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ORIGINAL RESEARCH

Real-World Treatment of Enterococcal Infections with Daptomycin: Insights from a Large European Registry (EU-CORE)

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ABSTRACT

Introduction: Evolution of antibacterial resistance in pathogenic enterococcal strains poses a growing therapeutic challenge. Daptomycin, a cyclic lipopeptide, exhibits broad antibiotic activity against Gram-positive bacteria.

Methods: The European Cubicin® Outcomes Registry and Experience, a multicenter, retrospective, non-interventional study, recorded clinical outcomes following daptomycin treatment.

Results: Overall, 472 patients (predominantly elderly Caucasian males) were treated for enterococcal infections. Of those, 72.7% received antibiotics prior to daptomycin treatment, whereas 77.1% received other antibiotics concomitantly. Failure of previous therapy, resistant or non-susceptible pathogen, and narrowing of antibiotic therapy were the main reasons for switching to daptomycin treatment. Nosocomial infections comprised 55.8% of the cohort. Bacteremia (29.9%), complicated skin and soft tissue infection (29.2%) and endocarditis (12.3%) were the most common primary infections. Clinical success was achieved in 77.1% of patients, with similar success rates across all primary infection categories. The overall clinical success rate was marginally higher (82.5% vs 74.6%, $p = 0.09$) with daptomycin use as first-line versus second-line therapy. Patients receiving higher doses of daptomycin exhibited the highest clinical success rates (85.7% for ≥8 mg/kg/day vs 75.8% for <8 mg/kg/day, $p = 0.08$). While 81 (17.2%) patients reported at least one adverse event (AE), only 11 (2.3%) and 3 (0.6%) had treatment-related AEs and serious AEs, respectively. Separate microbiologic findings

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from Leipzig University Hospital demonstrate small proportions of *Enterococcus faecium* isolates with daptomycin minimum inhibitory concentrations = 4 mg/L (4%) or ≥8 mg/L (0.8%), which are regarded as non-susceptible.

Conclusion: For enterococcal infections, daptomycin appears to be an effective and well-tolerated treatment option, exhibiting highest clinical success rates at higher doses.

Keywords: Daptomycin; Enterococcal infections; EU-CORE; Gram-positive infections; VRE

INTRODUCTION

Enterococci are facultative anaerobic bacteria tolerant of a wide range of environmental conditions and constitute normal commensal flora of the human gastrointestinal tract. Some species of this genus have a high intrinsic resistance to antibiotics [1, 2]. In addition, over the last two decades, particularly virulent strains of enterococci with acquired resistance to antibiotics, such as vancomycin, have emerged. Thus, associated treatment and infection control have become increasingly difficult [3]. The constitutive presence of enterococci in gastrointestinal tracts of hospitalized patients has assisted the transition from commensal organisms to nosocomial pathogens and the evolution of such drug resistance [4, 5]. Moreover, establishment of such multidrug-resistant pathogens is particularly common and therapeutically problematic in the hospital setting [6, 7], and thus constitutes a significant and growing public health challenge [8, 9].

Enterococci are often encountered in mixed infections and are particularly found in urinary tract infections, bacteremia, endocarditis, diverticulitis, peritonitis, and meningitis [3]. In recent years, the prevalence of species other than *Enterococcus faecalis* has increased. Particular *Enterococcus faecium* strains frequently showing multidrug resistance and non-susceptibility to vancomycin have emerged. Few therapeutic options are available for treating infections caused by vancomycin-resistant enterococci (VRE) [6].

Daptomycin is a cyclic lipopeptide with rapid bactericidal activity against a wide range of Gram-positive bacteria, including multidrug-resistant enterococci [10–14], and is effective in inhibiting or disrupting biofilm production in vitro [15–17]. Its mechanism of action is distinct from that of other antibiotics, including β-lactams, aminoglycosides, glycopeptides, fluoroquinolones, and macrolides. In the presence of physiological concentrations of ionized calcium, daptomycin interacts with the surface of Gram-positive bacteria, leading to disruption of membrane function [18].

