without increased vancomycin MIC value) and multidrug-resistant enterococci.(Gonzalez-Ruiz et al. 2016) Besides favourable microbial activity, *in vitro* models have shown the ability of this drug to penetrate biofilm matrix, a biological structure that has been involved in bone, joint, and material associated infections.(Jacqueline and Caillon 2014; Gbejuade et al. 2015) Daptomycin has been registered for the treatment of right-sided endocarditis, *Staphylococcus aureus* bacteremia and complicated skin and soft tissues infections with recommended once daily intravenous dosing of 6 mg/kg or 4 mg/kg.(Liu et al. 2011; Habib et al. 2015) However, due to the evolution of antimicrobial resistance, and to its intrinsic microbiological properties daptomycin was used in many other settings in particular for the treatment of bone and joints infections with or without the presence of prosthetic material, and for the treatment of diabetic foot infections (DFI).(Malizos et al. 2016) In a pooled analysis of the two large real-world registries, CORE in USA, and EU-CORE in Europe, daptomycin usage has been analysed in 11,557 patients, from whom 8.6% were treated for osteomyelitis, with or without material, with an estimated clinical success rate of 77.7%. The promising role of daptomycin in such infections has been strengthened by the ability to use higher dosage of this molecule, up to 12 mg/kg, but also with *in vitro* studies showing its ability to penetrate bone tissue. (Malizos et al. 2016; Seaton et al. 2016; Senneville et al. 2016)

Traunmüller et al., provided the first *in vitro* data regarding daptomycin bone penetration in 2010 by using microdialysis probe implanted into metatarsal bone and soft tissues during surgery.(Traunmüller et al. 2010a) The authors showed that bone/plasma area under curve (AUCs) of daptomycin concentration was 1.08 in patients with DFI and osteomyelitis, after 4 to 5 injections of a 6 mg/kg daptomycin regimen. In a second study conducted by Montagne et al. in 2014, daptomycin bone penetration reached much lower level.(Montagne et al. 2014) The authors studied daptomycin bone concentration after a single intravenous dose infusion of 8 mg/kg in patients that underwent knee or hip replacement. In this context of healthy bone tissue, median bone penetration only reached 9%, but with final concentrations that remained above 1 mg/L which is the recommended MIC breakpoint for *S. aureus*. Results of those studies lead to the same conclusion but might appear conflicting regarding the daptomycin concentration level achieved in bone.

The objective of our study was to determine daptomycin bone concentration in 14 patients with DFI that underwent bone resection surgery after multiple daptomycin infusions and determine daptomycin bone inhibitory quotients for Gram positive species considering their respective Epidemiological Cut-off values (ECOFFs), 90% and 50% Minimal Inhibitory Concentrations (MIC<sub>90</sub>, MIC<sub>50</sub>), and clinical breakpoints according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST).(EUCAST 2019)

## **Materials and methods**

### **Setting**

This monocentric prospective study was conducted in Strasbourg University Hospital from 2012 to 2018. The study protocol was approved by the local Ethics Comity of the University Hospital of Strasbourg (PRI – HUS n°4683) and was performed according to the revised version of the Declaration of Helsinki. All subjects provided written informed consent prior the entry into the study. This study was also registered at [clinicaltrials.gov](https://clinicaltrials.gov) under number NCT01306825.

### **Study population and patient flow chart**

Adult patients hospitalized with end-stage DFI (3 to 4 PEDIS grade) who required surgical bone debridement and amputation were invited to participate to the study if a treatment with daptomycin was needed and administered for more than 3 days at a 6mg/kg/day dosing (Figure 1). Subjects were excluded from the study if they were younger than 18 years of age, if there was no need for surgery, if creatinine clearance was <30ml/min according to the Modification of Diet in Renal Disease (MDRD) calculation.

### **Drug administration**

Daptomycin was administrated intravenously by bolus injections of 6 mg/kg over 30 minutes, once daily as recommended by the manufacturer. Patients received at least three days daptomycin before surgery, but surgery had to be performed within 14 days after inclusion.

