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David Brandariz-Núñez[1]
Andrea Luances-Rodríguez[1]
Pablo Feijoo-Vilanova[1]
José María Gutiérrez-Urbón[1]
Luis Ramudo-Cela[1,2]
María Isabel Martín-Herranz[1,2]
Luis Margusino-Framiñán[1,2]

Dalbavancin as consolidation therapy for infective endocarditis in patients with comorbidity. A real world experience

[1]Pharmacy Department. Universitary Complex Hospital A Coruña (CHUAC). A Coruña, Spain.
[2]Research Group of Hospital Pharmacy. Institute of Biomedical Research A Coruña (INIBIC), A Coruña University (UDC). A Coruña, Spain

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ABSTRACT

Introduction. Infective endocarditis (IE) is a potentially life-threatening infection, the incidence of which has increased in recent decades, particularly among elderly patients with comorbidity. The primary objective of this study was to evaluate the effectiveness of dalbavancin in the consolidation therapy of IE in patients with comorbidity six months after the end of treatment (EOT).

Material and methods. An observational and retrospective study was conducted on patients with a Charlson Comorbidity Index (CCI) ≥ 3 who were diagnosed with IE and received consolidation therapy with dalbavancin.

Results: Forty-eight patients were included, 58.3% were male, mean age of 76.2 years (IQR: 66-88), and a mean age adjusted CCI of 6.5 (IQR: 5-7.5). Definite IE was diagnosed in 77% of cases. The most frequently isolated microorganisms were *Staphylococcus aureus* (45.8%) followed by *Enterococcus* spp. (31.3%). Complications of IE were observed in 67.7% of cases, and cardiac surgery was performed in 27% of patients. The primary reason for using dalbavancin was outpatient parenteral antibiotic therapy in 85.4% of cases. The effectiveness at EOT was 93.8%. At six months, six IE-related deaths, four unrelated deaths, and two IE relapses were observed. The effectiveness was 77%. Adverse effects related to DBV were reported in 4.2% of cases, of which 2% were considered serious.

Conclusion. Dalbavancin has proven to be an effective alternative as consolidation antibiotherapy for IE in elderly patients with comorbidity. Moreover, a very favorable safety profile with few associated adverse effects has been observed in this population.

Keywords: dalbavancin, infective endocarditis, comorbidity, infective endocarditis complications.

Correspondence:
David Brandariz-Núñez
Pharmacy Department, Universitary Complex Hospital A Coruña (CHUAC). A Coruña, Spain.
E-mail: vrandariz@gmail.com

Dalbavancina como terapia de consolidación para endocarditis infecciosa en pacientes con comorbilidad. Una experiencia en mundo real

RESUMEN

Introducción. La endocarditis infecciosa (EI) es una infección potencialmente mortal, cuya incidencia ha aumentado en las últimas décadas, especialmente entre los pacientes ancianos con comorbilidad. El objetivo primario de este estudio fue evaluar la eficacia de dalbavancina en la terapia de consolidación de la EI en pacientes con comorbilidad seis meses después del final del tratamiento.

Material y métodos. Se realizó un estudio observacional y retrospectivo en pacientes con un Índice de Comorbilidad de Charlson (ICC) ≥ 3 diagnosticados de EI y que recibieron terapia de consolidación con dalbavancina.

Resultados. Se incluyeron 48 pacientes, 58,3% varones, edad media de 76,2 años (IQR: 66-88) y un ICC ajustado por edad medio de 6,5 (IQR: 5-7,5). Se diagnosticó EI definitiva en el 77% de los casos. Los microorganismos aislados con mayor frecuencia fueron *Staphylococcus aureus* (45,8%) seguido de *Enterococcus* spp. (31,3%). Se observaron complicaciones de la EI en el 67,7% de los casos, y se practicó cirugía cardiaca en el 27% de los pacientes. El motivo principal del uso de DBV fue la terapia antibiótica parenteral ambulatoria en el 85,4% de los casos. La eficacia al final del tratamiento fue del 93,8%. A los seis meses, se observaron seis muertes relacionadas con EI, cuatro muertes no relacionadas y dos recaídas de EI. La eficacia fue del 77%. Se notificaron efectos adversos relacionados con la DBV en el 4,2% de los casos, de los cuales el 2% se consideraron graves.

