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A critical view on the current use of daptomycin in Spain: The daptomise study

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ABSTRACT

Background: The Study on the Clinical Use of DAPTOMycin in Spain (DAPTOMISE Study) is a national surveillance program of daptomycin use. The objectives of this study are to evaluate the current variability in daptomycin consumption across the different hospitals and the adequacy of therapy, specially focused on underdosing.

Methods: All adult and pediatric patients who received, at least, one dose of daptomycin in a single week in 98 institutions in Spain were included. The adequacy of daptomycin use was evaluated with respect to the indication, dosage, adjustments after microbiology results, switching to an oral agent and length of treatment.

Results: A total of 615 patients received daptomycin during the study week. The prevalence use was 2.3 patients / 100,000 inhabitants per week, 12.4 patients / 1000 admissions and 9.2 Days of Therapy (DOT) / 1000 hospital stays. These rates varied between hospitals: from 0 to 13.9 patients / 100,000 inhabitants, from 0 to 76.1 patients / 1000 admissions and from 0 to 49.4 DOT / 1000 hospital stays. The most frequent infections were bacteremia (31.6 %) and skin and soft tissue infections (17.9 %). Microbiological results were available in only 65.4 % of infections. The most frequent microorganisms were *Staphylococcus aureus* (192 isolates, of which 87 were resistant to methicillin) and coagulase-negative staphylococci (124 isolates). A total of 136 prescriptions (22.1 %) were underdosed. Dosages < 8 mg/kg were used for 35.6 % of endovascular infections and for 26.2 % of osteoarticular infections. Overall, 57.2 % of prescriptions were not optimal in, at least, one item. Clinical cure rate was 76.1% and mortality attributable to the infection 8.1%.

Conclusion: This is the first registry that identifies the prevalence of use of daptomycin in Spain and shows a high variability in the consumption between the different hospitals. Daptomycin underdosing was present in more than 20 % of cases.

1. Introduction

Daptomycin is a lipopeptide with potent bactericidal activity against most Gram-positive organisms [1]. In adult patients, it is

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only approved for the treatment of complicated skin and soft tissue infections (SSTIs; 4 mg/kg/day), right-sided infective endocarditis (RIE; 6 mg/kg/day) due to *S. aureus*, and bacteremia associated with complicated SSTI or RIE (6 mg/kg/day) [2].

Although more than 15 years has elapsed since daptomycin approval, large discrepancies remain between the dosages recommended in the data sheet and practice guidelines. The latter recommend doses up to 12 mg/kg/day in serious infections, as several in vitro and clinical studies suggest that higher doses may provide improved effectiveness and resistance prevention [3–5]. However, the lack of concordance in the recommendations facilitates frequent underdosing in clinical practice, an issue needing proper analysis to date. Two large registries, Cubicin® Outcomes Registry and Experience (CORE; USA) and European Cubicin® Outcomes Registry and Experience (EU-CORE; Europe, Latin American, and Asia) described the use and clinical outcomes of daptomycin across wide geographical regions [6]. However, these results date back to the period 2004 – 2012, and since then, the use of daptomycin has significantly increased.

In Spain, there is no registry to identify the variability in the use of daptomycin. In this study, we report the prevalence of daptomycin use and its adequacy in a nationwide survey with a special focus on dosages. Secondary objectives comprise the effectiveness and safety outcomes in the source population.

2. Material and methods

2.1. Study design

This was an observational cross-sectional study developed in 98 hospitals in Spain. In order to collect data representative for the Spanish hospital population, the Spanish Society of Hospital Pharmacy (SEFH) extended a personalized invitation to participate to hospital pharmacists distributed throughout Spain.

Centers taking part were invited to include all cases (including neonates and children) receiving daptomycin in a single week. Patients were included in the study if they had received, at least, a single dose of daptomycin, either during hospital admission, in an outpatient clinic or at home. Subsequently, medical records were reviewed until daptomycin discontinuation or hospital discharge, whichever occurred later. Hospital pharmacists entered data in the web-based REDCap® application of the SEFH.

Data collection included characteristics of all participating hospitals and individual patients related data:

(i) The hospital form included the population covered, the number of beds, the number of adult and pediatric admissions and the number of adult and pediatric stays during the inclusion period. We also collected data on whether an antimicrobial stewardship program was available in the hospital, the readiness of a local protocol for the use of daptomycin and the need for prior authorization for its use.
(ii) The registry of patient data included patient demographics, underlying conditions, Charlson comorbidity index, infection site, microbiological confirmed pathogens, source control of infection when applicable, antimicrobial therapy administered before and concomitant to daptomycin, reasons for daptomycin use, dosages of daptomycin treatment, length of daptomycin use, adverse events, and outcomes.

Culture, identification of micro-organisms and susceptibility testing were performed at each participating center according to their own practice.

2.1.1. Calculation of point prevalence

We calculated the prevalence of daptomycin use for the source population using 3 approaches: (i) the number of patients under treatment with at least one dose of daptomycin during the study week per 100,000 inhabitants; (ii) the number of patients under treatment with at least one dose of daptomycin per 1000 admissions; and (iii) the number of days of therapy (DOT) per 1000 hospital stays.