Daptomycin was first approved in 2003, and is indicated for the treatment of complicated skin and soft tissue infections (cSSTIs; 4 mg/kg every 24 h), right-sided endocarditis due to *Staphylococcus aureus* and for bacteremia associated with cSSTI or right-sided endocarditis (6 mg/kg every 24 h) [19]. It has been previously shown that daptomycin (6 mg/kg/day) was highly effective against susceptible and multidrug-resistant *E. faecalis* and *E. faecium* in vitro and also in a rat model of experimental endocarditis [20]. Moreover, treatment with daptomycin in patients with invasive or bacteremic enterococcal infections leads to higher frequency of cure (up to 90% or more) when concomitant and adequate focus relief was performed [21].

The objective of this sub-analysis from the European Cubicin® Outcomes Registry and Experience (EU-CORE℠) study was to evaluate the safety and clinical outcome of patients with

enterococcal infections treated with daptomycin.

METHODS

Patients and Data Collection

Daptomycin use in a clinical setting frequently differs from controlled clinical trial or indicated use. EU-CORE is a retrospective, multicenter, multinational study conducted across 18 countries—12 in Europe (Austria, Bulgaria, France, Germany, Greece, Italy, Romania, Russia, Slovenia, Spain, Turkey, and United Kingdom), 5 in Latin America (Argentina, Brazil, Colombia, Mexico, and Venezuela) and 1 in Asia (India). It collected data on patients receiving daptomycin in a real-world clinical setting. Patients were enrolled into the study if they had been treated with at least one dose of daptomycin and for whom all mandatory information, as required in the case report forms, was recorded. Patients received daptomycin therapy between January 2006 and April 2012 and were followed up for 30 days after the end of treatment. Two-year follow-up data were collected until 2014 for patients with endocarditis, intracardiac/intravascular device infection, osteomyelitis, or orthopedic device infection. A written informed consent was obtained when required by the Institutional Review Board/Ethical Committee and/or local data privacy regulations. Patients who received daptomycin as part of a controlled clinical trial were not eligible for inclusion in the study. Interim results of the EU-CORE registry were previously reported [22, 23].

A standardized case report form and protocol were used to collect demographic and clinical information on patients who had been treated with daptomycin. Demographic, antibiotic, microbiologic, and clinical data were collected from medical records at each site. Data collection was carried out as previously described by Gonzalez-Ruiz et al. [19].

Clinical Outcomes and Safety

Investigators assessed the clinical outcome at the end of daptomycin therapy according to the following protocol-defined criteria: cured, clinical signs and symptoms resolved, no additional antibiotic therapy was necessary, or infection cleared with a negative culture reported; improved, partial resolution of clinical signs and symptoms and/or additional antibiotic therapy was warranted; failed, inadequate response to daptomycin therapy, worsening or new/recurrent signs and symptoms, need for a change in antibiotic therapy, or a positive culture reported at the end of therapy; and non-evaluable, unable to determine response due to insufficient information [24].

Clinical success was used to collectively describe patients with an outcome of cured or improved. Time to improvement was also recorded. Duration of treatment was measured as the number of inpatient and outpatient days during which the patient received daptomycin therapy, even if these were non-consecutive. There were no restrictions on concomitant treatment in the EU-CORE study. The safety population comprised all eligible patients who had any safety parameters assessed, and the efficacy population comprised all eligible patients for whom clinical outcome was assessed. Safety was assessed for up to 30 days after the end of daptomycin treatment.

All reported deaths, adverse events (AEs) and serious AEs (SAEs), regardless of their relationship to daptomycin, were recorded, and the severity of AEs was determined.

Microbiology

For the EU-CORE study, antibiotic susceptibility profiles based on testing performed at the local laboratories were listed for each bacterial species. Antibiograms were analyzed through tabulations of susceptibility classifications (defined as susceptible/intermediate/resistant) based on the susceptibility breakpoints used by the local laboratory and minimum inhibitory concentration (MIC) values when available.