Conclusiones. Dalbavancina ha demostrado ser una alternativa eficaz como antibioterapia de consolidación para la EI en pacientes ancianos con comorbilidad. Además, en esta población se ha observado un perfil de seguridad muy favorable con escasos efectos adversos asociados.

Palabras clave: dalbavancina, endocarditis infecciosa, comorbilidad, complicaciones de endocarditis infecciosa.

INTRODUCTION

Infective endocarditis (IE) is a potentially life-threatening infection, the incidence of which has increased in recent decades, particularly among elderly patients with comorbidity [1]. Within this demographic, enterococci and *Staphylococcus aureus* are frequently cited as the primary causative agents [2]. The treatment regimen for IE typically entails prolonged administration of intravenous (IV) antibiotics, often necessitating extended hospitalization periods, frequently coupled with surgical intervention to address the source of infection [3,4].

Dalbavancin (DBV) is a lipoglycopeptide derived from teicoplanin with activity against Gram-positive cocci (GPC), including *Streptococcus* spp., *Enterococcus* spp., and *Staphylococcus* spp. [5]. In terms of pharmacokinetics, it boasts a prolonged half-life, allowing for sustained therapeutic concentrations in both plasma and tissues, thereby enabling antibiotic coverage for 1 or 2 weeks following a single IV dose of 1000 mg or 1500 mg, respectively [6]. The metabolism of DBV remains largely unknown, with over half of the compound excreted unchanged in both urine and feces. No dose adjustment is required for individuals with mild to moderate renal impairment, any degree of hepatic impairment, or those undergoing renal replacement therapy. However, dose adjustment is necessary in cases of severe renal dysfunction. Currently, DBV holds exclusive approval for the treatment of acute bacterial skin and skin structure infections, supported by findings from pivotal trials DISCOVER 1 and 2 [8]. In the realm of bloodstream infections, weekly administration of DBV has demonstrated superior efficacy compared to parenteral vancomycin in catheter-related infections [9]. However, evidence regarding the efficacy of DBV in GPC-associated IE among elderly patients with comorbidity remains limited [10-13].

The primary objective of this study was to evaluate the effectiveness of DBV in the consolidation therapy of IE in patients with comorbidity six months after the end of treatment (EOT). Secondary objectives were to determine all-cause mortality at six months after EOT and adverse effects (AEs) related to DBV.

MATERIAL AND METHODS

Study design and population. An observational and retrospective study was conducted on patients with comorbidity and GPC-associated IE, who underwent consolidation treatment with DBV. The study took place in a highly complex tertiary center with 1,423 hospital beds and a reference population of 551,703 inhabitants. The recruitment period spanned from January 2018 to September 2023. The inclusion criteria comprised patients with a Charlson Comorbidity Index (CCI) ≥ 3, who had received at least one dose of DBV, and who were clinically afebrile with negative blood cultures prior to DBV administration. Patients were followed up for six months after their last dose of DBV, constituting the follow-up phase. Clinical management and DBV treatment were adjusted according to the hospital's standard clinical practices.

Outcomes and study definitions. IE was defined by applying the modified Duke criteria updated in 2023 [14]. Early-onset IE was considered if it developed within 12 months after valve replacement, while late-onset IE occurred from 12 months after surgery. Consolidation therapy was considered when DBV was administered as sequential treatment for IE rather than as the initial therapeutic line. The effectiveness of DBV was assessed based on IE failure and cure at EOT and at six months post-EOT. Cure of infection was defined as the absence of microbiological failure and/or clinical signs or symptoms of infection. Microbiological failure was defined as breakthrough bloodstream infection during IE treatment or isolation of the same microorganism in blood culture after completing antibiotic therapy. Failure was defined as a composite of variables: persistence of signs or symptoms of infection, microbiological failure, death, or relapse of IE. Relapse of IE was defined as a second episode of IE caused by the same microorganism during the follow-up period. Mortality was categorized as EOT mortality (death from any cause during hospital stay or within the first month after discharge), mortality during follow-up from the second month after discharge, related (caused by IE complications) or unrelated to IE. The safety profile of DBV was evaluated by documenting AEs attributed to DBV and their severity, as assessed by the necessity to discontinue the antibiotic or the need for therapeutic intervention to manage AEs. The CCI was utilized to assess the 10-year life expectancy of the patients [15]. Plasma level monitoring was not conducted during the study. In patients lacking DBV susceptibility testing, vancomycin sensitivity was regarded as a surrogate indicator of DBV susceptibility [16].

