



BRIEF REPORT

# Should High-dose Daptomycin be an Alternative Treatment Regimen for Enterococcal Endocarditis?

Maddalena Peghin · Alessandro Russo · Filippo Givone ·  
Martina Ingani · Elena Graziano · Matteo Bassetti

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## ABSTRACT

**Introduction:** Previous series on the use of daptomycin in enterococcal infective endocarditis (EIE) have shown various outcomes, including higher mortality rates. We analyzed the effectiveness of high-dose daptomycin for the treatment of EIE.

**Methods:** We performed a prospective study from 2010 to 2018 in a referral center in patients with native (NVE) and prosthetic valve endocarditis (PVE) due to *Enterococcus* spp. The standard high-dose daptomycin at our institution is 10–12 mg/kg/day (CLCr > 30 ml/min). We compared the efficacy of a daptomycin-based regimen (DBR) versus daptomycin-sparing regimen (DSR) and daptomycin monotherapy versus combination therapy. Primary endpoints of the study were evaluation of risk

factors associated with 30-day mortality and failure at end of therapy.

**Results:** We collected 43 EIE cases; 29 were NVE (67.4%). Overall, 16 (37.2%) were treated with DBR, mainly with combination regimens (11, 68.7%), in the majority of cases in association with  $\beta$ -lactam (7, 43.7%). The mean administered dose of daptomycin was 10.125 mg/kg/day (range 8–12 mg/kg/day). Overall, patients treated with DBR compared with patients treated with DSR had no higher mortality rates and/or failure at end of therapy (6.2% vs. 22.2%;  $P$  0.41 and MICs 0.25–2 mg/l, 6.2% vs. 3.7%;  $P$  1.0). In the sub-group of patients with NVE and PVE treated with DBR and DSR, no difference was found regarding the primary endpoints on the single or combined use of daptomycin.

**Conclusion:** Our findings suggest that high-dose daptomycin might be used as an alternative treatment regimen in EIE.

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**Keywords:** Daptomycin; Enterococcal infective endocarditis; *Enterococcus* spp.; High-dose daptomycin

M. Peghin (✉) · A. Russo · F. Givone · M. Ingani ·  
E. Graziano · M. Bassetti  
Infectious Diseases Division, Department of  
Medicine, University of Udine and Azienda Sanitaria  
Universitaria Integrata di Udine, Udine, Italy  
e-mail: maddalena.peghin@gmail.com

M. Bassetti  
Department of Health Sciences, University of  
Genoa, Genoa, Italy

## INTRODUCTION

Over the past decades, continuous changes in epidemiologic and clinical characteristics of infective endocarditis (IE) have shown that enterococci have emerged as the third most

common pathogen (10–15% of IE cases) following staphylococci and streptococci [1, 2].

Treatment of enterococcal IE (EIE) is known to be challenging, because enterococci have shown the ability to develop antibiotic resistance with increasing high-level aminoglycoside resistance (HLAR) and cure of IE usually requires a prolonged course of antibiotics (up to 6 weeks) with potential adverse events [3, 4]. In addition to established antimicrobials (ampicillin plus ceftriaxone or ampicillin with aminoglycosides), old (teicoplanin, vancomycin) and novel antibiotics (dalbavancin) have been investigated to improve the effectiveness of antibacterial strategies [5–7].

Daptomycin is a cyclic lipopeptide antibiotic with highly concentration-dependent bactericidal activity against gram-positive bacteria and has been highly prescribed in the setting of resistant enterococci [8]. Daptomycin was approved for the treatment of right-sided endocarditis caused by *Staphylococcus aureus* at a dose of 6 mg/kg, although clinical and microbiologic data support improved efficacy at higher doses [9]. In addition, several in vitro studies and some case reports have demonstrated synergistic activity against enterococci with the combination of daptomycin and other antibiotics [10, 11]. Daptomycin at higher doses ranging from 8 to 14 mg/kg/day has been used in EIE with variable and conflicting results, including non-favorable microbiologic and clinical response [12–14].

We have integrated the use of high-dose (> 10 mg/kg) daptomycin [15] in monotherapy or combination therapy in our treatment armamentarium for EIE. The aim of this study is to report the experience with daptomycin compared with the standard treatment option [3] at our institution.

## METHODS

We performed a prospective 9-year study (2010–2018) at the Santa Maria Misericordia Hospital in Udine, a tertiary-care teaching hospital (1000 beds) that is a referral regional center for IE with a heart surgery department. All consecutive adult patients (> 18 years) with

native (NVE) and prosthetic valve endocarditis (PVE) sustained by *Enterococcus* spp. were included.