2.1.2. Definitions

Classification of infections was according to the criteria of the US Centers for Disease Control and Prevention (CDC) [7]. We considered clinical cure when patients had no clinical or microbiological evidence of infection at the end of daptomycin treatment. Mortality was divided in two considerations: attributable (if the patient continued to present signs and symptoms related to the infection at the time of death) or non-attributable to the infection. We defined treatment failure as the absence of clinical cure, the presence of recurrence of the infection or attributable mortality.

Investigators took into account the type of infection, patient weight and kidney function to determine the adequacy of daptomycin dosage. We considered *adequate dosages* those between 4 and 8 mg/kg, except for endovascular and osteoarticular infections. In both cases, only dosages between 8 and 12 mg/kg were considered *adequate*, according to the recommendations of current guidelines [8–12]. *Underdose* and *overdose* were considered when the dosages were under or over these ranges respectively, or in case of incorrect adjustment to renal function.

In addition to the adequacy of the dosage, investigators evaluated the indication, adjustment according to microbiological results, switch to an oral alternative when feasible, and duration of treatment. The treatment indication was correct when infection by Gram-positive bacteria (excluding pneumonia) was present or clinically suspected, according to local guidelines and on local susceptibility patterns. The treatment was correctly adjusted to the microbiological results when the antibiotic was adapted to the microorganism identification and antibacterial susceptibility tests. The duration of treatment was adequate if it followed the recommendations of local or international guidelines [8–12].

Daptomycin treatment was considered adequate when all the five previous items (dosage, agent choice, microbiological adjustment, change to oral route when feasible and duration) were correct. An outcome was non-evaluable when investigators were unable to determine the adequacy of treatment because the records did not contain adequate information.

Allocation of adverse events (AEs) was according to the definition of the World Health Organization (WHO) [13]. Serious AEs were defined as drug reactions that required treatment interruption, it they were life-threatening, or led to prolonged hospitalization or caused disability or resulted in death of the patients. Otherwise, AEs were categorized as mild.

2.2. Statistical analysis

We present the qualitative variables with their frequency distribution. Continuous variables are described as median and interquartile range (IQR). Categorical variables were compared using Chi-square test or Fisher's exact test, as appropriate. Continuous variables were compared with Mann-Whitney U-test and Student´s t-test, depending on the distribution. Differences were statistically significant for $P < 0.05$. All tests of statistical significance were two-tailed. We performed the statistical analysis with the software package STATA IC v.14.0.

2.3. Ethics

Research Ethics Committee of Gregorio Marañón University Hospital (Madrid) and the Spanish Agency of Medicines and Medical Devices approved the study protocol (FAR-DAP-2019–01).

3. Results

3.1. Characteristics of the participating hospitals

Ninety-eight Spanish hospitals participated in the study, 98.0% of which were general hospitals. These hospitals cover a total population of 27,002,557 inhabitants, which represents 57 % of the entire Spanish population. These hospitals serve a median of 289,950 inhabitants (IQR 156,386–370,000) and their median number of beds is 412 beds (IQR 241–758).

During the study week, these hospitals had a total of 49,419 admissions (46,191 adults and 3228 children) and 270,354 stays (256,388 adults and 13,966 children). Per hospital, the median number of admissions and stays were 383 (IQR 249–591) and 1905 (IQR 949–3556), respectively.

Overall, 83.7 % of hospitals had an antimicrobial stewardship program, and 51.0% had specific guidelines for the use of daptomycin. For this use, 50.0% of hospitals required prior approval, at least for certain infections (Table 1).

3.2. Prevalence of daptomycin use

Overall, 615 patients received at least one dose of daptomycin during the study week. These patients belonged to 78 of the 98 participating hospitals. The median number of patients per center was 3 (IQR 1–9).

Table 1
Characteristics of the participating hospitals.

No. of hospitals	98
Per type (n, %)	
General hospitals	96 (98.0)
Medium or long-stay centers	2 (2.0)
Hospitals with pediatric units	88 (89.8)
Public	83 (84.7)
Private	15 (15.3)
Geographical area (n, %)	
East[a]	40 (40.8)
Center[b]	24 (24.5)
North[c]	19 (19.4)
South[d]	15 (15.3)
Total population covered	27,002,557
Total No. of beds	51,224
No. of beds per hospital (median, IQR)	412 (241–758)
Total No. of admissions during the study week	46,652
Adult	43,684
Pediatric	2968
Total No. of stays during the study week	247,267
Adult	234,351
Pediatric	12,916
Hospitals with available antimicrobial stewardship program (n, %)	82 (83.7)
Hospitals with specific guidelines for the use of daptomycin (n, %)	50 (51.0)
Hospitals that require prior approval for the use of daptomycin (n, %)	49 (50.0)

IQR, interquartile range
[a] It includes the following Autonomous Communities: Aragon, Catalonia, Community of Valencia, Murcia and Balearic Islands.
[b] It includes the following Autonomous Communities: Castilla y Leon, Castilla la Mancha, Extremadura and Madrid.
[c] It includes the following Autonomous Communities: Galicia, Asturias, Cantabria, the Basque Country, Navarra and La Rioja.
[d] It includes the following Autonomous Communities: Andalusia and Canary Islands.

