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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, only limited data are available on its bone penetration in this particular population. The aim of this study was to determine daptomycin bone concentrations in patients with DFI undergoing surgery after multiple daptomycin infusions and to determine bone daptomycin inhibitory quotients (IQs) for the predominant gram-positive species involved in DFI.
Methods: Fourteen adult patients hospitalized with DFI treated with daptomycin and requiring surgical bone debridement and amputation were included in this single-centre prospective study. Daptomycin concentrations in serum and bone were determined by HPLC at steady state. Bone IQs were then calculated according to different minimum inhibitory concentrations (MICs; range 0.25–4 mg/l) that are representative of the main MICs for *Staphylococcus aureus*, coagulase-negative staphylococci (CoNS), and *Enterococcus sp* populations.
Results: Residual and peak concentrations varied from 4.5 mg/l to 39.9 mg/l and from 31.8 mg/l to 110.9 mg/l, respectively. Bone daptomycin concentrations at the moment of surgery varied from 1.2 mg/l to 17 mg/l. Up to a MIC of 1 mg/l, which is the epidemiological cut-off value (ECOFF) and breakpoint value for *S. aureus* and CoNS, all bone daptomycin IQs were positive. The highest bone IQs were observed with *Staphylococcus* species. Calculated bone IQs for *Enterococcus* species were often weak at MIC values near the ECOFF.
Conclusions: Daptomycin penetrates bone well 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*.

Introduction

Daptomycin is a cyclic lipopeptide antibiotic with rapid and concentration-dependent bactericidal activity against gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (with or without increased vancomycin minimum inhibitory concentration (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, *S. aureus* bacteremia, and complicated skin and soft tissue 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 has been 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 the USA and EU-CORE in Europe, daptomycin usage was analysed in 11 557 patients, of whom 8.6% were treated for osteomyelitis, with or without

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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 dosages of this molecule, up to 12 mg/kg, but also by 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. They used a microdialysis probe implanted into the metatarsal bone and soft tissues during surgery (Traunmüller et al., 2010a). The authors showed that the bone/plasma area under the curve (AUC) of daptomycin concentration was 1.08 in patients with DFI and osteomyelitis, after four to five injections of a 6 mg/kg daptomycin regimen. In a second study conducted by Montange et al. in 2014, daptomycin bone penetration reached a much lower level (Montange et al., 2014). The authors studied daptomycin bone concentrations after a single intravenous dose infusion of 8 mg/kg in patients undergoing 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*. The results of those studies led to the same conclusion, but might appear conflicting regarding the daptomycin concentration level achieved in bone.

The objective of the present study was to determine daptomycin bone concentrations in 14 patients with a DFI who underwent bone resection surgery after multiple daptomycin infusions and to determine daptomycin bone inhibitory quotients (IQs) for gram-positive species considering their respective epidemiological cut-off values (ECOFFs), 90% and 50% MICs (MIC_{90}, MIC_{50}), and clinical breakpoints according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (EUCAST, 2019).

Materials and methods

Setting

This single-centre prospective study was conducted in Strasbourg University Hospital from 2012 to 2018. The study protocol was approved by the local ethics committee 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 to entry into the study. This study was also registered at clinicaltrial.gov under number NCT01306825.

Study population and patient flow chart

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

Drug administration

Daptomycin was administered intravenously by bolus injections of 6 mg/kg over 30 min, once daily as recommended by the manufacturer. Patients received at least 3 days of 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 sample were collected. The peak concentration was measured in blood 1 h after the end of a daptomycin infusion. For residual dosage, blood was collected at 24 h, 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 a sterile container, and immediately transported to the laboratory for culture and storage.

Microbiology

Bacterial strain identification was assessed by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) and antimicrobial susceptibility testing was performed according to the EUCAST recommendations (EUCAST, 2019).