### **Sample collection**

For each patient, two blood samples and one bone samples were collected. Peak concentration was measured in blood one hour after the end of a daptomycin infusion. For residual dosage, blood was collected at 24h, just before the next daptomycin infusion. All blood measurements were performed

the day of surgery. Bone tissues were collected at any time during surgery, placed in sterile container, and directly transported to the laboratory for culture and storage.

### **Microbiology**

Bacterial strain identification was assessed by Matrix-Assisted Laser Desorption Ionization-Time of Flight (MALDI-TOF) and antimicrobial susceptibility testing was made according to the EUCAST recommendations.(EUCAST 2019)

### **HPLC assay of daptomycin**

Daptomycin concentrations were measured by high performance liquid chromatography according to a previously described method.(Lefèvre et al. 2012)

**Serum concentrations:** Serum samples collected from patients were stored at -80°C until analysis. At the time of analysis, serums were thawed at room temperature and 500 µl of each sample were deproteinized by addition of an equal volume of a 1:2 (vol/vol) methanol-acetonitrile mixture. After vortexing for 5s, the mixture was submitted to a slow rotation at 30rpm/min, then this mixture was centrifuged at 10,000-x g for 5 min, and finally 20 µl of the resulting supernatant was injected into the liquid chromatograph.

**Bone concentrations:** After sampling, the bone tissue was carefully rinsed with sterile water to discard any blood contamination, dried, weighted, and stored at -80°C until analysis. The day of analysis, frozen bone samples were placed at room temperature to defrost. They were thereafter finely hand-crushed using a mortar and a pestle. Five hundred µl of a pH 7.4 phosphate buffer were then added to the powder and the mixture was gently shaken for 24

h at +4°C to extract the daptomycin from the bone powder. Previous experiments were carried out to ensure that 24h was far enough to completely extract the antibiotic from the powder.

Daptomycin was then assayed in the supernatant of this mixture after a 5min centrifugation at 10,000 x g. Results were expressed as µg daptomycin / g of bone

### **Chromatographic conditions**

Twenty µl of the supernatant (serum or bone) was injected into a Prominence HPLC system (Shimadzu USA Manufacturing Inc., Canby, OR) comprising an LP-20AT pump and a SPD-20A UV-visible detector. A Rheodyne model 7725i manual sample injector (Rheodyne, Rohnert Park, CA) was used with a 20-µl loop. Chromatographic separation was achieved on a reversed-phase C<sub>18</sub>, 150 x 4.6-mm, 3-µm Uptisphere column (Interchim, Montluçon, France) with a mobile phase consisting of an isocratic mixture of 20 mM phosphate buffer and 40% acetonitrile. The pH was adjusted to 3.5 with phosphoric acid. A 1.0-ml/min flow rate was used, and the detection wavelength was set at 224 nm. Under these conditions, the retention time for daptomycin was 7.5 min. The LC solution Shimadzu software (Shimadzu France, Champs sur Marne, France) was used for acquiring and processing the data. The quantification limit of the daptomycin assay was 0.5 µg/ml supernatant. The method was linear over the concentration range from 0.5 to 500 µg/ml, with a mean correlation coefficient of 0.9988. Quality control standards were prepared at a final concentrations of 1.0, 50.0, and 250 µg/ml. Interday and intraday accuracies of the method ranged from 92.0 to 103% and 93.8 to 101%, respectively. The precision values (coefficients of variation) ranged from 0.98 to 3.58% for the intraday precision and 2.66 to 3.03% for the interday precision.

## Results

### Patients and isolates

Fourteen patients with DFI were included in the study. The patient's demographic and clinical characteristics are detailed in Table 1. Mean daptomycin treatment duration before surgical procedure was 4.4 days (range 3-12 days) with a minimal length of three days. Ten patients (71.4%) had combined antibiotic therapy including piperacillin/tazobactam. A transmetatarsal amputation was performed in 10 patients (71.4%), a transphalangeal in two (14.3%), and a transtibial in two (14.3%). Various pathogens were isolated, mostly staphylococcal species, including coagulase negative staphylococci in 5 patients (35.7%), methicillin-resistant *S. aureus* in 3 (21.4%), methicillin-susceptible *S. aureus* in 4 (28.6%). Other pathogens were anaerobic bacteria, *Enterococcus* sp., *Streptococcus* sp., *Pseudomonas* sp. and *Enterobacteriaceae*.