Table 2
Prevalence of daptomycin use in the study population.

Prevalence rate	Overall (n = 98)	East (n = 40)	Center (n = 24)	North (n = 19)	South (n = 15)
No. Patients / 100,000 inhabitants	2.3	1.8	2.6	3.4	1.3
No. Patients / 1000 admissions	12.4	10.9	12.7	16.4	8.8
DOT / 1000 hospital stays	9.2	8.2	9.4	10.8	8.4

DOT, days of therapy.

The prevalence of daptomycin use was 2.3 patients / 100,000 inhabitants per week, corresponding to 12.4 patients / 1000 admissions and, in terms of DOT, to 9.2 DOT / 1000 hospital stays. These rates varied between hospitals: from 0 to 13.9 patients / 100,000 inhabitants, from 0 to 76.1 patients / 1000 admissions and from 0 to 49.4 DOT / 1000 hospital stays. See Table 2 for the description of the geographic distribution of the prevalence rates.

The prevalence of daptomycin use was lower in those centers whose prescriptions required prior approval by the local antimicrobial stewardship team (10.3 vs 14.1 patients / 1000 admissions, $P < 0.001$).

3.3. Demographic and clinical characteristics of the patients

Table 3 displays the demographic and baseline characteristics of the 615 patients receiving daptomycin.

Patient age ranged from 14 to 98 years [median 70 years; IQR 57–78 years] and 64.1 % were male. The most common underlying condition was cardiovascular disease (53.0 %), followed by diabetes mellitus (32.7 %), chronic kidney disease (26.0 %) and chronic pulmonary disease (23.4 %). The median of the Charlson comorbidity index was 3 (IQR: 1–5). The majority of patients receiving daptomycin belonged to Surgery and Orthopedics (28.9 %), Internal Medicine (15.6 %) and Critical Care (11.5 %) departments. Only 3.7 % of patients received daptomycin in the outpatient setting.

3.3.1. Indications of daptomycin and microbiology

Prescription of daptomycin was empirical in 299 patients (48.6 %) and targeted in 299 patients (48.6 %). In 17 patients (2.7 %) daptomycin was considered as prophylaxis, either medical or surgical. Type of primary infection and causative micro-organisms are shown in Table 4. The most frequent infections were bacteremia (31.6 %), skin and soft tissue infections (SSTI) (17.9 %), infective endocarditis (IE) (13.5 %) and osteoarticular infections (13.4 %).

Overall, 55.4 % of patients had received prior antimicrobial treatment for the same infection. The most common prior antibiotic therapies were vancomycin (8.8 %), meropenem (7.5 %), amoxicillin/clavulanate (6.7 %), piperacillin/tazobactam (5.8 %) and linezolid (5.0 %). The main reasons for initiation of daptomycin were: first-line of treatment according to physician criterion (44.5 %), microbiological adjustment (21.5 %), failure of previous treatment (17.2 %), and toxicity of previous treatment (kidney damage –2.8 %-, myelotoxicity –2.0 %-). Overall, 77.4 % patients received concomitant antibiotic therapy with daptomycin. Antibiotic association most commonly prescribed were piperacillin/tazobactam (30; 4.9 %) and meropenem (29; 4.7 %).

The median follow-up period was 19 days (IQR 10–37). At the end of this period, microbiological results were available in 391 patients (65.4 % of infections). Of these, 370 (94.6 %) were caused by a single microorganism. *S. aureus* was the most frequently isolated microorganism (192 microbiological isolates, of which 87 were resistant to methicillin), followed by coagulase-negative staphylococci (CoNS) (124 isolates) and *Enterococcus* spp. (56 isolates).

Table 3
Baseline patient characteristics and treatment (N = 615).