Data collection. Data was collected through the electronic clinical records, including age and sex, comorbidities and CCI, duration of hospital stay and admission to the intensive care unit (ICU); type of IE according to the diagnosis, valve involved and location and presence IE complications; type and duration of previous treatment received (since blood culture negative and/or surgery, if postsurgical culture positive) and concomitant antibiotic treatment; microorganism involved, minimum inhibitory concentration (MIC) of vancomycin and DBV (Etest® method) and susceptibility according to the European Committee for Antimicrobial Susceptibility Testing (EUCAST); dose, dosing regimen, number of doses and duration of DBV treatment, adjusted renal dose, reason for DBV administration and reduction of hospitalisation duration (excluding cases with prolonged suppressive antibiotic treatment) compared to conventional theoretical intravenous treatment and total duration of antibiotics received; cardiac surgery and/or other related surgeries and follow-up blood cultures; cure of infection or failure and microbiological failure at EOT and at six months, mortality at EOT, mortality at 6 months related or not to IE, relapse of IE and AEs related to DBV along their severity.

Ethics considerations. The study adhered to the ethical standards outlined in the Helsinki Declaration. It underwent review by the Galician Drug Ethics Committee (CEIm-G) and

Table 1 Demographic, clinical and treatment characteristics of patients with IE treated with DBV (n=48)

Variable	n (%)
Demographic	
Age (years), mean (IQR)	76.2 (66-88)
Age ≥ 80 years	21 (43.8)
Male gender	28 (58.3)
Medical history	
Solid neoplasm	13 (27)
Hematological neoplasm	5 (10.4)
Solid organ transplant	2 (4.2)
Immunosuppressive treatment	4 (8.3)
Obese	9 (18.8)
Chronic renal disease	13 (27)
Chronic hepatic disease	6 (12.5)
Hemodialysis	1 (2)
Diabetes mellitus	19 (39.6)
Congestive heart failure	17 (35.4)
Cerebrovascular disease	7 (14.9)
Previous IE	6 (12.5)
Chronic lung disease	5 (10.4)
Acute coronary syndrome	6 (12.5)
HIV	1 (2)
CCI, mean (IQR)	6.5 (5-7.5)
IE Type	
Type of valve	
Native valve	24 (50)
Prosthetic valve	18 (37.5)
Early	5 (10.4)
Late	13 (27)
Intracardiac device	5 (10.4)
Intracardiac device and valve	1 (2)
Valve affected	
Aortic	24 (50)
Mitral	11 (22.9)
Tricuspid	6 (12.5)
Aortic and mitral	2 (4.2)

Variable	n (%)
Microbiological isolation	
S. aureus	22 (45.8)
MSSA	13 (27)
MRSA	9 (18.8)
Enterococcus spp.	15 (31.3)
E. faecalis	14 (29.2)
E. faecium	1 (2)
Streptococcus spp.	4 (8.3)
Coagulase-negative staphylococci	7 (14.6)
Unknown	1 (2)
IE complications	32 (67.7)
Septic shock	4 (8.3)
Septic embolism	14 (29.2)
Musculoskeletal manifestations[a]	10 (20.8)
Cardiac complication	18 (37.5)
Heart failure	20 (41.7)
Perivalvular abscess	3 (6.25)
Conduction alteration	2 (4.2)
Neurological complication	6 (12.5)
Ischemic Stroke	5 (10.4)
Cerebral haemorrhage	1 (2)
Acute renal failure	10 (20.8)
Rheumatologic manifestations	2 (4.2)
Leukocytoclastic vasculitis.	2 (4.2)
Treatment	
Reason for DBV use	
OPAT	41 (85.4)
Toxicity of previous treatment	5 (10.4)
Venous access related problems	2 (4.2)
Number of doses of DBV received, mean (IQR)	1.7 (1-2)
Duration of DBV treatment (weeks), mean (IQR), median	3.2 (2-4), 2
Reduction in hospitalisation duration (weeks), mean (IQR)	2.3 (2-4)
Dose adjusted to renal function	4 (8.3)
Cardiac surgery	14 (29.2)
Duration of previous antibiotic treatment, mean (IQR)	3.6 (2-4)
Combination treatment with DBV	14 (29.2)
Rifampicin	13 (27)
Cefditoren	1 (2)

IE, infective endocarditis; DBV, dalbavancin; HIV, human immunodeficiency virus; CCI, Charlson comorbidity index; MSSA, methicillin-sensitive *S. aureus*; MRSA, methicillin-resistant *S. aureus* OPAT, outpatient parenteral antibiotic therapy.