For all enterococcal isolates from the Leipzig University Hospital, Germany, MICs were determined using the ISO 20776-1 (http://www.iso.org) microbroth dilution method. Susceptibilities were assessed using breakpoints established by the Clinical Laboratory Standards Institute (CLSI; http://www.clsi.org). The current CLSI susceptibility breakpoint for daptomycin is ≤4 mg/L. In view of the limited clinical data available, the European Committee on Antimicrobial Susceptibility Testing (EUCAST; http://www.eucast.org) has published the epidemiological cutoff values of 4 mg/L for both *E. faecalis* and *E. faecium*.

Statistical Analysis

Statistical analysis was performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA). Numerical variables were summarized as arithmetic mean, standard deviation, median, minimum, first quartile, third quartile, and maximum for continuous variables. Categorical variables were summarized by absolute and relative frequencies, and missing values were not included in the calculation of relative frequencies. Categorical data were analyzed by the Chi-square or Fisher's exact test and p values (two-tailed) of <0.05 were considered to be statistically significant.

RESULTS

Patient Demographic and Clinical Characteristics

Of the 6075 patients (5467 from Europe, 409 from Latin America and 199 from Asia) enrolled in the EU-CORE study, 472 (7.8%) patients had enterococcal infections as the primary diagnosis. All were included in both the safety and efficacy populations (Table 1).

Patients were predominantly adults with a median age of 65 (range 1–94) years and a median body weight of 75 (range 6–177) kg. The majority were male (63.3%) and Caucasian (87.7%; Table 1). Comorbidity was frequent, as would be expected in patients with invasive enterococcal infections. Cardiovascular disease was the most common underlying disease, reported in 55.9% of the cohort, followed by diabetes mellitus (27.8%), renal disease (22.0%), gastrointestinal disease (21.0%), cancer (19.5%), and pulmonary disease (13.6%).

Of the 163 patients for whom data were available, 91 (55.8%) patients acquired nosocomial infections, 63 (38.7%) patients acquired infection in a community setting, and 9 (5.5%) patients in a nursing home/extended care setting.

Primary Infections

Of the wide range of primary infection types treated with daptomycin, bacteremia (29.9%), cSSTI (29.2%) and endocarditis (12.3%) were the most common (Table 2). Patients with foreign body/prosthetic infection (8.5%), urinary tract infection/pyelonephritis (4.7%), osteomyelitis (4.4%), and infections classified as other (11%) were also enrolled.

Table 1 Demographic and clinical characteristics

Characteristics	$N = 472$	
Age (years), median (range)	65	(1–94)
Age (years), *n* (%)		
<65 (including <18)	236	(50.0)
<18	5	(1.1)
≥65 (including ≥75)	236	(50.0)
≥75	110	(23.3)
Gender, *n* (%)		
Male	299	(63.3)
Ethnicity, *n* (%)		
Caucasian	414	(87.7)
Body weight (kg), median (range)	75	(6–177)
Frequent significant underlying disease, *n* (%)		
Cardiovascular disease	264	(55.9)
Diabetes mellitus	131	(27.8)
Renal disease	104	(22.0)
Gastrointestinal disease	99	(21.0)
Malignancy	92	(19.5)
Pulmonary disease	64	(13.6)
Renal function, *n* (%)		
Creatinine clearance <30 mL/min	68	(14.8)
Setting prior to onset of infection, *n* (%)[a]		
Hospital	91	(55.8)
Nursing home/extended care	9	(5.5)
Community	63	(38.7)
Unknown	309	

[a] Denominators of different settings excluded patients with unknown information

Previous and Concomitant Antibiotic Therapies

Of the 472 patients, 343 (72.7%) patients received antibiotics prior to daptomycin therapy. While 152 (32.2%) patients received penicillins, 132 (28.0%) received glycopeptides (of whom 93 [19.7%] were administered vancomycin as a prior therapy). Furthermore, 108 (22.9%) patients received carbapenems and 91 (19.3%) patients received cephalosporins.

The main reasons for switching to daptomycin were failure of previous antibiotic therapy (32.6%), a resistant or non-susceptible pathogen (14.4%), toxicity/intolerance (8.7%), and narrowing of antibiotic therapy (8.1%). Concomitant antibiotic therapy with daptomycin was received by 357 (77.1%) inpatients; carbapenems (35.4%), β-lactams (26.9%), and fluoroquinolones (11.7%) were the most frequently used concomitant antibiotics.