Baseline patient characteristics[a]	
Age (years), median (IQR)	70 (57–78)
Pediatric	4 (0.6)[b]
Male sex	394 (64.1)
Body weight (kg), median (IQR)	74 (65–83)
Underlying diseases	
Cardiovascular disease	326 (53.0)
Diabetes mellitus	201 (32.7)
Chronic kidney disease	160 (26.0)
Chronic pulmonary disease	144 (23.4)
Solid-organ malignancy	117 (19.0)
Liver disease[c]	66 (10.7)
A	36 (5.8)
B	22 (3.6)
C	8 (1.3)
Hematological malignancy	51 (8.3)
Solid-organ transplant	22 (3.6)
HIV infection	16 (2.6)
Bone marrow transplant	14 (2.3)
Immunosuppresive therapy (previous month)	124 (20.2)
Charlson comorbidity index, median (IQR)	3 (1–5)
Hospitalization Unit	
Surgery and Orthopedics	178 (28.9)
Internal Medicine	96 (15.6)
Critical Care	71 (11.5)
Infectious Diseases	51 (8.3)
Hematology	34 (5.5)
Emergency Department	32 (5.2)
Cardiology	31 (5.0)
Home Hospitalization	23 (3.7)
Nephrology	20 (3.3)
Oncology	19 (3.1)
Other	60 (9.8)
Treatment	
Prior antibiotic therapy to daptomycin	341 (55.4)
Type of daptomycin treatment	
Empirical	299 (48.6)
Targeted	299 (48.6)
Prophylaxis	17 (2.8)
Main reasons for daptomycin use	
First line therapy according to physician criteria	274 (44.5)
Microbiological adjustment	132 (21.5)
Previous clinical or microbiologic failure	106 (17.2)
Renal impairment	17 (2.8)
Facilitate patient discharge	16 (2.6)
Allergy to other antibiotics	13 (2.1)
Myelotoxicity	12 (2.0)
Other/unknown	45 (7.3)
Daptomycin dosage	
< 6 mg/kg/day	76 (12.4)
6–7.9 mg/kg/day	178 (28.9)
8–9.9 mg/kg/day	121 (19.7)
10–12 mg/kg/day	207 (33.7)
> 12 mg/kg/day	2 (0.3)
No data	31 (5.0)

[d]Ninety-eight (15.9%) patients received daptomycin every 48 h due to the presence of renal failure.
HIV, human immunodeficiency virus; IQR, interquartile range.
[a] Data are n (%) unless otherwise stated.
[b] Four patients aged between 14 and 17 years old.
[c] Child-Pugh score.

3.4. Daptomycin therapy and appropriateness of use

The median duration of daptomycin treatment was 11 days (IQR 5–20). Daptomycin doses ranged from 3 mg/kg/day to 14 mg/kg/day. The regimen most commonly prescribed was 10.0 mg/kg/day (n = 179; 29.1 %). Overall, 53.7 % of patients received doses ≥ 8 mg/kg/day and in 12.4 % they were < 6 mg/kg/day (Table 3). Daptomycin doses according to the infection type are shown in Fig. 1.

3.4.1. Inadequacy of daptomycin dosage

Overall, 204 prescriptions (33.2 %) were misdosed (22.1 % underdosed and 11.1 % overdosed). Adequacy of dosage by type of infection is detailed in Fig. 2. The most commonly underdosed prescriptions corresponded to the following type of infections: bacteremia (36.8 %), other endovascular infections (32.0 %) and osteoarticular infections (27.3 %). Overall, dosages < 8 mg/kg were used in 35.6 % of 307 endovascular infections and in 26.2 % of 80 osteoarticular infections. Furthermore, 25 % of the 92 patients with a creatinine clearance < 30 ml/min did not receive the corresponding reduced dose of daptomycin.

3.4.2. Other aspects of inadequacy

Table 5 summarizes all reasons for inappropriate prescriptions and the rate of inadequacy by main prescribing departments. Overall, 352 prescriptions (57.2 %) were considered inappropriate for, at least, one item. Underdosing was the most frequent reason for inadequacy (22.1 %), followed by absence of oral sequential antibiotic therapy (16.3 %) and incorrect microbiological adjustment (15.8 %).

The Emergency Department had the highest rate of inadequacy (75.0 %), and the Cardiology Department the lowest (35.5 %). The remaining departments had a similar rate of inadequacy, ranging from 54.2 % to 61.8 %.

3.5. Clinical outcomes

Clinical cure was achieved in 447 of 587 evaluable patients (76.1 %). Mortality index in patients receiving daptomycin was 13.8 % and mortality index attributable to infection was 8.1 %. Fig. 3 shows the clinical outcomes according to the type of infection. Clinical cure rates ranged from 53.8 % to 90.9%. The infection with the highest attributable mortality rate was IE (19.8 %).

Clinical cure rates according to the microorganism were significantly lower for *E. faecium* (58.5 %) and methicillin-resistant *S. aureus* (MRSA) (78.2 %), compared to methicillin-sensitive *S. aureus* (MSSA) (84.9 %), CoNS (90.6 %), *E. faecalis* (90.9 %) and *Streptococcus spp.* (93.3 %).

There was a non-significant trend towards treatment failure among those patients with endovascular infections who were underdosed compared to those who received adequate dosage (Fig. 4). These increases in treatment failure were 26.3% in patients with other endovascular infections (30.8 % vs 57.1 %, P = 0.251), 4.7 % in IE (28.6 % vs 33.3 %, P = 0.720) and 3.3 % in bacteremia (10.8 % vs 14.1 %, P = 0.528). The Table S1 (Supplementary material) describes the mortality index attributable to infection for each range of daptomycin dosage.

Early discontinuation of daptomycin was observed in 20.2% of patients. The most frequent reasons for interruption were the need of microbiological adjustment (13.6%), treatment failure (2.3%), AE related to daptomycin treatment (1.0%) and the need to switch to an oral alternative to facilitate patient discharge (1.0%).