IE was defined according to the Duke's modified criteria. Indication for surgery was based on ESC clinical guidelines [3].

Minimum inhibitory concentrations (MICs) were determined by use of either *E* test or Sensititre. MIC  $\geq$  256 mg/l was recorded as HLAR and MIC > 4 mg/l as daptomycin non-susceptible, in accordance with the European Committee on Antimicrobial Susceptibility Testing (EUCAST) recommendations.

The standard recommended high dosage of daptomycin in EIE at our institution is 10–12 mg/kg/day (10–12 mg/kg/48 h if CLCr < 30 ml/min, including hemodialysis and CAPD) infused over 15 min [15].

Primary endpoints of the study were evaluation of risk factors associated with 30-day mortality rates and with failure at end of therapy. We compared a daptomycin-based regimen (DBR) vs. daptomycin-sparing regimen (DSR) as a first-line or salvage therapy and daptomycin monotherapy versus daptomycin used in combination.

Patients were judged to have clinical failure if they had no response to the antimicrobial treatment based on ongoing fever, leukocytosis, other clinical parameters and/or relapse of IE. Treatment failure was defined as an inadequate response to antibiotic with persistence of fever and/or persistent bacteremia after 6 days of adequate therapy, requiring an antibiotic change.

Quantitative variables were reported as the mean ( $\pm$  standard deviation), and qualitative variables were reported as number and percentage. Statistical analyses were performed with SPSS-PC+, version 22.0 (SPSS, Chicago, IL). The study was approved by the local institutional review board.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the University of Udine and Azienda Sanitaria Universitaria Integrata di Udine (IRB NR 505) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The need for informed consent was waived by the IRB because of the observational nature and minimal risk of the study.

**Table 1** Demographic features, comorbidities, characteristics and outcome of 43 episodes of EIE treated with DCR and DSR

Variables	All, <i>n</i> 43 (%)	DBR <i>n</i> 16 (%)	DSR, <i>n</i> 27 (%)	<i>P</i>
Age (years), mean + SD	67.3 ± 15.6	67.1 ± 15.7	67.3 ± 15.5	0.81
Male	29 (67.4)	10 (62.5)	19 (70.4)	0.73
Underlying condition				
Diabetes	8 (18.6)	6 (37.5)	2 (7.4)	<b>0.04</b>
Chronic renal failure	15 (34.8)	6 (37.5)	9 (33.3)	1.0
Transplantation	1 (2.3)	1 (6.2)	0	0.37
Neoplasm	3 (6.9)	2 (12.5)	1 (3.7)	0.54
Liver cirrhosis	1 (2.3)	0	1 (3.7)	0.31
COPD	5 (11.6)	3 (18.8)	2 (7.4)	0.3
Modified Charlson score, median (range)	4.4 ± 2.5	4.1 ± 2.9	4.5 ± 2.4	0.55
Type of IE				
Native valve endocarditis	29 (67.4)	10 (62.5)	19 (70.4)	0.7
Prosthetic valve endocarditis	14 (32.5)	6 (37.5)	8 (29.6)	0.72
Heart valve affected				
Aortic	31 (72.1)	11 (68.8)	20 (74.1)	0.69
Mitral	12 (27.9)	2 (12.5)	10 (37)	0.15
Right-sided IE	2 (4.6)	1 (6.2)	1 (3.7)	1.0
Complications <sup>a</sup>	6 (13.9)	3 (18.8)	3 (11.1)	0.5
Surgery performed	18 (41.8)	7 (43.7)	11 (40.7)	0.9
Duration of treatment	52 ± 22.6	45 ± 21.1	56 ± 23.2	<b>0.02</b>
30-Day mortality rate	7 (16.2)	1 (6.2)	6 (22.2)	0.41
Failure at the end of treatment	2 (4.6)	1 (6.2)	1 (3.7)	1.0

Bold value indicates statistical significance ( $p < 0.05$ )

DBR daptomycin-containing regimen, DSR daptomycin-sparing regimen, IE infective endocarditis

<sup>a</sup> Complications: heart failure, new renal failure, embolism, paravalvular complications, stroke

## RESULTS

### General Characteristics of the Cohort and Strains

During the 8-year study period, enterococcal IE accounted for 43 of 405 (10.6%) IE episodes, including 29 NVE, (67.4%) and 14 PVE (32.6%). The median age of the cohort was 67 years, and 29 (67.4%) patients were male. The main

comorbidities are shown in Table 1. There was no statistically significant difference between groups regarding baseline clinical characteristics, except for diabetes.