### Daptomycin concentrations and inhibitory quotients

Peak and residual daptomycin serum concentrations and daptomycin bone concentrations measured from patients are shown in Figure 2 and detailed in Table 2. Serum residual and peak concentrations were measured at the day of surgery after various numbers of daptomycin administrations: 3 administrations (n=10), 4 administrations (n=1), 5 administrations (n=1), 10 administrations (n=1) and 14 administrations (n=1).

Residual and peak serum concentrations varied from 4.2-to 39.9 mg/L and from 31.8 to 110.9 mg/L, respectively. As for serum concentrations, bone samples were taken during surgery and the concentrations were measured at various times after daptomycin administration (range 3.1 to 22.7 hours). Bone daptomycin concentrations varied from 1.2 to 17 mg/Kg.

Bone inhibitory quotients (Bone concentrations/MIC, IQ) were then calculated according to different MICs (range 0.25 to 8 mg/L) that are representatives of main MICs of *S. aureus*, CNS and *Enterococcus* sp. populations (Table 1 and Figure 3).

Up to a MIC of 2 mg/L, which is upper than the E-COFF and breakpoint (BP) value for *S. aureus* and CNS, all bone IQs were positive. At the *E.faecalis* E-COFF value (4 mg/L), half of bone IQs were positive. At the *E. faecium* E-COFF value (8 mg/L), all bone IQs were under 1.

## **Discussion**

DFI is a major complication of diabetes, and if not managed appropriately, it can lead to low extremity amputation.(Markakis et al. 2016) Apart appropriate wound care, antibiotic therapy is required when infection penetrates fascia, muscle, joint or bone.(Lipsky et al. 2012) Because Gram-positive bacteria are the most frequently isolated bacteria in DFI, daptomycin was successfully used to treat them.(Lipsky and Stoutenburgh 2005; Uçkay et al. 2015) Despite its widely accepted utilization in this indication, few data are available on daptomycin bone penetration. For this reason, we aimed to determine bone concentration in 14 patients with DFI.

Our results show that despite the low vascularity associated with DFI, daptomycin well penetrates bone in patients treated for it and reached sufficient concentration in bone. Since our residual and peak concentrations are somewhat equivalent to those observed in other studies in this particular population making our daptomycin bone concentrations relevant.(Traunmüller et al. 2010a; Montange et al. 2014)

We then calculated bone IQ, which represents the ratio of the concentration that can be achieved at the specific site of infection to the MIC of the drug with respect to the infecting organism.(Ellner and Neu 1981)

Interestingly, when considering MICs of daptomycin for the major Gram-positive bacteria involved in DFI, inhibitory quotients are often at level likely to be compatible with therapeutic efficacy. This is especially true for *Staphylococcus* species. If considering *S. aureus*, intravenous dose of 6 mg/Kg allowed bones IQs to be always greater than 4 and often greater than 10 at MIC equivalent to the MIC<sub>90</sub> of this species.(Gallon et al. 2009; Jones et al. 2017) By comparison, bone IQs for vancomycin, teicoplanin and linezolid at their respective MIC<sub>50</sub> for *S. aureus* ranged from 0.85 to 3.7, 0.6 to 2.4, and 7.55, respectively.(Ziglam and Finch 2001; Draghi et al. 2005; Garazzino et al. 2008; Traunmüller et al. 2010b) Bones daptomycin IQs remain positive up to a MIC of 1 mg/L, which is the current EUCAST clinical breakpoint for *S. aureus* and CNS.(EUCAST 2019) Again, bones IQs at the considered CNS MIC<sub>90</sub> for vancomycin, teicoplanin and linezolid ranged from 0.42 to 2.4, 0.16 to 0.6, and 15, respectively.(Ziglam and Finch 2001; Draghi et al. 2005; Garazzino et al. 2008; Traunmüller et al. 2010b)

Therefore, the dosage regimens of 6 mg/kg allowed bone daptomycin concentrations that could be effective against *Staphylococcus* infections and at least equivalent to other drugs classically used in this indication. Besides, as many studies shown that daptomycin could be safety used at higher dosage, up to 12 mg/Kg, daptomycin seems to be of particular interest in treatment staphylococcal DFI.(Senneville et al. 2016)

However, when considering *Enterococcus* sp., daptomycin bones IQs were often weak. If we consider these species at their own E-COFF, which is the MIC that distinguishes organisms without and with phenotypically expressed resistance mechanisms, bones IQs were most of the time under 1, indicating that daptomycin may be not relevant in *Enterococcus* sp. DFI treatment. Utilization of higher dosage might improve bones IQs, but more researches are needed to conclude.