Daptomycin Prescribing Patterns

The most commonly prescribed dose of daptomycin was 6 mg/kg/day (47.0%), and 20.1% of patients received >6 mg/kg/day (Table 3). A dose of >6 mg/kg/day was most frequently administered in endocarditis, osteomyelitis and foreign body/prosthetic infection. The median duration of daptomycin therapy was 12 (range 1–83) days for inpatients ($n = 461$) and 19 (range 3–68) days for outpatients ($n = 36$).

Clinical Outcomes

Overall clinical success rate was 77.1%. Notably, only 7.2% of patients were documented as having failed treatment and 15.7% of patients were non-evaluable. Rates of clinical success across different infections and infecting enterococcal pathogens are shown in Figs. 1 and 2, respectively. The overall clinical success rate for different infections was slightly higher

Table 2 Type of primary infection and enterococcal pathogen

Primary infection	Patients, *n* (%)	Enterococcal pathogen		
		Enterococcus faecalis, *n* (%)	*Enterococcus faecium*, *n* (%)	*Enterococcus* species, *n* (%)
Bacteremia	141 (29.9)	58 (41.1)	72 (51.1)	11 (7.8)
Complicated skin and soft tissue infection	138 (29.2)	71 (51.4)	54 (39.1)	13 (9.4)
Endocarditis	58 (12.3)	43 (74.1)	8 (13.8)	7 (12.1)
Foreign body/prosthetic infection	40 (8.5)	27 (67.5)	9 (22.5)	4 (10.0)
Urinary tract infection/pyelonephritis	22 (4.7)	7 (31.8)	10 (45.5)	5 (22.7)
Osteomyelitis	21 (4.4)	14 (66.7)	6 (28.6)	1 (4.8)
Other[a]	52 (11.0)	16 (30.8)	25 (48.1)	11 (21.2)
Total	472 (100.0)	236[b] (50.0)	184[c] (39.0)	52 (11.0)

[a] Includes uncomplicated skin and soft tissue infection, necrotizing infections, central nervous system infection, surgical/non-surgical antibiotic prophylaxis, metastatic abscess, septic arthritis, or not otherwise specified

[b] Vancomycin-resistant *E. faecalis* = 18/236 (3.8%): three bacteremia, six complicated skin and soft tissue infection, three foreign body/prosthetic infection, two urinary tract infection/pyelonephritis, three osteomyelitis, and one other

[c] Vancomycin-resistant *E. faecium* = 46/184 (9.7%): 25 bacteremia, nine complicated skin and soft tissue infection, three endocarditis, three foreign body/prosthetic infection, two urinary tract infection/pyelonephritis, and four other

Table 3 Daptomycin dose by primary infection

Primary infection	Patients, *n* (%)	Daptomycin dose				
		4 mg/kg/day, *n* (%)	6 mg/kg/day, *n* (%)	>6 mg/kg/day, *n* (%)[a]	≥8 mg/kg/day, *n* (%)	Other dose, *n* (%)[b]
Bacteremia	141 (29.9)	20 (14.2)	77 (54.6)	22 (15.6)	12 (8.5)	22 (15.6)
Complicated skin and soft tissue infection	138 (29.2)	54 (39.1)	50 (36.2)	20 (14.5)	13 (9.4)	14 (10.1)
Endocarditis	58 (12.3)	1 (1.7)	32 (55.2)	23 (39.7)	15 (25.9)	2 (3.4)
Foreign body/prosthetic infection	40 (8.5)	3 (7.5)	19 (47.5)	15 (37.5)	12 (30.0)	3 (7.5)
Urinary tract infection/pyelonephritis	22 (4.7)	13 (59.1)	8 (36.4)	1 (4.5)	0 (0)	0 (0)
Osteomyelitis	21 (4.4)	3 (14.3)	9 (42.9)	8 (38.1)	6 (28.6)	1 (4.8)
Other[c]	52 (11.0)	9 (17.3)	27 (51.9)	6 (11.5)	5 (9.6)	10 (19.2)
Total	472 (100.0)	103 (21.8)	222 (47.0)	95 (20.1)	63 (13.3)	52 (11.0)