*Enterococcus faecalis* accounted for 39 episodes (90.7%), while *E. faecium* for 4 (9.3%). All strains treated with daptomycin were susceptible (MICs ranged from 0.25 to 4 mg/l), with 13 strains with MIC ≤ 1 mg/l and 3 strains with MIC 2–4 mg/l. Thirteen *Enterococcus* strains

**Table 2** Characteristics and outcome of 16 infective endocarditis episodes treated with daptomycin monotherapy or combination therapy

PTS	Type of infection	Surgery indicated	Type of <i>enterococcus</i>	Daptomycin MIC	Daptomycin dose (mg/kg)	Days of daptomycin treatment	Combo <sup>a</sup>	30-Day mortality	Failure	Relapse	HLAR	Betalactams allergy
1	NVE	Yes	<i>E. faecalis</i>	1	10	19	-	No	No	No	Yes	Yes
2	NVE	Yes	<i>E. faecalis</i>	1	10	21	-	No	No	No	No	No
3	NVE	Yes	<i>E. faecalis</i>	0.5	10	31	Cefazoline	No	No	No	Yes	No
4	NVE	Yes	<i>E. faecalis</i>	1	10	23	Ampicillin	No	No	No	Yes	No
5	NVE	No	<i>E. faecalis</i>	2	12	42	-	No	No	No	Yes	No
6	NVE	No	<i>E. faecalis</i>	1	10	43	-	No	No	No	Yes	No
7	NVE	Yes	<i>E. faecalis</i>	0.5	10	38	Ampicillin	No	No	No	No	No
8	NVE	Yes	<i>E. faecalis</i>	1	8	50	Ampicillin	No	No	No	Yes	No
9	PVE	No	<i>E. faecalis</i>	1	12	42	Gentamicin	No	No	No	No	Yes
10	PVE	Yes	<i>E. faecalis</i>	0.25	8	67	Gentamicin	No	No	No	No	Yes
11	PVE	Yes	<i>E. faecalis</i>	0.5	10	55	Gentamicin	No	No	No	No	No
12	PVE	Yes	<i>E. faecalis</i>	1	10	42	Gentamicin	No	No	No	No	No
13	NVE	Yes	<i>E. faecium</i>	0.5	10	42	-	No	No	No	Yes	No
14	NVE	Yes	<i>E. faecium</i>	2	10	58	Ampicillin	No	No	No	Yes	No
15	PVE	Yes	<i>E. faecium</i>	1	10	48	Ampicillin	Yes	No	No	Yes	No
16	PVE	No	<i>E. faecium</i>	2	12	42	Ampicillin	No	Yes	No	Yes	No

NVE native valve endocarditis, HLAR high-level aminoglycoside resistance, PVE prosthetic valve, *pts* patients

<sup>a</sup> Standard doses for listed antibiotics for patients with normal renal function: ampicillin standard 4 g every 6 h continuous infusion (CI) for normal renal function IV. Therapeutic drug monitoring (TDM) based. Gentamicin 3 mg/kg/day IV. TDM based. Cefazolin 600 mg every 8 h IV

showed HLAR (12 *E. faecalis* and 1 *E. faecium*) (Table 2).

### Use of Daptomycin, Outcome and Comparison

Of the 43 patients included in the study, 16 (37.2%) were treated with DBR, 14 (32.5%) were ampicillin/gentamicin-treated patients, 9 (20.9%) were ampicillin/ceftriaxone-treated patients, and the rest were patients with alternative regimens (2 with vancomycin, 1 with linezolid, 1 with levofloxacin). Three of 16 patients in the DBR group (18.7%) had a history of beta-lactam allergy. In the DBR group, daptomycin combination therapy was performed in 11 patients (68.7%), in 6 cases (54.5%) in association with ampicillin, in 4 cases (36.5%) with gentamicin and in the remaining case (9%) with ceftaroline. The mean administered dose of daptomycin was 10.125 mg/kg/day intravenously (range 8–12 mg/kg/day). Mean length of antimicrobial therapy was 45 days in the DBR group and 56 days in the DSR ( $P = 0.02$ ). No related adverse events (rhabdomyolysis and eosinophilic pneumonia) occurred in patients undergoing treatment with high-dose daptomycin.

Overall surgery was performed in 41.8% of patients (Tables 1, 2). All-cause mortality at 30 days was reported in seven (16.2%) patients. Overall, patients treated with DBR compared with patients treated with DSR had no higher mortality rates and/or failure at end of therapy (6.2% vs. 22.2%;  $P = 0.41$  and MICs 0.25–2 mg/l 6.2% vs. 3.7%;  $P = 1.0$ ). In the sub-group of patients with NVE and PVE treated with DBR and DSR, no difference was found regarding the primary endpoints on the single or combined use of daptomycin (Table 2). There was only one relapse in the DBR group.

