



EN-DALBACEN 2.0 Cohort: real-life study of dalbavancin as sequential/consolidation therapy in patients with infective endocarditis due to Gram-positive cocci

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ABSTRACT

Objectives: Infective endocarditis (IE) has high mortality and morbidity and requires long hospital stays to deliver the antibiotic treatment recommended in clinical practice guidelines. We aimed to analyse the health outcomes of the use of dalbavancin (DBV) in the consolidation treatment of IEs caused by Gram-positive cocci and to perform a pharmacoeconomic study.

Materials and methods: This observational, retrospective, Spanish multicentre study in patients with IE who received DBV as part of antibiotic treatment in consolidation phase were followed for at least 12 months. The study was approved by the Provincial Committee of the coordinating centre.

Results: The study included 124 subjects, 70.2% male, with a mean age of 67.4 years and median Charlson index of 4 (interquartile range: 2.5–6). Criteria for definite IE were met by 91.1%. Coagulase-negative staphylococci (38.8%), *Staphylococcus aureus* (22.6%), *Enterococcus faecalis* (19.4%), and *Streptococcus* Spp. (9.7%) were isolated more frequently, all susceptible to vancomycin. Before DVB administration, 91.2% had undergone surgery; 60.5% had received a second regimen for 24.5 d (16.6–56); and 20.2% had received a third regimen for 14.5 d (12–19.5). DBV was administered to facilitate discharge in 95.2% of cases. At 12

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months, the effectiveness was of 95.9%, and there was 0.8% loss to follow-up, 0.8% IE-related death, and 3.2% relapse. Adverse events were recorded in 3.2%. The hospital stay was reduced by 14 d, and there was a mean savings of 5548.57 €/patient vs. conventional treatments.

Conclusion: DBV is highly effective, safe, and cost-effective as consolidation therapy in patients with IE by Gram-positive cocci, with few adverse events.

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1. Introduction

The incidence of infective endocarditis (IE) has increased over the past few decades due to longer patient survival, instrumentation/interventionism (e.g., vesical catheterization, haemodialysis), and advances in diagnostic techniques, among other reasons [1]. The most frequently involved microorganisms are Gram-positive cocci (GPC), most commonly *Staphylococcus aureus*, which is the causative organism in 24%–32% of IE cases in the United States [2]. Despite improvements in medical and surgical treatments, IE mortality remains elevated, at about 30% during the first year of follow-up [2].

The medical treatment of IE requires parenteral antibiotherapy for at least 4 weeks, which can rise to 6–8 weeks in patients with IE due to *Enterococcus* Spp. or in some cases of prosthetic valve IE [3]. Clinical practice guidelines recommend an at-home antibiotic treatment program for this purpose to avoid prolonged hospital stays [3], although this is not feasible for all patients, and not all hospitals have the resources for its implementation. A clinical trial found no significant difference in therapeutic efficacy between oral and intravenous antibiotic treatments in stable IEs with no need for surgery, cleared bacteraemia, and absence of fever or complications, caused by a microorganism susceptible to at least two oral antibiotics [4]. However, the results suggested that only about 20% of patients can benefit from this approach, that adherence problems can compromise oral antibiotherapy, especially in polymedicated patients, and that adverse events can result from the prolonged antibiotic treatment, including intestinal microbiota alterations.

Dalbavancin (DBV) is an antibiotic of the lipoglycopeptide family active against GPC. Its pharmacokinetic and pharmacodynamic characteristics mean that the administration for 1 week of 1000 or 1500 mg/iv produces sufficient plasmatic and tissue concentrations to cover 1 or 2 weeks of treatment, respectively. Few clinical data have been published on DVB in patients with IE and/or bacteraemia by GPC [5,6]. In 2019, our group described outcomes obtained with DBV as consolidation therapy in a small number of patients with IE (n = 34) and/or bacteraemia without IE (n = 49) by GPC, reporting an effectiveness of 96.7% [7]. The objective of the present study was to evaluate our 5-year experience in the treatment of IE by GPC with DBV as sequential treatment, determining its effectiveness, safety, mortality, and pharmacoeconomic effect in a larger patient sample.