[a] Includes ≥8 mg/kg/day

[b] Includes >4 to <6 mg/kg/day, <4 mg/kg/day and unknown

[c] Includes uncomplicated skin and soft tissue infection, necrotizing infections, central nervous system infection, surgical/non-surgical antibiotic prophylaxis, metastatic abscess, septic arthritis, or not otherwise specified

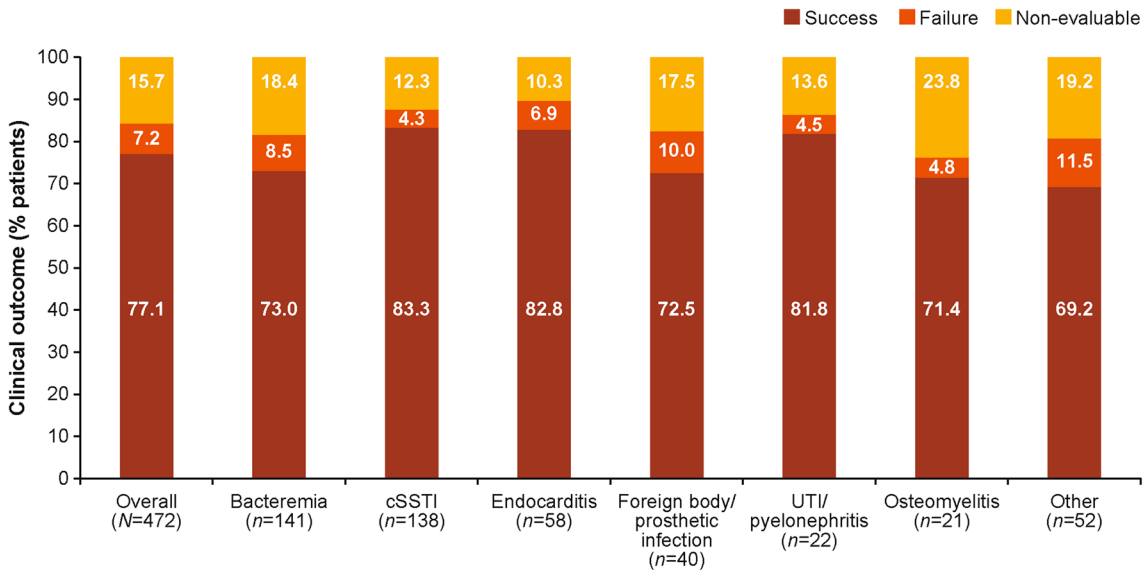

Fig. 1 Clinical outcome by primary infection type. *cSSTI* complicated skin and soft tissue infection, *UTI* urinary tract infection

when daptomycin was used as first-line (82.5%) than second-line (74.6%) therapy ($p = 0.09$).

The clinical success rate by infection type independent of the treatment dose ranged between 69.2% and 83.3%. The clinical success rate for cSSTI was 83.3%, endocarditis 82.8%, urinary tract infection/pyelonephritis 81.8%, bacteremia 73.0%, foreign body/prosthetic infection 72.5%, and osteomyelitis 71.4% (Fig. 1). Clinical success rates were overall similar for doses <8 mg/kg/day (75.8%), but were higher in patients treated with doses ≥8 mg/kg/day (85.7%, $p = 0.08$). The median time to improvement was 4 (range 1–30) days from initiation of daptomycin treatment. Overall, clinical success rates were similar whether patients received no concomitant antibiotic therapy (78.0%) or any concomitant antibiotic therapy (77.3%).

Microbiology

On the basis of the reported percentage of susceptible isolates, daptomycin was more active than vancomycin against *E. faecalis* (94.9% vs 89.1%), *E. faecium* (96.9% vs 66.2%), and *Enterococcus* species (83.3% vs 56.4%; Table 4).