3.5.1. Safety and tolerability

Overall, 3.7% of patients reported serious AEs. The most frequently reported AEs were the increase of creatine phosphokinase (CPK) levels more than 5 times the upper limit of normal (1.8 %), exanthema (0.7 %), low platelet count (0.5 %), anemia (0.3 %), eosinophilia (0.3 %) and renal toxicity (0.3 %). The prevalence of serious AEs were similar among patients treated with doses ≥ or < 8 mg/kg (3.1 % and 4.4 %, respectively -P = 0.503-).

Weekly monitoring of CPK was performed in only 27.1 % of patients treated with daptomycin for a period longer than 7 days. In these patients, the median increase in CPK was 38 U/L (IQR 11–118).

Table 4
Type of primary infection, type of treatment and causative micro-organisms[a].

	n (%)	Empirical treatment	Targeted treatment	MSSA	MRSA	CoNS	*Enterococcus faecalis*	*Enterococcus faecium*	*Streptococcus spp.*	Other	Negative culture[b]
Endovascular infections											
Bacteremia	189 (31.6)	36 (19.0)	153 (80.9)	47	46	65	8	13	4	6	0 (0.0)
Endocarditis	81 (13.5)	36 (44.4)	45 (55.6)	21	11	17	1	2	1	2	13 (16.0)
Pacemaker infection	11 (1.8)	4 (36.4)	7 (63.6)	2	2	1	1	0	0	2	1 (9.1)
Other endovascular infection	26 (4.3)	21 (80.8)	5 (19.2)	1	3	2	1	0	1	1	11 (42.3)
Skin, soft tissue, bone and joint infections											
SSTI	107 (17.9)	75 (70.1)	32 (29.9)	16	14	7	6	3	4	4	33 (30.8)
Osteoarticular infection	80 (13.4)	44 (55.0)	36 (45.0)	13	6	24	1	1	3	6	14 (17.5)
Osteomyelitis	19 (3.2)	10 (52.6)	9 (47.4)	3	3	3	0	0	1	0	3 (15.8)
Other infections											
Fever without source	32 (5.4)	32 (100)	0 (0.0)	0	1	3	1	1	0	0	16 (50.0)
Intra-abdominal infection	28 (4.7)	21 (75.0)	7 (25.0)	1	0	1	1	10	1	0	9 (32.1)
Urinary tract infection	16 (2.7)	12 (75.0)	4 (25.0)	1	0	0	2	4	0	0	3 (18.8)
Unknown	9 (1.5)	8 (88.9)	1 (11.1)	0	1	1	0	0	0	0	5 (55.6)
Overall	**598 (100)**	**299 (50.0)**	**299 (50.0)**	**105**	**87**	**124**	**22**	**34**	**15**	**21**	**108 (18.1)**

SSTI, skin and soft tissue infection.
[a] No data shown for 17 (2.8%) patients who received daptomycin as prophylaxis, either medical or surgical.
[b] Microbiological results were not available in 82 patients (13.7% of patients).

4. Discussion

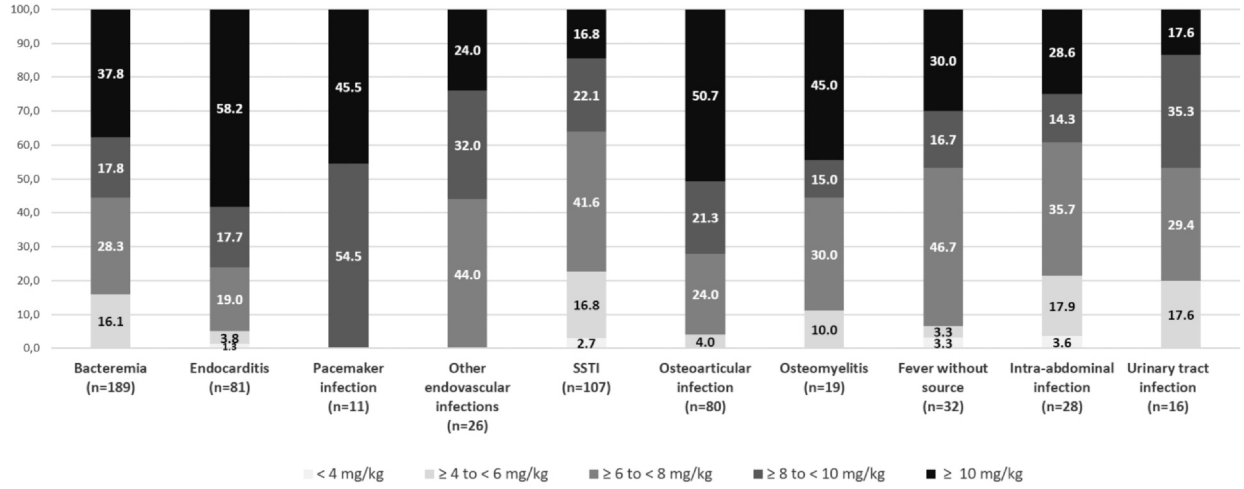
Here we report the first surveillance program of daptomycin use throughout Spain. We identified a national prevalence of daptomycin use of 12.4 patients / 1000 admissions and 9.2 DOT / 1000 stays, although we found a high variability in these rates between the different hospitals. We also observed a trend to use higher doses of daptomycin compared to the previous two large international registries [6], although underdosing of daptomycin is still common for some serious infections. In particular, one third of endovascular infections were treated with daptomycin doses ≤ 8 mg/kg.