2. Patients and methods

2.1. Study design

This multicentre, observational, retrospective study included hospitalized patients with IE caused by GPC administered with at least one dose of DBV according to the criteria of the attending physician.

2.2. Patient inclusion period

The study included all patients with IE due to GPC who received at least one dose of DBV from 2016 to June 30 2021 and were followed up for at least 12 months after DBV treatment. The study was approved by the ethics committee of the coordinating hospital (HUVN) (CEIm Granada) and was performed according to the International Council for Harmonization Good Clinical Practice Guidelines.

2.3. Population

Inclusion criteria were age >17 years, diagnosis of IE, microbiological isolation of GPC (in blood cultures, endovascular tissue, pacemaker leads, or automated external defibrillator), and prescription of at least one dose of DBV as IE consolidation therapy. Exclusion criteria were diagnosis of IE not produced by GPC, negative cultures of blood, valve, or electro-cardiac device samples, and pregnancy.

2.4. Variables

Study variables were gathered from the clinical records of patients in accordance with the Organic Law of Personal Data Protection, 3/2018 of December 5, and digital rights guarantees in regulations (EU) 2016/679 of the European Parliament and Council of April 27, 2016.

The following data were entered in a standardized SPSS database: age; sex; dates of hospital admission and discharge, specifying the corresponding departments; age-adjusted Charlson index core; IE characteristics (definite/probable, native/prosthetic, early/late, and presence on device (e.g., pacemaker, automated external defibrillator); previous and concomitant antibiotic treatments of the infection; microorganism responsible for the infection and its antibiogram; dates and doses of DBV administration; adverse events after DBV treatment; the presence of diarrhoea due to *Clostridium difficile*; the need for surgery during the hospital stay or first 12 months following discharge, with date; hospital readmission(s) within 12 months of the last DBV dose; and clinical situation at 12 months after the last DBV dose. After data for these variables had been received for all patients, they were remotely monitored by the coordinating centre.

2.5. Definition of variables

IE was defined according to the modified Duke criteria of 2015 [3]. IE on prosthetic valve was considered early when its onset was during the first 12 months following surgery and late thereafter [8].

Microbiological failure was defined by persistent or breakthrough bloodstream infection during IE treatment [9] or by isolation of the same microorganism in the blood culture of a patient requiring surgery after completing antibiotic therapy.

Table 1
Infective endocarditis characteristics.

	N = 124
Age (years), mean (SD)	67.4 (15.4)
Male, n (%)	87 (70.2)
Charlson index, median (IQR)	4 (2.5–6)
Chronic kidney failure (clearance <60 mL/min), n (%)	33 (26.6)
Haemodialysis, n (%)	2 (1.6)
Peritoneal dialysis, n (%)	1 (0.8)
Diabetes mellitus, n (%)	38 (30.6)
Neurological disease, n (%)	18 (14.5)
HIV infection, n (%)	2 (1.6)
Solid organ transplantation, n (%)	2 (1.6)
Active neoplasm, n (%)	9 (7.3)
Chronic liver disease, n (%)	6 (4.8)
Corticoids/other immunosuppressive drugs in previous month, n (%)	10 (8.1)
Type of infection, n (%)	
Definite IE	113 (91.1)
Probable IE	11 (8.9)
Type of endocarditis, n (%)	
Native	58 (46.8)
Late prosthetic	30 (24.2)
Early prosthetic	24 (19.4)
Pacemaker lead endocarditis	11 (8.9)
Pacemaker lead and valve	1 (0.8)
Valve affected, n (%)	
Aortic	64 (56.6)
Mitral	36 (31.9)
Tricuspid	11 (9.7)
Pulmonary	2 (1.8)
Causative organism, n (%)	
CNS	48 (38.7)
MSSA	28 (22.6)
<i>E. faecalis</i>	24 (19.4)
<i>Streptococcus</i> Spp.	18 (9.7)
<i>E. faecium</i>	3 (2.4)
MRSA	1 (0.8)
<i>Abiactophia defectiva</i>	1 (0.8)
<i>Enterococo caseliflavus</i>	1 (0.8)

CNS, coagulase-negative staphylococci; HIV, human immunodeficiency virus; IE, infective endocarditis; IQR, interquartile range; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*.