Our daptomycin bone penetration study was conducted according to previously described procedure.(Landersdorfer et al. 2009) Residual and peak concentrations measured in this study were not obtained after an equivalent number of daptomycin administrations (range 3 to 12 administrations). However, since all patients received at least 3 administrations of daptomycin, all concentrations were assessed at the steady state. The levels of peak and residual blood concentrations are not correlated with the number of administrations, reflecting the inter-patients variability inherent to the heterogeneity of their recruitment. The same occurs for bone tissue concentrations. Time by time means calculations for each kind of samples is not relevant due to the poor number of patients at each time. Interestingly, some patients had low bone concentrations of daptomycin despite high peak or residual serum concentrations while some other patients had low serum concentrations yet had comparable bone concentrations, indicating that high serum concentrations did not necessarily correspond to high concentrations in bone and vice versa. Besides, as bone resections weren't done at the time of blood sampling, bone penetration coefficient calculation is irrelevant. As daptomycin is a concentration-dependent drug, AUC/MIC best describes the efficacy of the dose regimen. However, real clinical practice does not easily allowed this approach. Measurement of daptomycin bone concentrations at different times after drug administration is useful when a population pharmacokinetic analysis is performed, but the few number of patients did not allow performing it. So we chose to calculate bone IQs for each patient, with all limits that implies. Nevertheless, our data represent "real life practice" and even if our choice could be questionable, they strongly suggest that daptomycin well penetrates bone in patients treated for DFI.

In summary, daptomycin well penetrates bone in patients treated for DFI. At a recommended dosage of 6 mg/Kg, bone concentrations are likely to be effective against staphylococcal infections. The recently higher recommended dosage regimens should optimize the efficacy against *Enterococcus*.

**Conflict of interest:**

The authors have no conflict of interest to declare for this work.

**Funding sources:**

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**Ethical approval:**

The study protocol was approved by the local Ethics Comity of the University Hospital of Strasbourg (PRI – HUS n°4683) and was performed according to the revised version of the Declaration of Helsinki.