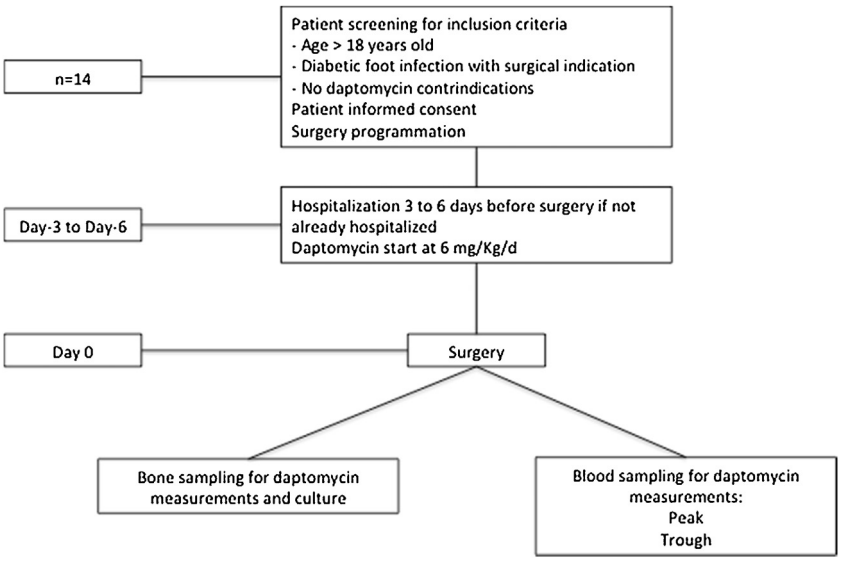

Figure 1. Patients screening and time scale of the study.

HPLC assay of daptomycin

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

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

For bone concentrations, after sampling, the bone tissue was carefully rinsed with sterile water to discard any blood contamination, dried, weighed, and stored at −80 °C until analysis. The day of analysis, frozen bone samples were placed at room temperature to defrost. They were then finely hand-crushed using a pestle and mortar. Five hundred microlitres 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 conducted to ensure that 24 h was long enough to completely extract the antibiotic from the powder.

Daptomycin was then assayed in the supernatant of this mixture after a 5 min centrifugation at 10 000 × *g*. Results were expressed in micrograms of daptomycin per gram of bone.

Chromatographic conditions

Twenty microlitres of the supernatant (serum or bone) were injected into a Prominence HPLC system (Shimadzu USA Manufacturing Inc., Canby, OR, USA) comprising an LP-20AT pump and a SPD-20A UV–visible detector. A Rheodyne model 7725i manual sample injector (Rheodyne, Rohnert Park, CA, USA) was used with a 20-µl loop. Chromatographic separation was achieved on a reversed-phase C_{18} 150 × 4.6-mm, 3-µm Uptisphère 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. LC Solution Shimadzu software (Shimadzu France, Champs sur Marne, France) was used to acquire and process 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 µg/ml to 500 µg/ml, with a mean correlation coefficient of 0.9988. Quality control standards were prepared at final concentrations of 1.0 µg/ml, 50.0 µg/ml, and 250 µg/ml. Inter-day and intra-day accuracies of the method ranged from 92.0% to 103% and from 93.8% to 101%, respectively. The precision values (coefficients of variation) ranged from 0.98% to 3.58% for the intra-day precision and from 2.66% to 3.03% for the inter-day precision.

Results

Patients and isolates

Fourteen patients with DFI were included in the study. The demographic and clinical characteristics of the study patients are detailed in Table 1. The mean duration of daptomycin treatment before the surgical procedure was 4.4 days (range 3–12 days), with a minimum length of 3 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 (CoNS) in five patients (35.7%), methicillin-resistant *S. aureus* (MRSA) in three (21.4%), and methicillin-susceptible *S. aureus* (MSSA) in four (28.6%). Other pathogens were anaerobic bacteria, *Enterococcus sp*, *Streptococcus sp*, *Pseudomonas sp*, and *Enterobacteriaceae*.