IE relapse was defined by a second episode of IE caused by the same microorganism within 3 months [9].

IE reinfection was defined by a new IE within 12 months of DBV treatment caused by a different microorganism to that in the original infection or by the same microorganism >3 months after resolution of the previous infection.

Mortality was classified as hospital mortality (death from any cause during hospital stay or first 30 d following discharge) and mortality at 12 months related to IE (e.g., heart failure due to valve dysfunction) and not related to IE (e.g., cancer).

Age-adjusted Charlson index was used to evaluate the life expectancy at 10 years of patients [10].

Consolidation therapy was considered when DBV was administered as sequential treatment of IE rather than first therapeutic line.

Chronic kidney failure was defined by creatinine clearance <60 mL/min.

2.6. Statistical analysis

In a descriptive analysis, absolute frequencies with 95% confidence interval were calculated for qualitative variables with a normal distribution, and medians with interquartile range (IQR) for those with a non-normal distribution, as established by the Kolmogorov-Smirnov test. The percentage effectiveness at 12 months was calculated by performing two analyses: one taking account of all patients who received at least one dose of DBV and

Table 2
Treatments received.

Heart surgery, valve replacement, and/or device extraction, n (%)	57 (45.9)
- Surgery before DBV administration	52 (91.2)
- Surgery after DBV administration	5 (8.8)
Antibiotic treatment before DBV, n (%)	
first antibiotic treatment, n (%):	122 (98.4)
- Combined	83 (66.9)
- Days of administration, median, and IQR	9.5 (4–13)
second antibiotic treatment, n (%):	75 (60.5)
- Combined	30 (40)
- Days of administration	24.5 (16.5–56)
third antibiotic treatment, n (%):	25 (20.2)
- Combined	8 (32)
- Days of administration, median (IQR)	14.5 (12–19.5)
Previous antibiotics, n (%)	122 (98.4)
Ampicillin	30 (24.4)
Ceftriaxone	43 (34.7)
Ceftazoline	8 (6.5)
Cloxacillin	24 (19.6)
Daptomycin	60 (48.4)
Fosfomycin	2 (1.6)
Gentamycin	22 (18)
Levofloxacin	1 (0.8)
Linezolid	10 (8.1)
Rifampicin	12 (9.8)
Vancomycin	21 (17.2)
Reason for DBV administration, n (%)	
Facilitate discharge	118 (95.2)
Prior treatment failure	3 (2.4)
Adverse events	2 (1.6)
Poor venous access	1 (0.8)
Initial DBV dose, n (%)	
500 mg	1 (0.8)
750 mg	2 (1.6)
1000 mg	55 (44.4)
1500 mg	66 (53.2)
Total DBV dose administered (mg), median (IQR)	1500 mg (1500–2093.7)
Duration of DBV administration in weeks, median (IQR)	2 (2–3.75)
Most frequent DBV regimens, n (%)	
1500 mg (1 d)	44 (33.3)
1000 mg (1 d), 500 mg (8 d)	25 (20.2)
1000 mg 1 d	19 (15.3)
1500 mg (1 d), 1000 mg (15 d)	5 (4)
Other regimen	31 (24.2)
DBV-covered days, median (IQR)	14 (14–25)
DBV administered with concomitant antibiotic, n(%)	16 (12.9)
- Amoxicillin	2 (12.5)
- Levofloxacin or moxifloxacin	3 (18.8)
- Rifampicin	10 (62.5)
- Metronidazole	1 (6.3)

DBV, dalbavancin; IQR, interquartile range.

completed the follow-up, and the other also including the patients lost to the follow-up.