[a]Osteomyelitis, spondylodiscitis, pyomyositis with abscesses of musculoskeletal location.

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Statistical analysis. A descriptive study was conducted on the collected variables. Qualitative variables were presented as numbers and frequencies, while quantitative variables were summarized using measures of central tendency (mean and median) and measures of dispersion (interquartile range). The comparison of qualitative variables was carried out using the Fisher's exact test. A *p*-value less than 0.05 was considered statistically significant. All statistical analyses were performed using JASP Team (2024), JASP (Version 0.18.3).

Table 2 **Effectiveness and safety outcomes of IE patients treated with DBV (n=48).**

Outcomes	n (%)
Effectiveness	
EOT	
Mortality	3/48 (6.2)
Cure of infection	45/48 (93.8)
Follow-up phase (six months)	
Mortality	10/48 (20.8)
Related to IE	6/48 (12.5)
Not related to IE	4/48 (8.3)
Microbiological failure	2/48 (4.2)
Relapse	2/48 (4.2)
Cure of infection	37/48 (77)
Security	
Related AEs	2/48 (4.2)
Severe AEs	1/48 (2)

IE, infective endocarditis; DBV, dalbavancin; EOT, end of treatment; AEs, adverse effec

RESULTS

Patient's characteristics and treatment. Forty-eight patients with comorbidity and GPC-associated IE were included in our study, 58.3% were male, mean age was 76.2 years (IQR: 66-88) and mean age-adjusted CCI was 6.5 (IQR:5-7.5). According to diagnosis, definite IE was present in 77% of patients. It was native in 47.9%, prosthetic in 39.6% and intracardiac device in 10.4%. The most frequent microbiological isolates were *S. aureus* (45.8%) followed by *Enterococcus* spp. (31.3%). Demographic, clinical, microbiological and treatment characteristics are shown in Table 1. MIC to DBV was tested in 33.3% of cases (Table 1 - Supplementary material). The mean duration of hospital stay was 39 days (IQR:22.3-50.3) and 20.8% of cases required ICU admission. Control blood cultures were performed after DBV administration in 75% of the cases. Additional patient characteristics are displayed in Table 1 - Supplementary material.

Effectiveness and security. Cure of infection at EOT was 93.8%. Table 2 shows the effectiveness and security of the 48 patients treated with DBV. Three patients experienced fatal outcomes related to IE at EOT (cases 14, 29 and 48). In all of them, cardiac surgery was not recommended due to their age, comorbidity, and functional status. Case 14 was a frail elderly who two weeks after hospital discharge suffered a progressive worsening of his general condition with acute renal failure and fatal outcome. The case 29 suffered clinical deterioration with acute decompensated heart failure and death two weeks after leaving hospital. Case 48 expired due to severe aortic insufficiency with cardiogenic shock two weeks later discharge clearance. During the follow-up period, two relapses and seven deaths were reported, three related to IE complications (cases 11, 38 and 40). The mean time from hospital discharge to death was 67.2 days (54.3-89.6). Case 38 presented a relapse with poor evolution, multi-organ failure and finally death two and a half months after discharge from hospital. Case 11 was an elderly dependent patient who, three months after hospital discharge, was admitted for decompensated heart failure for depletive treatment, without success. Finally, case 40 presented significant anasarca caused by heart failure and acute renal failure with death, two months after release from hospital. Figure 1 presents effectiveness results of DBV according to the presence or absence of IE related complications, the type of IE, and the microorganism involved. The additional data related to effectiveness of DBV are shown in Table 1 - Supplementary material.

Regarding security, AEs related to DBV have been documented in 4.2% of patients (Table 2). A case with impaired renal function after 3 doses and a case of acute thrombopenia with epistaxis in a patient with a history of autoimmune thrombopenia. This was the only event (2%) considered as severe, requiring antibiotic withdrawal and additional treatment (corticosteroids and immunoglobulins). All AEs were reversible upon completion of DBV treatment.