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

Variable	Patients ($n = 14$)
Demographic characteristics	
Age (years), median (IQR)	62.6 (56–67)
Male sex, *n* (%)	12 (85.7)
Weight (kg), median (IQR)	101.5 (83–104)
BMI (kg/m^2), 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)
Foot clinical presentation	
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)
Biological parameters	
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 leucocyte count (10^9/ml), median (IQR)	7.74 (6.9–9.9)
C-reactive protein (mg/l), median (IQR)	40 (17–108)
Microbiological findings in the bone	
MSSA, *n* (%)	4 (28.6)
MRSA, *n* (%)	3 (21.4)
Methicillin-sensitive CoNS, *n* (%)	1 (7.1)
Methicillin-resistant CoNS, *n* (%)	4 (28.6)
Enterococcus sp, *n* (%)	2 (14.3)
Streptococcus sp, *n* (%)	2 (14.3)
Gram-negative bacilli, *n* (%)	5 (35.7)
Pseudomonas sp, *n* (%)	2 (14.3)
Anaerobic, *n* (%)	7 (50)
Antibiotic treatment	
Daptomycin duration (days), median (IQR)	4 (4–6)
Daptomycin, *n* (%)	14 (100)
Piperacillin–tazobactam, *n* (%)	10 (71.4)
Amoxicillin–clavulanate, *n* (%)	1 (7.1)
Surgical treatment	
Transmetatarsal amputation, *n* (%)	10 (71.4)
Transphalangeal amputation, *n* (%)	2 (14.3)
Transtibial amputation, *n* (%)	2 (14.3)

IQR, interquartile range (Q_1–Q_3); BMI, body mass index; CoNS, coagulase-negative staphylococci; MSSA, methicillin-sensitive *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*.

Daptomycin concentrations and inhibitory quotients

Peak and residual daptomycin serum concentrations and daptomycin bone concentrations measured in the patients are shown in Figure 2 and detailed in Table 2. Serum residual and peak concentrations were measured on the day of surgery after various numbers of daptomycin administrations: three administrations ($n = 10$), four administrations ($n = 1$), five administrations ($n = 1$), 10 administrations ($n = 1$), and 14 administrations ($n = 1$).

Residual and peak serum concentrations varied from 4.2 mg/l to 39.9 mg/l and from 31.8 mg/l 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 3.1–22.7 h). Bone daptomycin concentrations varied from 1.2 mg/kg to 17 mg/kg.

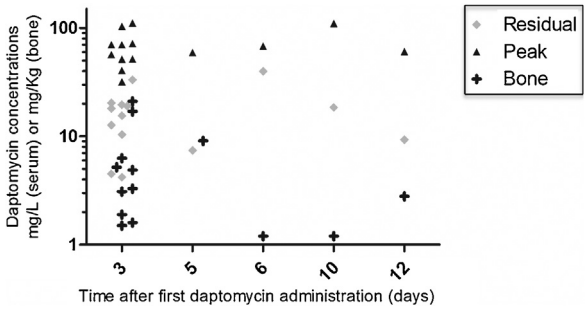

Figure 2. Daptomycin concentrations in serum at peak, trough, and in bones versus the sampling day after first daptomycin administration.

Bone IQs (bone concentration/MIC) were then calculated according to different MICs (range 0.25–8 mg/l) that are representative of the main MICs of *S. aureus*, CoNS, and *Enterococcus sp* populations (Table 1 and Figure 3).

Up to a MIC of 2 mg/l, which is above the ECOFF and breakpoint values for *S. aureus* and CoNS, all bone IQs were positive. At the *Enterococcus faecalis* ECOFF value (4 mg/l), half of bone IQs were positive. At the *Enterococcus faecium* ECOFF 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 lower extremity amputation (Markakis et al., 2016). Apart from appropriate wound care, antibiotic therapy is required when the infection penetrates the fascia, muscle, joint, or bone (Lipsky et al., 2012). As 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 for this indication, only limited data are available on daptomycin bone penetration. For this reason, the present study aimed to determine bone concentration in 14 patients with DFI.

The study results showed that despite the low vascularity associated with DFI, daptomycin penetrates bone well in patients treated for this infection and reached a sufficient concentration in the bone. The residual and peak concentrations were found to be somewhat equivalent to those observed in other studies in this particular population, making the daptomycin bone concentrations relevant (Traunmüller et al., 2010a; Montange et al., 2014).