2.7. Pharmacoeconomic study

Costs of the DBV treatment were compared with costs of the six treatments most frequently administered before the switch to DBV, weighting them to obtain an estimated cost. Other costs were provided by the Accounts department in September 2022 (Supplementary Table S1). In the comparative analysis, the costs of microbiological analyses, the management of therapeutic failures, and adverse events were considered equivalent. Costs of the DBV approach included the drug, consultation with infectious disease specialist (to evaluate the clinical status of the infection and manage the treatment), and nursing consultation (for dose administrations). Costs of the previous treatments included the price of the antibiotics for the theoretical duration of their administration plus

the mean stay (in weeks) theoretically covered by the DBV dose. The economic effect of the DBV treatment was expressed as savings per patient.

3. Results

3.1. Population

The study included 124 patients with IE; the mean age was 67.4 years; 70.2% were male; and the median age-adjusted Charlson index was 4 (IQR: 2.5–6). The most frequent comorbidity was diabetes mellitus (30.6%), followed by chronic kidney failure (26.6%). IE was definite in 91.1% of cases and probable in 8.9%. It was native in 46.8%, late prosthetic in 24.2%, early prosthetic in 19.4%, on pacemaker lead in 8.9%, and on pacemaker lead and valve in 0.8%. The aortic valve was the most frequently involved (56.6%), followed by mitral (31.9%), tricuspid (9.7%), and pulmonary (1.8%) valves. Isolated microorganisms included coagulase-negative *staphylococci* (38.7%), *Staphylococcus aureus* (22.6%), *Enterococcus faecalis* (19.4%), *Streptococcus* Spp. (9.7%), *E. faecium* (2.4%), methicillin-resistant *S. aureus* (0.8%), *Abiotrophia defectiva* (0.8%), and *E. caseliflavus* (0.8%). Table 1 provides results for the remaining variables. Vancomycin MIC values available for strains of *S. aureus* and CoNS are listed in Supplementary Table S2.

The total DBV dose administered to treat IE was 1500 mg (IQR 1500–2093.7) for a median of about 2 weeks (IQR: 2–3.75). It was administered to facilitate discharge in 95.2% of patients, as rescue treatment in 2.4%, and as a result of adverse effects of previous antibiotics in 1.6% and poor venous access in 0.8%. Surgery for IE was undergone by 57 patients (45.9%), performed before DBV administration in 52 of them (91.2%). Initial hospital antibiotic treatment for IE was combined in 66.9% ($n = 83$) of cases and administered for a mean of 9.5 d (IQR: 4–13); 60.5% ($n = 75$) of patients received a second regimen for a median of 24.5 d (IQR: 16.5–56), with combined antibiotics in 40% of cases; finally, 20.2% ($n = 25$) received a third antibiotic regimen before the switch to DBV for a median of 14.5 d (IQR: 12–19.5). The most frequently administered antibiotics were daptomycin (48.4%), ceftriaxone (34.7%), ampicillin (24.4%), cloxacillin (19.9%), and vancomycin (17.2%). Table 2 provides the data for the remaining variables.

3.2. Outcomes

One hundred twenty-four patients were followed for at least 12 months. Four of these had a relapse, one was lost to the follow-up, one died from IE on day 67 following discharge, and five from non-related causes at a median of 6 months after discharge (IQR 4.8–8.9) (1 aortic pseudoaneurysm rupture, 1 sepsis during kidney transplantation, 1 advanced heart disease with cardiorespiratory insufficiency, 1 advanced cancer, and 1 malignant haematological disease) (Table 3). The IE-related death was in a 77-year-old woman with a history of aortic pseudoaneurysm and severe aortic stenosis, ventricular dysfunction, and heart failure, with aortic bioprosthesis, chronic kidney failure, diabetes, malignant haematological disease, and Charlson index of 7; the IE was late prosthetic on aortic valve by *S. epidermidis* (MIC to methicillin of 2, vancomycin 2, and daptomycin 0.25). Surgery was ruled out due to the high risk, and she was prescribed 500 mg iv daptomycin/24 h and 800 mg ceftaroline for 20 d. At discharge, she received a single dose of 1500 mg DBV. She was readmitted at 20 d for dyspnea and died from heart failure.