Susceptibility data of enterococci to daptomycin stating the exact MICs were not available from the EU-CORE registry. To address this issue, the MIC determinations for daptomycin for primary isolates of *E. faecalis* and *E. faecium* strains detected in clinical specimens at the Leipzig University Hospital, Germany, in 2014 were analyzed (Fig. 3). Displaying the expected Gaussian distribution curve, the data showed only small proportions of *E. faecalis* and *E. faecium* isolates with daptomycin MICs = 4 mg/L (1.9% and 4%, respectively) or ≥8 mg/L (1.3% and 0.8%, respectively). Among these *E. faecalis* and *E. faecium* isolates, the VRE rate was 0.8% and 36.2%, respectively. Using the current CLSI susceptibility breakpoint for daptomycin (≤4 mg/L), resistance rates of 1.3% for *E. faecalis* and 0.8% for *E. faecium* need to be considered.

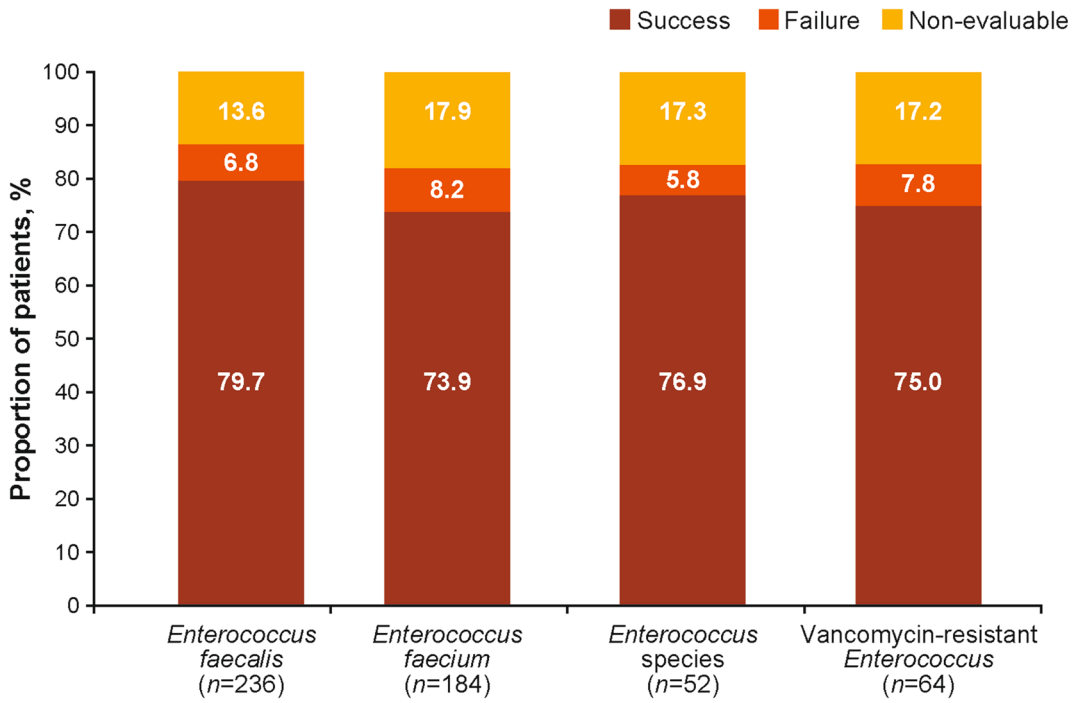

Fig. 2 Clinical outcome by primary infecting enterococcal pathogen

Table 4 Reported enterococcal susceptibility to daptomycin and vancomycin

Pathogen	Drug	Patients, (*n*)	Susceptible, *n* (%)	Intermediate susceptible, *n* (%)	Resistant, *n* (%)
Enterococcus faecalis	Daptomycin	99	94 (94.9)	–	3 (3.0)
	Vancomycin	201	179 (89.1)	2 (1.0)	18 (9.0)
Enterococcus faecium	Daptomycin	65	63 (96.9)	1 (1.5)	–
	Vancomycin	154	102 (66.2)	–	46 (29.9)
Enterococcus species	Daptomycin	18	15 (83.3)	1 (5.6)	1 (5.6)
	Vancomycin	39	22 (56.4)	3 (7.7)	14 (35.9)