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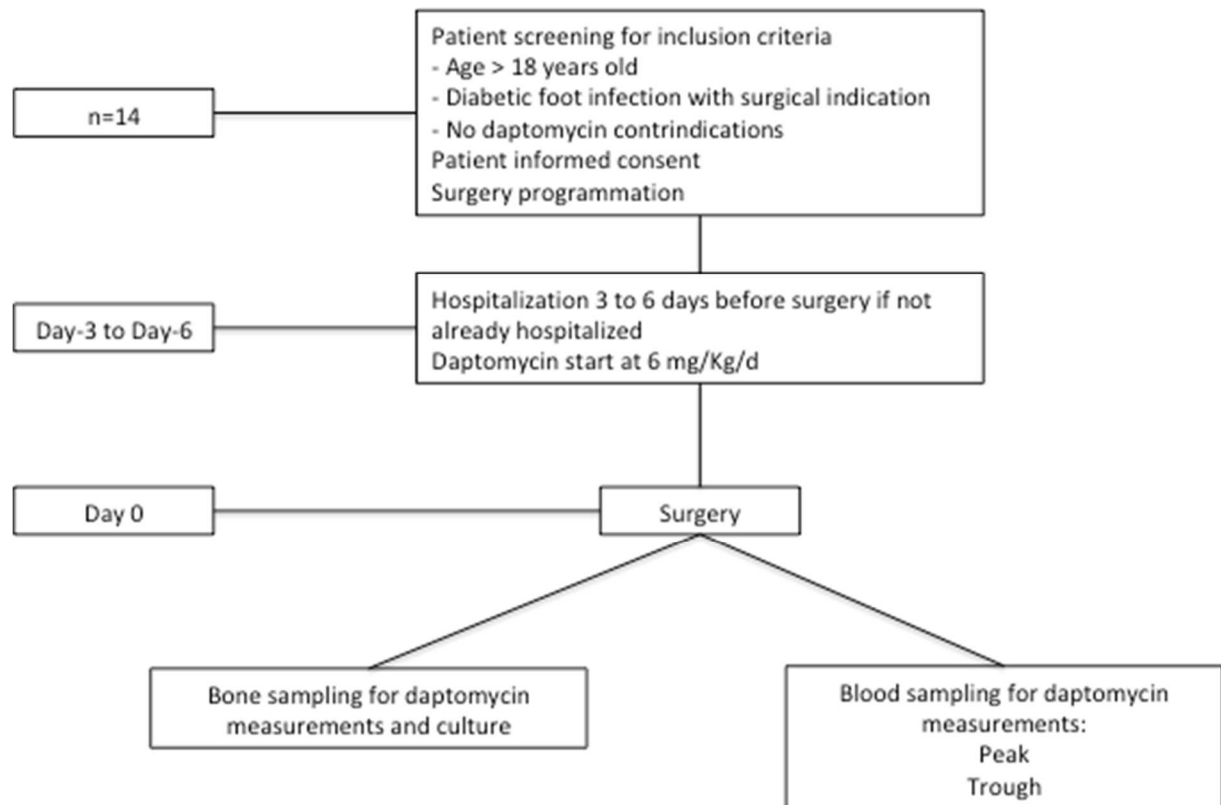
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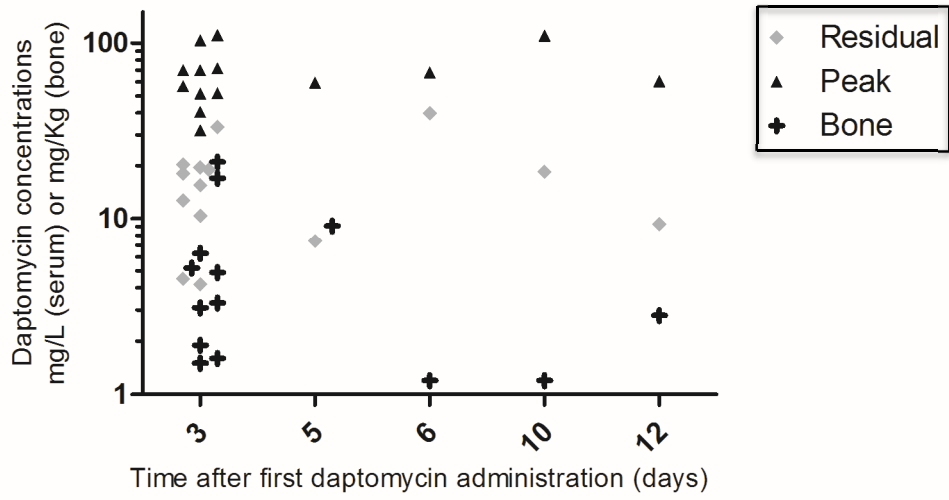