Effectiveness (clinical success) at 12 months was 95.2% when the patient lost to the follow-up was included, and 95.9% when only patients completing the 1-year follow-up were considered. Blood cultures were taken from 79.8% of patients after the DBV

Table 3
Outcomes.

	N = 124
Clinical success, n (%)	
- Effectiveness including loss of follow-up (one IE-related death, four relapse, one loss)	118 (95.2)
- Effectiveness including subjects who completed follow-up (one IE-related death, four relapse)	119 (95.9)
Microbiological healing, n (%)	
- Blood cultures performed after DBV	99 (79.8)
- Negative blood cultures after DBV	99 (100)
Hospital stay reduction (d), median (IQR)	14 (14–25)
IE relapse and readmission within 12 months after DBV treatment, n (%)	4 (3.2)
Loss to follow-up, n (%)	1 (0.81)
Death, n (%)	
- IE-related death	1 (0.8)
- Non-related death	5 (9.7)
Aortic valve pseudoaneurysm	1 (20)
Sepsis related to kidney transplant	1 (20)
Advanced heart disease with cardiorespiratory insufficiency	1 (20)
Advanced oncological disease	1 (20)
Underlying haematological disease	1 (20)
- Median (IQR) months after DBV treatment of IE non-related deaths	6 (4.8–8.9)
- Days after DBV treatment of IE-related deaths	67

DBV, dalbavancin; IE, infective endocarditis; IQR, interquartile range.

Table 4
Adverse effects.

	N = 124
Some adverse effect, n (%)	4 (3.2)
Mild urticarial rash	1 (0.8)
Asthenia	1 (0.8)
Diarrhoea due to <i>Clostridium</i> , n (%)	2 (1.6)

treatment, and all were negative. Finally, DBV treatment reduced the hospital stay by 14 d (IQR: 14–25). Table 3 lists the results for the remaining variables.

3.3. Adverse events

Only four patients (3.2%) had some type of adverse event: One had generalized urticarial rash after the only dose received, two had colitis by *C. difficile*, and one had asthenia (Table 4). One of the patients with diarrhoea due to *C. difficile* was a 63-year-old woman with kidney transplant who had IE on mitral valve by *E. faecium* and a history of two episodes of diarrhoea due to *C. difficile*; she received various meropenem cycles during her hospitalization for infection by Gram-negative bacilli and a 56-d course of daptomycin and ceftaroline; these drugs were replaced with DBV (1125 mg and second dose of 1000 mg at 14 d) due to therapeutic failure. The other patient was a 58-year-old woman with IE due to *S. mitis* on bicuspid aortic valve and severe stenosis with a Charlson index of 3. She was hospitalized for 45 d, undergoing valve replacement and receiving 4 g iv ceftriaxone/24 h for 44 d; DBV was administered in a single dose of 1000 mg to facilitate discharge and reduce her stay by 1 week.

3.4. Pharmacoeconomic study

The cost of DBV per patient, at a median dose of 1500 mg, was 1807.31 €. The cost of the other IE treatments, which required a hospital stay of 14 d, was 7355.88 €, considering a cost of 29.83 €/d. The savings achieved by administration of the DBV treatment vs. the other treatments was estimated at 5548.57 € per patient (Table 5).

Table 5
Pharmacoeconomic analysis.

	Drug cost	Specialist consultation	Nursing consultation	Total
Treatment with DBV 1500-mg dose	1341.90 €	400.83 €	64.58 €	1807.31 €
	Drug cost	Hospital stay (14 d)	Total	
Usual IE treatment 14-d hospital stay	417.62 €	6938.26 €	7355.88 €	
	Drug cost	Consultations and stays	Difference per patient	
Difference between DBV and usual treatment (Ref. DBV)	924.28 €	−6,472.85 €	−5,548.57 €	

DBV, dalbavancin; IE, infective endocarditis.