DISCUSSION

In this real-life study, we present a cohort of patients with IE undergoing DBV consolidation therapy, characterized by advanced age and comorbidity. Prolonged hospitalization resulting from intravenous antibiotic treatment poses significant challenges, including difficulties in venous access, catheter-related infections, and IV-associated falls, thereby considerably impacting the patients' functional status [17]. DBV demonstrates favourable pharmacokinetic/pharmacodynamic (PK/PD) characteristics, allowing for extended dosing intervals that facilitate early patient discharge [6]. The primary reason for DBV utilization in our study was OPAT, which demonstrated a reduction in hospitalization duration of approximately 2 weeks per patient. Additionally, this approach yields positive economic implications compared to conventional antibiotic treatment, as previously noted by other authors [13,18]. Other advantages of DBV include reducing adherence issues and pharmacological interactions (DBV does not interfere with cytochrome P450), especially in polymedicated patients with comorbidity [7].

In our study, the effectiveness rate of DBV in the sequential treatment of IE in patients with comorbidity was 93.8% at EOT and 77% at six months. In the elderly population, previous evidence has shown a significant increase in in-hospital mortality rates, ranging from around 18% to 22%, especially among octogenarian patients with comorbidity, reaching close to 40% [1,19]. The observed effectiveness of DBV in the consolidation treatment of IE is satisfactory to date but difficult to establish due to the lack of uniformity in the definition of infection