The bone IQ was then calculated, 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 the MICs of daptomycin for the major gram-positive bacteria involved in DFI, inhibitory quotients (IQs) are often at a level likely to be compatible with therapeutic efficacy. This is especially true for *Staphylococcus* species. If considering *S. aureus*, an intravenous dose of 6 mg/kg allowed bone IQs to always be >4 and often >10 at MIC equivalent to the MIC_{90} of this species (Gallon et al., 2009; Jones et al., 2017). By comparison, bone IQs for vancomycin, teicoplanin, and linezolid at their respective MIC_{50} 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). Bone daptomycin IQs remain positive up to a MIC of 1 mg/l, which is the current EUCAST clinical breakpoint for *S. aureus* and CoNS (EUCAST, 2019). Again, bone IQs at the considered CoNS MIC_{90} 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 regimen of 6 mg/kg allowed bone daptomycin concentrations that could be effective against *Staphylococcus* infections and at least equivalent to other drugs classically used for this indication. Besides, as many studies have shown that daptomycin can be used safely at higher dosages of up to 12 mg/kg, daptomycin seems to be of particular interest for the treatment of staphylococcal DFI (Senneville et al., 2016).

However, when considering *Enterococcus sp*, daptomycin bone IQs were often weak. If we consider these species at their own ECOFF, which is the MIC that distinguishes organisms without and with phenotypically expressed resistance mechanisms, bone IQs were <1 most of the time, indicating that daptomycin may not be relevant for the treatment of *Enterococcus sp* DFI. The utilization of a higher dosage might improve bone IQs, but more research is needed to draw conclusions.

This daptomycin bone penetration study was conducted according to a 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 3–12 administrations). However, since all patients received at least three administrations of daptomycin, all

Table 2
Daptomycin peak and residual blood concentrations and bone concentrations after *n* administrations. Calculated inhibitory quotients (IQs) according to various minimum inhibitory concentrations (MICs).

Patient number	Total number of daptomycin administrations	Number of daptomycin administrations before serum concentration determination (*n*)	Serum daptomycin concentrations (mg/l)		Time between last daptomycin administration and bone biopsies (hours)	Bone daptomycin concentrations (mg/kg)	Bone IQ					
							MIC (mg/l)					
			Peak	Trough			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

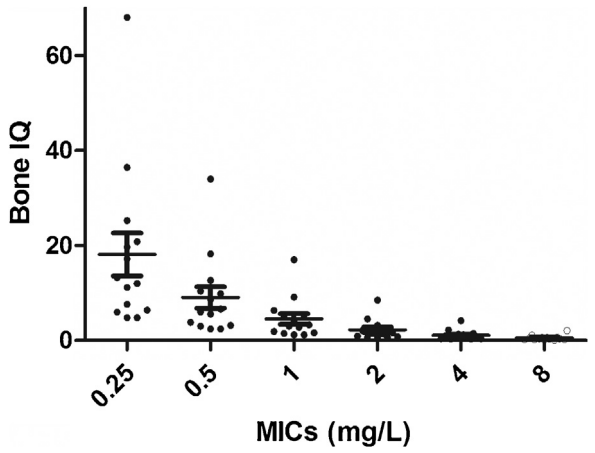

Figure 3. Bone inhibitory quotients (IQs) calculated from all our bone concnetrations divided each time (each column) by various MICs (0.25 to 8 mg/L). Each of these MICs is of importance for the target bacteria of daptomycin. These various representative MICs are: 0.25 mg/L (MIC_{90} for *S. aureus*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

concentrations were assessed at the steady state. The levels of peak and residual blood concentrations were not correlated with the number of administrations, reflecting the inter-patient variability inherent to the heterogeneity of their recruitment. The same occurs for bone tissue concentrations. Time by time mean calculation for each kind of sample was not relevant due to the small number of patients at each time. Interestingly, some patients had low bone concentrations of daptomycin despite high peak or residual serum concentrations, while other patients had low serum concentrations but 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 were not done at the time of blood sampling, the bone penetration coefficient calculation is irrelevant. As daptomycin is a concentration-dependent drug, the AUC/MIC best describes the efficacy of the dose regimen. However, real clinical practice does not easily allow this approach. The measurement of daptomycin bone concentrations at different times after drug administration is useful when a population pharmacokinetic analysis is performed, but the small number of patients did not allow this to be performed. Hence we chose to calculate bone IQs for each patient, with all the limits that this implies. Nevertheless, the data represent 'real life practice' and even if our choice could be regarded as questionable, the data strongly suggest that daptomycin penetrates bone well in patients treated for DFI.

In summary, daptomycin penetrates bone well 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*.

Funding sources

This work was supported by a grant from Novartis, France (registered at N° 2009-4683).

Ethical approval

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

Conflict of interest

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

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