4. Discussion and conclusions

In this study, patients with IE by GPC were treated with DBV as sequential or consolidation therapy. They were typically elderly and male with major comorbidities (e.g., chronic kidney failure, diabetes, active neoplasm, immunosuppression), having a mean Charlson index of 4. Many of the patients included in this real-life observational study would have been excluded from a clinical trial. In this way, pivotal trials on the role of DBV in skin and soft tissue infections (DISCOVER 1 and 2) [11] excluded immunosuppressed patients and those with active neoplasms or chronic kidney failure; 15% of their patients had a history of parenteral drug addiction; and 15% had diabetes. Advantages of DBV include a reduction in the problems of adherence that polymedicated individuals might have and the avoidance of undesirable drug interactions, due to its administration pathway, long half-life, and low drug interaction profile [12].

With respect to the type of IE in the DBV-treated patients, it was on native valve in 46.8%, prosthetic valve in 43.6%, and pacemaker lead in only 8.9%. Left valves (88.5%) were the most frequently infected, and the aortic valve was involved in more than half of the cases. By order of frequency, the responsible microorganisms were coagulase-negative *staphylococci*, *S. aureus*, and, in approximately 20% of cases, *E. faecalis*. Excellent outcomes were achieved, with very low mortality and relapse rates and an effectiveness of 95.9%. Published data on DBV as IE treatment derive from observational, retrospective, single-centre studies with small patient samples (≤ 30 cases) [13–16], in which DBV was administered as primary or sequential treatment [15]. Good outcomes were described by some studies [17,18], although not in patients of difficult treatment such as parenteral drug addicts [14].

Strengths of the present study include its multicentre design, with the participation of similar centres with experience in the treatment of IE, large patient sample, and homogeneous analysis of the effectiveness of DBV as sequential or consolidation therapy. The results obtained meet the challenge of identifying a first-line option for the consolidation treatment of IE due to GPC in the outpatient setting.

The main reason for administering DBV to these patients was to accelerate their hospital discharge. Indeed, their hospital stay was reduced by 2 weeks, thereby reducing health care costs and improving the patients' quality of life. Its administration to patients with skin and soft tissue infections was previously found to shorten the stay of patients in comparison with standard antibiotic treatment, increasing their work productivity [19] and satisfaction [20].

A very low rate of adverse events was observed, as previously reported [17]. Diarrhoea caused by *C. difficile* in two of our patients is unlikely to be related to the DBV treatment, because both previously had a long course of antibiotics such as ceftriaxone or meropenem, which can produce dysbacteriosis in intestinal flora [18], and one had two previous episodes of colitis. In fact, in vitro studies have found DBV to be active against *C. difficile*, with a po-

tential role in its treatment [21]. In another study, DBV was found to have no effect on the intestinal microbiota [22].

Finally, we highlight the economic effect of outpatient treatment with DBV. As reported by other authors, the reduction in hospital stay compared with conventional parenteral antibiotic treatments yields a savings that more than compensates for the cost of DBV [23].

This study is limited by its retrospective design. In addition, it only included DBV-treated patients and lacked a comparator group, although comparison with other antibiotic regimens was not a study objective. However, its strengths include its multicentre design, large sample size, and its findings on the cost-effectiveness of DBV as sequential antibiotic treatment for IE in a specific setting.

In conclusion, DBV is a highly effective and safe consolidation therapy for patients with IE due to GPC who have adequate clinical and analytical status and only need to remain hospitalized for the recommended intravenous antibiotic treatment, with a very low frequency of adverse events. It is an especially cost-effective approach because it facilitates the discharge of patients, reducing their hospital stay. The reduction in hospital stay achieved with this drug has previously been associated with an increase in the quality of life and productivity of patients [19] and a decrease in their risk of acquiring nosocomial infections [24].

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Competing interests: None declared.

Ethical approval: This cohort of patients was established after obtaining approval from the ethical committee of the coordinating centre (Reference No. 0554-N-22). The study was exempt from requiring the informed consent of patients.

Availability of data and material: The researchers confirm the accuracy of the data provided for the study as well as their availability.

Appendix 1

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.ijantimicag.2023.106918](https://doi.org/10.1016/j.ijantimicag.2023.106918).

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