To date, no study has described the quantity and quality of daptomycin use in Spain, despite its increase in recent years and the current discrepancies between the recommendations provided in the data sheet and guidelines. Only two regions, Catalonia and Andalusia, has reported in-hospital consumption of daptomycin with a standardized methodology, using the Defined Daily Doses (DDD), with variable results. Catalonia reported a consumption of 14.2 DDD per 1000 stays in 2017 (later data are not available) whereas Andalusia only reported 7.3 DDD per 1000 stays in 2019 [14,15].

It is noteworthy the high differences in consumption of daptomycin between centers of the same complexity. Among 41 hospitals with more than 500 beds, the prevalence of daptomycin use ranged from 0 to 76.1 cases per 1000 admissions. In particular, we observed lower daptomycin consumption in those hospitals where daptomycin use required prior approval by the local antimicrobial stewardship team (10.3 vs 14.1 patients / 1000 admissions, P < 0.001).

In our study, 31 % of patients received daptomycin for the treatment of infections other than endovascular and SSTI, being osteoarticular infection the most prevalent off-label indication (13 %). In 7 % of the cases, daptomycin use was for the treatment of intra-abdominal or urinary infections.

We found a trend towards the use of high doses of daptomycin, being the prescription of 10 mg/kg the most common. This contrasts with the results of the previous CORE and EU-CORE registries, in which the majority of patients received 6 mg/kg (45 %) or 4 mg/kg



Dosage mg/kg (Md)	8.0	10.0	9.3	8.0	7.1	9.9	8.9	7.9	7.1	7.2
Days (Md)	11	14	28	7	11	12	15	6	7	6

Fig. 1. Daptomycin dosages and duration of therapy by infection type. SSTI, skin and soft tissue infection; Md, median.

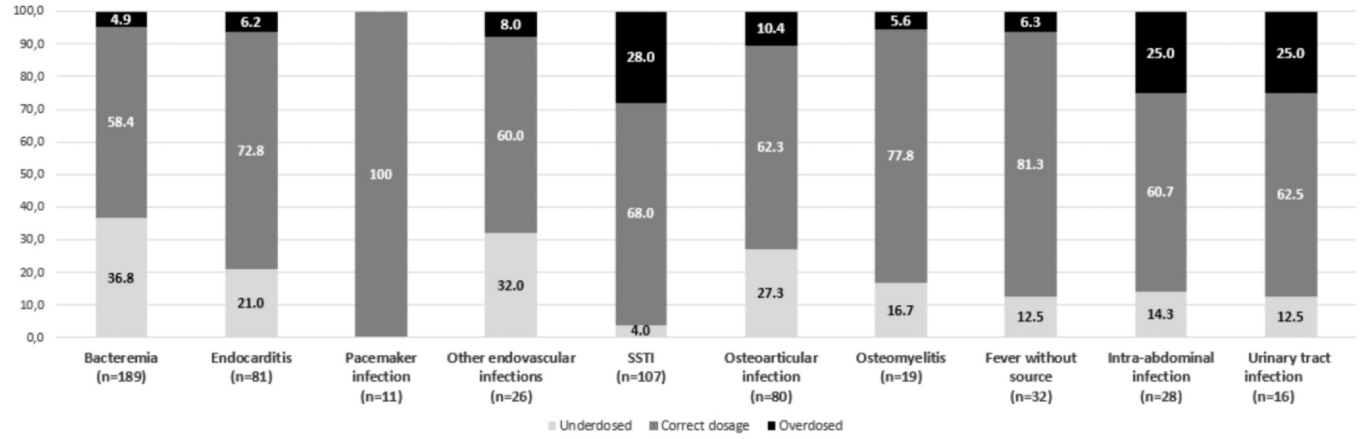


Fig. 2. Adequacy of daptomycin dosages by primary infection. SSTI, skin and soft tissue infection.

Table 5
Inadequacy of prescriptions for type of treatment and main prescribing departments.