Susceptibility data of isolates from some patients were missing

Safety

A total of 81 (17.2%) patients reported at least one AE and 63 (13.3%) reported SAEs. The most common AEs (>1% patients) are listed in Table 5. Most AEs and SAEs were considered as unrelated to daptomycin treatment by the investigator, with 11 (2.3%) and 3 (0.6%) treatment-related AEs and SAEs, respectively, being recorded. A total of 46 (9.7%) patients died during the study or follow-up (Table 5). The main causes of death were multi-organ failure, sepsis and septic shock. Discontinuation of daptomycin treatment due to an AE occurred in 6.1% of patients. There were a total of five patients with rhabdomyolysis AEs and SAEs, of whom three were considered by the investigator as possibly treatment related (two AEs and one SAE). Of the patients with treatment-related rhabdomyolysis, two discontinued the study.

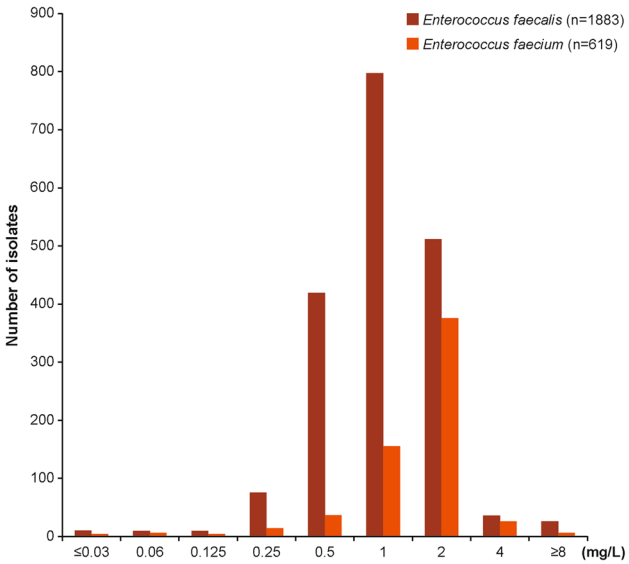

Fig. 3 Daptomycin susceptibility of enterococci—Leipzig University Hospital, Germany, January to December 2014

Table 5 Safety of daptomycin treatment

Safety parameters	***N* = 472** ***n* (%)**
Deaths	46 (9.7)
Serious adverse events	63 (13.3)
Adverse events	81 (17.2)
Adverse events leading to permanent drug discontinuation	29 (6.1)
Adverse events occurring in >1% of patients	
Multi-organ failure	12 (2.5)
Septic shock	10 (2.1)
Sepsis	9 (1.9)
Blood creatine phosphokinase increased	5 (1.1)

No AEs of eosinophilic pneumonia were reported.

Serum creatine phosphokinase (CPK) was measured at baseline for 293 patients, and the majority (85.0%) had normal values. At baseline, four (1.4%) patients had CPK levels >10× upper limit of normal (ULN). Eight patients had a shift of CPK elevation from ≤10× ULN at baseline to >10× ULN. Increased blood CPK was reported as an AE in five (1.1%) patients and as an SAE in one (0.2%) patient.

DISCUSSION

The EU-CORE study illustrates real-world usage of daptomycin in the treatment of enterococcal infections. The many multinational sites enrolled in the EU-CORE study allowed a wide spectrum of patients. Overall, treatment of enterococcal infections with daptomycin was associated with high rates of clinical success. Daptomycin showed good effectiveness whether used as first- or second-line therapy.

Available interventions for VRE are mostly based on expert opinion recommendations [25]. A recent meta-analysis has showed that the two most commonly prescribed drugs, daptomycin and linezolid, were equally efficacious in blood stream infections due to VRE [26]. A 2-year retrospective study conducted at the Detroit Medical Center also showed that daptomycin was as efficacious as linezolid and β-lactams in

treating bacteremia due to VRE [27]. However, prolonged linezolid treatment has been associated with multiple safety concerns [28, 29].