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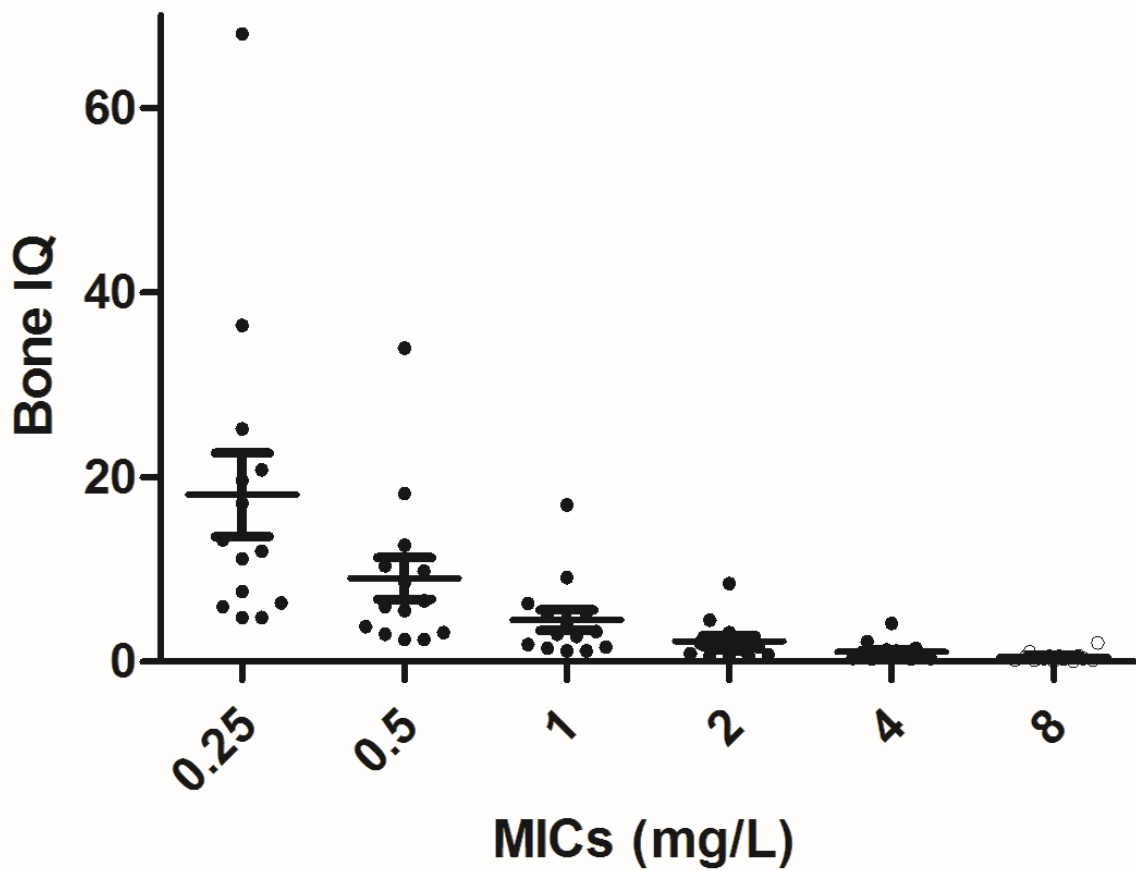
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**Figure 1.** Patients screening and time scale of the study.