	Overall (n = 615)	Prophylaxis (n = 17)	Empirical (n = 299)	Tailored (n = 299)	Surgery and Orthopedics (n = 178)	Internal Medicine (n = 96)	Critical Care (n = 71)	Infectious Diseases (n = 51)	Hematology (n = 34)	Emergency Department (n = 32)	Cardiology (n = 31)
Antibiotic choice	86 (14.0)	2 (11.8)	55 (18.4)	29 (9.7)	26 (14.6)	11 (11.5)	5 (7.0)	10 (19.6)	5 (14.7)	14 (43.8)	2 (6.5)
Dosage	204 (33.2)	5 (29.4)	97 (32.4)	102 (34.1)	57 (32.0)	32 (33.3)	22 (31.0)	14 (27.5)	9 (26.5)	13 (40.6)	8 (25.8)
Underdosing	136 (22.1)	3 (17.6)	52 (17.4)	81 (27.1)	35 (19.7)	24 (25.0)	12 (16.9)	11 (21.6)	4 (11.8)	10 (31.3)	5 (16.1)
Overdosing	68 (11.1)	2 (11.8)	45 (15.0)	21 (7.0)	22 (12.4)	8 (8.3)	10 (14.1)	3 (5.9)	5 (14.7)	3 (9.4)	3 (9.7)
Microbiological adjustment	97 (15.8)	4 (23.5)	69 (23.1)	24 (8.0)	24 (13.5)	15 (15.6)	8 (11.3)	8 (15.7)	10 (29.4)	6 (18.8)	2 (6.5)
Administration route	100 (16.3)	1 (5.9)	52 (17.4)	47 (15.7)	22 (12.4)	18 (18.8)	9 (12.7)	5 (9.8)	12 (35.3)	5 (15.6)	3 (9.7)
Length of therapy	36 (5.9)	0 (0.0)	20 (6.7)	16 (5.4)	9 (5.1)	7 (7.3)	7 (9.9)	3 (5.9)	3 (8.8)	0 (0)	0 (0)
Overall	**352 (57.2)**	**10 (58.8)**	**187 (62.5)**	**155 (51.8)**	**97 (54.5)**	**52 (54.2)**	**40 (56.3)**	**28 (54.9)**	**21 (61.8)**	**24 (75.0)**	**11 (35.5)**

(30 %) [6]. However, 22 % of our patients were still treated with lower dosages than those recommended by current guidelines, being particularly challenging in case of bacteremia (37 %) and osteoarticular infections (27 %).

Using high-dose daptomycin (> 8 mg/kg) in severe gram-positive infections is supported by the dose-related PK/PD target attainment, activity in biofilm-associated infections, and high inoculum killing. An AUC/MIC of less than 666 has been associated with higher mortality [16]. Achieving these PK/PD targets is linearly dose dependent, with 8 mg/kg more likely to achieve target exposures [6,16].

Nowadays, several national and international treatment guidelines recommend high-dose (8–10 mg/kg/day) daptomycin for IE, bacteremia and prosthetic joint infection [8–11]. High-dose daptomycin may also be advantageous in patients with sepsis and high distribution volumes, or if there is a difficulty in achieving adequate local antibiotic concentration at the infection site [17–19].

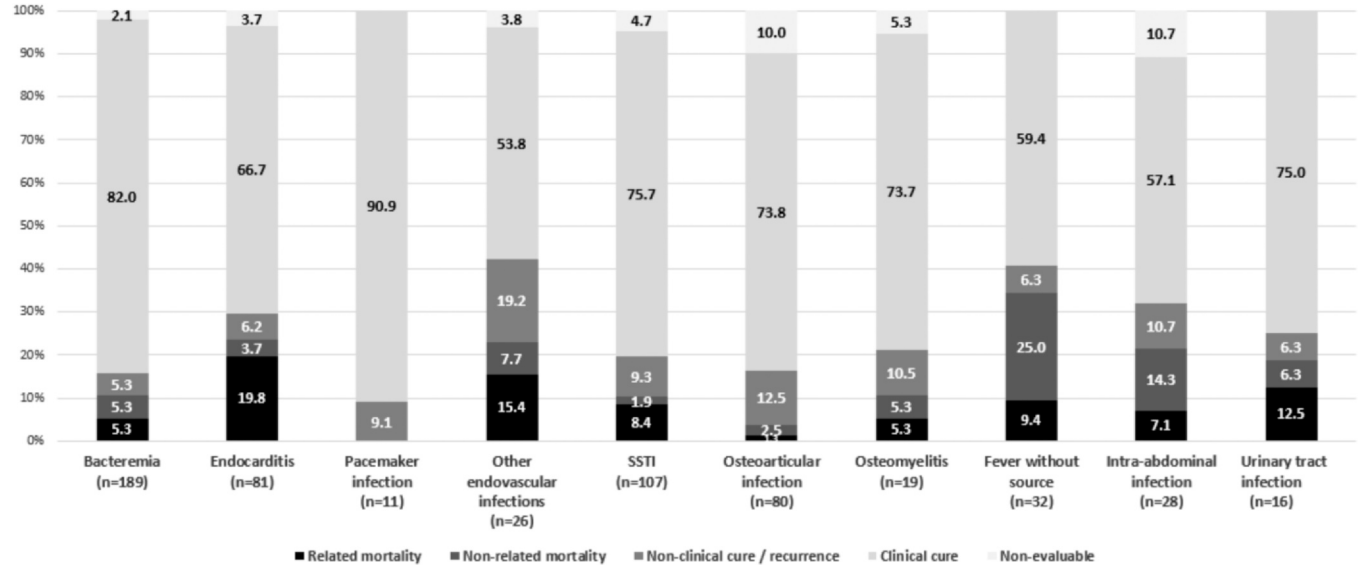


Fig. 3. Clinical outcomes by primary infection type. SSTI, skin and soft tissue infection.