## DISCUSSION

To the best of our knowledge, this is the largest series of enterococcal endocarditis patients treated with a high-dose daptomycin regimen, suggesting that it could be an alternative treatment option for enterococcal NVE and PVE.

Our results are in contrast with previous retrospective studies that found worse microbiologic and clinical response in patients with EIE treated with DBR [12]. *Enterococcus* spp. typically exhibit a higher in vitro MIC to daptomycin than *S. aureus*, with a threshold for susceptibility that is four times as high ( $\leq 4$  vs.  $\leq 1$  mg/l for *S. aureus*), and daptomycin non-susceptibility among enterococci, currently defined as MIC  $> 4$  mg/l, is a growing concern [16]. In our study, all strains treated with daptomycin were susceptible, with 13 strains with MIC  $\leq 1$  mg/l and 3 strains with MIC 2–4 mg/l. Actually current CLSI guidelines have proposed new breakpoints, suggesting that a breakpoint  $\leq 1$   $\mu$ g/ml is likely more predictive of “true” susceptibility, particularly in endovascular infections. In addition, for susceptible-dose dependent strains (MIC 2–4  $\mu$ g/ml), increased daptomycin doses (10–12 mg/kg/day) are recommended with potential consideration for combination therapy [17].

In keeping with our center experience and previous studies, to overcome this issue, two approaches can be performed. On the one hand, the use of higher dosing and then the use of daptomycin combination therapy could influence the efficacy of daptomycin and also prevent development of resistance leading to both clinical and microbiologic failures [7, 15]. In our study, most patients were treated with high daptomycin doses (mean 10.125 mg/kg/day). Probably the delayed response observed in previous studies on EIE could be explained by the lower doses used (average dose of 8.5 mg/kg/day) [12], since the use of increased dosage has reported higher and more sustained killing, including for *E. faecium* [14, 15, 18, 19].

In our series, most patients received combination therapy (68.7%), mainly in association with  $\beta$ -lactam (7, 43.7%) followed by aminoglycoside (4, 25%). Several in vitro studies have shown that daptomycin combination with  $\beta$ -lactam agents such as ampicillin, ceftriaxone and ceftaroline/ceftobiprole could result in a synergistic effect due to increased binding to the cell membrane target [11, 20]. However, the co-administration of gentamicin has not shown a meaningful effect on the pharmacokinetic or bactericidal activity of daptomycin on

*Enterococcus* spp. [21]. Of note, the emergence of resistance has been shown to be delayed by  $\beta$ -lactam, but not by other antibiotics (gentamicin and rifampin) [7].

Moreover, daptomycin is not altered in bio-film bacteria in the stationary growth phase, which makes it a major agent for the treatment of EIE, including PVE [15]. Of note, in line with previous literature, in our series, no patient experienced daptomycin-induced muscle toxicity or eosinophilic pneumonia, despite the high dosing regimen [22].

In our cohort, patients treated with DBR compared with patients treated with DSR had a trend toward lower mortality and a significantly shorter treatment duration (45 days in the DBR group and 56 days in the DSR;  $P = 0.02$ ). Treatment of EIE is known to be difficult, and medical management is a challenge. In patients undergoing heart surgery for IE, the optimal length of antibiotic therapy after surgical excision is an unresolved issue. Current European guidelines recommend administering the complete course of treatment if the resected tissue is culture-positive and completion of the prescheduled course if it is culture-negative [23]. In our center, we have a standardized protocol for EIE. Patients with EIE receive a complete 6-week course of treatment. The duration of treatment is individualized according to the complications of IE and the result of valve culture. In patients who have undergone valve replacement for IE, if valve culture is negative, a 2-week postsurgical treatment course is usually performed, and if the valve culture is positive, a 4-week postsurgical treatment course is usually performed.

The main limitations of this study are its single-center design and the small sample size.

Second, a multivariate regression analysis would have offered robust support, but we found a statistical limitation related to the small size of the cohort.

However, as far as we know, this is the largest prospective series of EIE treated with high-dose daptomycin. The sampling approach for selecting subjects for DBR was not random and was subjective, but was performed by clinicians involved in daily practice in EIE management and reflects real-life practice in our center.

## CONCLUSION

In conclusion, our findings suggest that high-dosing daptomycin regimens could be used as an alternative treatment option in enterococcal NVE and PVE even in monotherapy. This strategy deserves to be studied in prospective and controlled clinical trials.

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**Compliance with Ethics Guidelines.** All procedures performed in studies involving human participants were in accordance with

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**Data Availability.** The data sets generated during and/or analyzed during the current study are not publicly available because of privacy concerns, but are available from the corresponding author on reasonable request.

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