**Figure 2.** Daptomycin concentrations in serum at peak, trough, and in bones versus the sampling day after first daptomycin administration



**Figure 3.** Bone inhibitory quotients (IQs) calculated from all our bone concentrations divided each time (each column) by various MICs (0.25 to 8 mg/L). Each of these MICs is of importance for the target bacteria of daptomycin. These various representative MICs are: 0.25 mg/L (MIC<sub>90</sub> for *S. aureus* and MIC<sub>50</sub> for CNS); 0.5 mg/L (MIC<sub>90</sub> for CNS); 1 mg/L (MIC<sub>50</sub> for *E. faecalis*, clinical breakpoints for *S. aureus* and CNS, E-COFF for *S. aureus* and CNS); 2 mg/L (MIC<sub>50</sub> for *E. faecium*); 4 mg/L (Clinical breakpoint for *E. faecalis* and *E. faecium*, E-COFF for *E. faecalis*); 8 mg/L (E-COFF for *E. faecium*)

**Table 1.** Demographic and clinical characteristics of study patients (n=14)

Variable	Patients (n=14)	
<b>Demographics</b>		
	Age (years), median (IQR <sup>1</sup> )	62.6 (56-67)
	Male sex, n (%)	12 (85.7)
	Weight (kg), median (IQR)	101,5 (83-104)
	BMI <sup>2</sup> (kg/m <sup>2</sup> ), median (IQR)	30.3 (28-35.6)
	Charlson comorbidity index, median (IQR)	3 (2-4)
	Diabetes mellitus, n (%)	14 (100)
	Peripheral arteriopathy, n (%)	12 (85.7)
	Peripheral neuropathy, n (%)	12 (85.7)
	Ischemic cardiomyopathy, n (%)	6 (42.8)
<b>Foot clinical presentation</b>		
	Erythema, n (%)	9 (64.3)
	Purulent discharge, n (%)	7 (50)
	Local tenderness or pain, n (%)	8 (57.1)
	Local abscess, n (%)	6 (42.9)
	Necrosis, n (%)	9 (64.3)
	Acute presentation, n (%)	9 (64.3)
<b>Biological parameters</b>		
	Urea, (mmol/L), median (IQR)	6.45 (4.9-9.7)
	Creatinine (μmol/L), median (IQR)	94.5 (65.3-126)
	Albumin (g/L), median (IQR)	37 (35-40)
	Total leucocytes count (10 <sup>9</sup> /ml), median (IQR)	7.74 (6.9-9.9)
	C reactive protein (mg/L), mean (IQR)	40 (17-108)
<b>Microbiological findings in the bone</b>		
	Methicillin-sensitive <i>S. aureus</i> , n (%)	4 (28.6)
	Methicillin-resistant <i>S. aureus</i> , n (%)	3 (21.4)
	Methicillin-sensitive CoNS <sup>3</sup> , n (%)	1 (7.1)
	Methicillin-resistant CoNS, n (%)	4 (28.6)
	<i>Enterococcus</i> sp., n (%)	2 (14.3)
	<i>Streptococcus</i> sp., n (%)	2 (14.3)
	Gram negative bacilli, n (%)	5 (35.7)
	<i>Pseudomonas</i> sp., n (%)	2 (14.3)
	Anaerobic, n (%)	7 (50)
<b>Antibiotic treatment</b>		
	Daptomycin duration (days), median (IQR)	4 (4-6)
	Daptomycin, n (%)	14 (100)
	Piperacillin/tazobactam, n (%)	10 (71.4)
	Amoxicillin/clavulanate, n (%)	1 (7.1)
<b>Surgical treatment</b>		
	Transmetatarsal amputation, n (%)	10 (71.4)
	Transphalangeal amputation, n (%)	2 (14.3)
	Transtibial amputation, n (%)	2 (14.3)

1 IQR, interquartile range, Q<sub>1</sub>-Q<sub>3</sub>

2 BMI, body mass index

3 CoNS, coagulase negative staphylococci

N° patient	Total number of daptomycin administration	n=Number of daptomycin administrations before serum concentration determination	Serum daptomycin concentrations (mg/L)		Time between last daptomycin administration and bone biopsies (hours)	Bone daptomycin concentrations (mg/Kg)	Bone IQ					
			Peak	Trough			MICs (mg/L)					
							0.25	0.5	1	2	4	8
1	4	3	70.1	18.1	3.7	4.9	37,2	18,6	9,3	4,7	2,3	1,2
2	4	3	56.9	33.3	7.6	5.2	39,5	19,8	9,9	4,9	2,5	1,2
3	11	10	109.9	18.5	15.1	1.2	9,1	4,6	2,3	1,1	0,6	0,3
4	4	3	110.9	19.6	10.7	1.6	12,2	6,1	3,0	1,5	0,8	0,4
5	7	6	68.1	39.9	19.3	1.2	9,1	4,6	2,3	1,1	0,6	0,3
6	4	3	70.0	19.0	6.5	6.3	47,9	23,9	12,0	6,0	3,0	1,5
7	4	3	103.5	20.3	8.5	17.0	129,2	64,6	32,3	16,2	8,1	4,0
8	4	3	51.8	12.7	3.7	1.9	14,4	7,2	3,6	1,8	0,9	0,5
9	4	3	71.9	10.4	19.3	1.5	11,4	5,7	2,9	1,4	0,7	0,4
10	6	5	59.4	7.4	3.4	9.1	69,2	34,6	17,3	8,6	4,3	2,2
11	4	3	51.7	4.2	3.1	3.0	22,8	11,4	5,7	2,9	1,4	0,7
12	4	3	40.5	4.5	21.0	4.3	32,7	16,3	8,2	4,1	2,0	1,0
13	4	3	31.8	15.5	17.0	3.3	25,1	12,5	6,3	3,1	1,6	0,8
14	13	12	60.5	9.3	22.7	2.8	21,3	10,6	5,3	1,4	1,3	0,7

Table2. Daptomycin peak and residual blood concentrations and bone concentrations after n administrations. Calculated Inhibitory Quotients (IQs) according to various MICs.