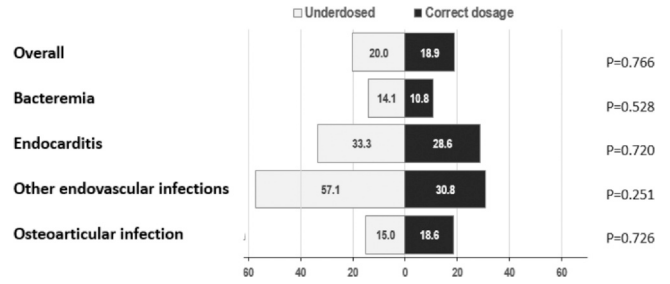


Fig. 4. Treatment failure[a,b] (%) by adequacy of daptomycin dosage. [a]Treatment failure was defined as the absence of clinical cure, the presence of recurrence of the infection or attributable mortality. Patients who experienced non-related mortality (n = 35) and patients with non-evaluable outcomes (n = 28) were excluded from the analysis. [b]Infections with < 5 patients underdosed are not represented.

Russo et al. evaluated daptomycin at different dosages in 327 patients with Gram-positive native valve endocarditis (NVE) or prosthetic valve endocarditis (PVE) [20]. Daptomycin 4–6 mg/kg was associated with higher odds of 30-day mortality among NVE cases (odds ratio [OR] = 2.2; 95% CI = 1.91–4.56; P = 0.02). The combination of EU-CORE and USA-CORE registry [6] data accumulated 798 IE cases showing numerical trends in clinical success rate favouring high-dose daptomycin, ≥ 8 mg/kg/d (84 %) compared with > 6 to < 8 mg/kg/d (71 %) and ≤ 6 mg/kg/d (74 %) [6]. Similarity, in 988 patients with prosthetic joint infection, the clinical success rate was higher in those patients receiving ≥ 8 mg/kg (88 %) compared to > 6 to < 8 mg/kg (80 %) and ≤ 6 mg/kg/d (73 %). In our registry, the percentage of patients with treatment failure was numerically higher in those patients with IE, bacteremia or other endovascular infections that received dosages < 8 mg/kg, although we were unable to find statistically significant differences. However, in addition to the dosage of daptomycin, many other factors may have impact on these outcomes, and this study was not designed to find these inferences.

In our study, the clinical success rate of daptomycin treatment was 76 %, which was very similar to the CORE/EU-CORE registry (77 %). However, we found a lower success rate for complicated SSTI (76 % vs 81 %) and IE (67 % vs 75 %), but a higher rate in case of bacteremia (82 % vs 69 %). In the CORE/EU-CORE registry, the majority of the bacteremic patients received doses < 8 mg/kg. With respect to the pathogen, their clinical success rate was very similar to ours in patients with MSSA (81 % vs 85 % in our study) and MRSA infections (78 % in both registries).

Regarding the safety of daptomycin in our population, we observed a low rate (3.7%) of serious AE, which are consistent with earlier published real-world reports from the USA and Europe [6,21]. In our study, the most frequently reported AE was the increase of blood CPK, although there was no correlation with daptomycin dose. Noteworthy, only in 27 % of patients CPK was monitored weekly, which contrasts with the recommendations of the data sheet. This is of particular concern in patients with kidney failure, whose rate of adequately CPK monitoring was only 31 %.

Finally, it is also noteworthy that despite more than 80 % of Spanish hospitals have an antimicrobial stewardship program, only 51 % have implemented specific guidelines for the use of daptomycin. This registry highlights the need to establish a national surveillance program, for example, through the implementation of a gram-positive infection alert system in hospitals. This system could help to reduce underdosing and to facilitate early adjustment to microbiological results. In our study, only 65 % of patients with daptomycin treatment had positive culture results, contrary to 82 % found in the CORE/EU-CORE registry. We should make the best efforts in the Emergency departments, as they have the highest inappropriate rate, and in Surgery and Orthopedics departments, as they are responsible for the highest daptomycin consumption.

The limitations of the observational design of the study include the subjective assessments of clinical outcomes and treatment adequacy as determined by individual investigators, and the impossibility of establishing a strong relationship between daptomycin dosages and outcomes. The analysis of the effectiveness and safety was carried out on the intention to treat population, not excluding those patients who received a single dose. However, this is the first large Spanish registry whose results mimic real-world clinical use of daptomycin and points to the need to improve prescribing practice.

5. Conclusion

There is a high variability in the use of daptomycin in Spanish hospitals. Underdosing exceeds 20% of prescriptions, being frequent in endovascular and osteoarticular infections. There is an urgent need to establish a national surveillance program that promotes the use of high-doses (≥8 mg/kg) of daptomycin in severe infections and the early adjustment to microbiological results.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Research Ethics Committee of Gregorio Marañón University Hospital (Madrid) and the Spanish Agency of Medicines and Medical Devices.

Declaration of Competing Interest

The authors have no relevant financial or non-financial interests to disclose.

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Contributions of Authors Statement

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by C.R, E.C. and S.D. The first draft of the manuscript was written by C.R and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jiph.2023.05.008.

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