Daptomycin has previously been shown to be active against *Enterococcus* species with vancomycin non-susceptible *E. faecalis* and *E. faecium* being 100.0% and 99.8% susceptible to daptomycin, respectively [30]. In the current study, daptomycin was reported as microbiologically more active than vancomycin against *Enterococcus* species.

Although licensed differently, many clinicians recommend daptomycin at a higher dose of 8–10 mg/kg/day for complicated bacteremia and native valve endocarditis [31]. Kullar et al. assessed the clinical and microbiologic outcomes of high-dose daptomycin therapy and reported that daptomycin doses of ≥8 mg/kg/day may be safe and effective in patients with complicated Gram-positive infections (including *Enterococcus* species) [32]. In the EU-CORE study, high-dose treatment resulted in a marginally higher overall clinical success rate (85.7% for doses ≥8 mg/kg/day compared with 75.8% for doses <8 mg/kg/day). As daptomycin MICs for *Enterococcus* species are typically higher than those for other Gram-positive organisms (0.5–4 vs 0.25–1 mg/L), patients with these serious infections may require higher doses of daptomycin for optimal treatment.

Recent microbiologic findings from the Leipzig University Hospital, Germany, which are not included in the EU-CORE data, demonstrate only small proportions of *E. faecalis* and *E. faecium* isolates with daptomycin MICs = 4 mg/L or ≥8 mg/L (Fig. 3). Among these *E. faecalis* and *E. faecium* isolates, the VRE rate was 0.8% and 36.2%, respectively. Using the current CLSI susceptibility breakpoint for daptomycin (≤4 mg/L), resistance rates of 1.3% for *E. faecalis* and 0.8% for *E. faecium* need to be considered. Previously, it was reported that high-dose (>6 mg/kg/day; median dose, 8.2 mg/kg/day) daptomycin treatment of enterococcal infections with MICs ≤4 mg/L was associated with high clinical success (81–100%), whereas treatment was unsuccessful with high daptomycin MIC (≥8 mg/L) [33]. Thus, high clinical cure rates would generally be expected when adequate concomitant source control is performed and when suggested MIC limits are respected.

The rates of AEs reported in this retrospective observational study were low and should not be compared to AE reporting during a randomized clinical trial. Daptomycin had generally a favorable safety profile with no new or unexpected safety findings in this population. SAEs and deaths were reflective of the severity of underlying infections and health status of patients.

These results complement data from randomized clinical studies [34] and show that daptomycin is a valuable treatment option in the management of enterococcal infections, especially with rising rates of multidrug-resistant enterococci exhibiting resistance to standard enterococcal antibiotics (i.e., ampicillin, vancomycin and aminoglycosides).

There are limitations to this retrospective analysis of the EU-CORE registry data. First, it does not allow comparison of treatments as in a randomized trial. In addition, while prior and concomitant use of other antibiotic agents as well as presence of mixed infections were documented, this was not controlled and might have complicated the interpretation of clinical outcome. No blinding or independent evaluations were incorporated and patient outcomes were solely determined by the

treating physician. Furthermore, disease severity was not accounted for in the analysis, and patient selection bias could not be discounted. However, variability in dosing and patient population reflects the real-world clinical setting for daptomycin use (i.e., treatment of diverse infections and concomitant use of antibiotics). It also provides a valuable insight into the real-world clinical practice (often sicker patients than those enrolled in clinical trials) and expands on the outcomes derived from the existing clinical trials.

CONCLUSIONS

Currently, there is not much comprehensive work published regarding optimal antibiotic selection for the treatment of VRE infections. Studies described in the literature are limited by small sample sizes, lack of patient-level data and inconsistent outcomes definitions. However, the data obtained in the EU-CORE study described here are encouraging and indicate a benefit of high-dose therapy. Future investigation, including randomized clinical trials adjusted to measured MIC levels, is warranted to support guidance for therapeutic regimens for VRE infections.

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Compliance with ethics guidelines. The study has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The protocol was approved by the health authority and the Institutional Review Board (IRB) or Ethics Committee (EC) in each country and written informed consent was obtained according to the requirements of the IRB or EC and/or the local data privacy regulations.

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