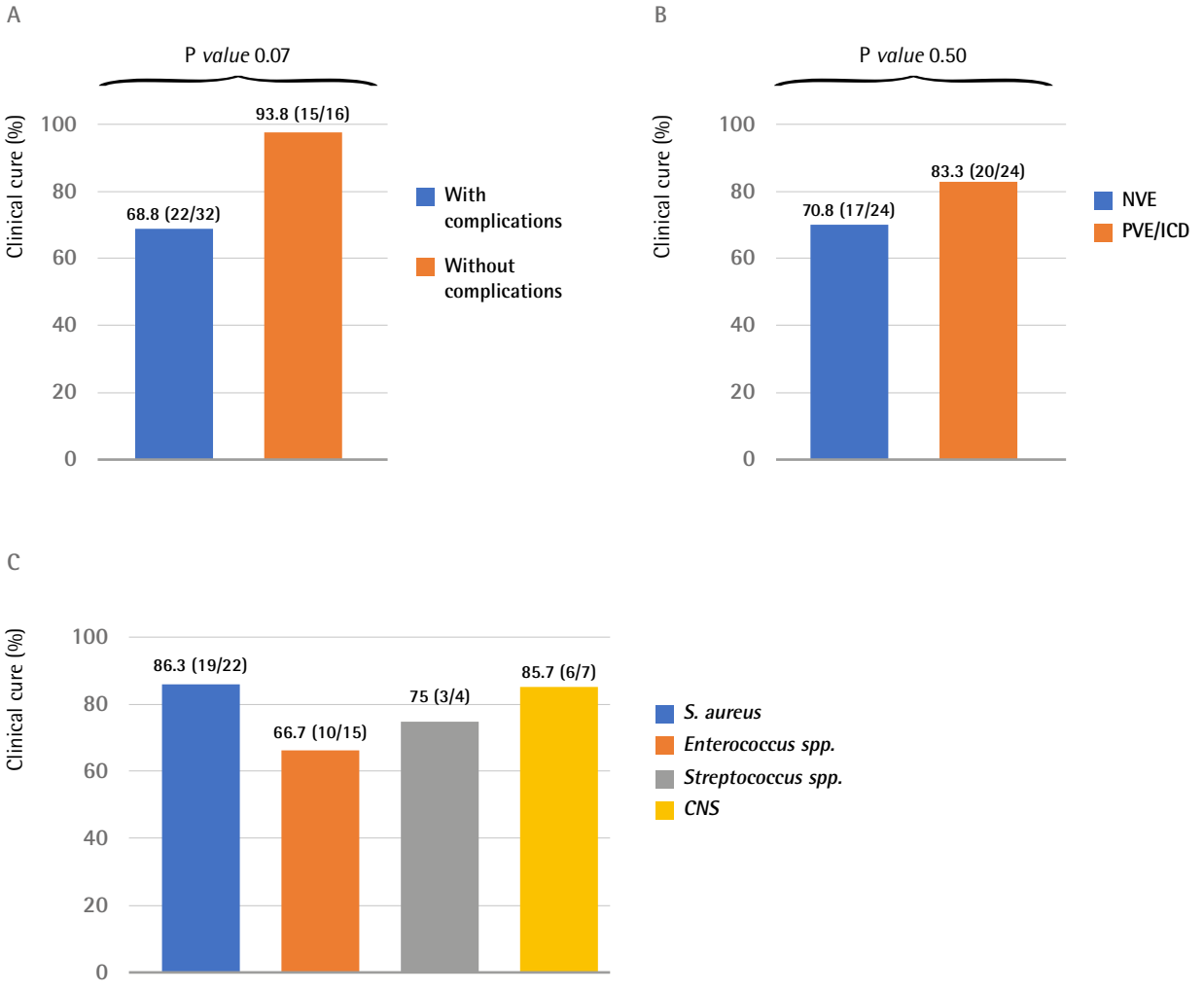

Figure 1 | **Effectiveness of DBV as consolidation at 6 month of IE patients: (A) according to the presence or absence of IE-associated complications, (B) according to the type of IE and (C) according to the microorganism involved.**

DBV, dalbavancin; IE, infective endocarditis; NVE, native valve endocarditis; prosthetic valve endocarditis; IDE, intracardiac devide endocarditis; CNS, coagulase negative *Staphylococcus.*

cure [10-13,20]. In a recent Spanish multicentre study involving 124 IE cases, clinical cure was achieved within 12 months in 95% of patients [21]. Discrepancies in efficacy compared to our study might be attributed to a younger, less comorbid population with a higher proportion undergoing curative cardiac surgery. Recent evidence indicates that surgery can significantly enhance survival within the first year [22]. In our study, only one-third of patients underwent cardiac surgery, thus a lower frequency of surgical interventions and higher mortality rates are characteristic of IE episodes in the elderly compared to the younger population [23]. Furthermore, two-thirds of our population experienced IE-related complications. Cardiac and neurological complications of IE are associated with a poorer prognosis of the infection [24,25]. The presence of complications in our cohort worsened DBV outcomes compared to those without complications.

At the microbiological level, enterococci-associated IE exhibited the poorest outcomes. A recent study comparing DBV to standard of care revealed that at 12 months, *E. faecalis* was responsible for the majority of treatment failures [26]. Nonetheless, other studies involving enterococci demonstrated successful outcomes with DBV in consolidation therapy [20,21]. Furthermore, advanced age and comorbidities that may contraindicate reparative surgery were characteristic factors of enterococcal IE, which could influence the prognosis in our study. Therefore, further research is warranted to elucidate the role of DBV in the treatment of IE caused by *Enterococcus* spp.

In 10% of cases, DBV was employed, withdrawn due to toxicity from previous antibiotics. Despite this, DBV has been shown to have a very favourable safety profile in our cohort of patients with significant comorbidity, with a low incidence of related AEs (4.2%). These findings are in accordance with previously published cohort studies with large numbers of patients [21,27]. In addition, AEs considered as serious were limited (2%), with only one patient requiring DBV withdrawal and additional treatment. In prosthetic cardiovascular infections with indication for implant removal, but without extraction due to contraindication, long-term antibiotic treatment or lifelong antibiotic treatment is recommended [28-30]. A patient who received prolonged treatment with DBV for six months showing adequate tolerance. This fact places DBV as a good alternative to oral therapy for intravascular infections requiring prolonged suppressive treatment, particularly in elderly patients with comorbidity.

Our study has some limitations that should be considered. It is an observational and retrospective study conducted in a single centre, with a heterogeneous population and without a comparator antibiotic treatment group.

In conclusion, DBV offers important advantages due to its pharmacokinetic profile that allows OPAT, shortening hospital stay and reducing complications associated with prolonged conventional intravenous antibiotic therapy. It also reduces adherence problems and drug interactions, especially in polymedicated patients with comorbidity. DBV has proven to be an effective alternative as a consolidation antibiotherapy for GPC-associated IE in elderly patients with comorbidity. Moreover, a very favourable safety profile with few associated AEs has been observed in this population.

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None to declare.

CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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