International Journal of Antimicrobial Agents 53 (2019) 165–170

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Short Communication

Teicoplanin for treating enterococcal infective endocarditis: A retrospective observational study from a referral centre in Spain

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ARTICLE INFO

Article history:
Received 16 May 2018
Accepted 6 October 2018

Editor: Jean-Marc Rolain

Keywords:
Infective endocarditis
Teicoplanin
Enterococcus faecalis
Enterococcus faecium
Outpatient parenteral antimicrobial therapy

ABSTRACT

This study aimed to evaluate the effectiveness and safety of teicoplanin for treating enterococcal infective endocarditis (EIE). A retrospective analysis of a prospective cohort of definite EIE patients treated with teicoplanin in a Spanish referral centre (2000–2017) was performed. The primary outcome was mortality during treatment. Secondary outcomes were mortality during 3-month follow-up, adverse effects and relapse. A total of 22 patients received teicoplanin, 9 (40.9%) as first-line (8 *Enterococcus faecium* and 1 *Enterococcus faecalis*) and 13 (59.1%) as salvage therapy (13 *E. faecalis*). Median (IQR) age was 71.5 (58.3–78) years and Charlson comorbidity index was 4.5 (3–7). Five (22.7%) affected prosthetic valves. Median duration of treatment in survivors was 53 (42.5–61) days for antibiotics and 27 (17–41.5) days for teicoplanin [median dose 10 (10–10.8) mg/kg/day]. Reasons for teicoplanin use were resistance to β-lactams (40.9%), adverse events with previous regimens (31.8%) and outpatient parenteral antimicrobial therapy (OPAT) (27.3%). Teicoplanin was withdrawn due to adverse events in 2 patients (9.1%). Five patients (22.7%) died during treatment: four in the first-line (three with surgery indicated but not performed) and one in the salvage therapy group (surgery indicated but not performed). Two deaths (11.8%) occurred over the 3-month follow-up. There were no relapses during a median of 43.2 (22.1–69.1) months. Teicoplanin can be used as an alternative treatment for susceptible *E. faecium* IE and as a salvage therapy in selected patients with *E. faecalis* IE when adverse events develop with standard regimens or to allow OPAT.

1. Introduction

Enterococci are the third most common cause of infective endocarditis (IE), being responsible for ca. 10–15% of all cases [1]. Enterococcal IE (EIE) mainly affects older patients with prosthetic valves and the infection is often nosocomially acquired [1–3]. *Enterococcus faecalis* is the species most commonly isolated causing almost 90% of EIE cases, followed by *Enterococcus faecium* causing almost 5%, and other species [4].

Treatment of EIE is known to be difficult and medical management is a challenge. This is mainly because of the often poor bactericidal activity of penicillin or ampicillin when used as monotherapy, the potential toxicity of aminoglycosides and the increasing incidence of high-level aminoglycoside resistance (HLAR) [5].

Standard treatment for *E. faecalis* IE is ampicillin in combination with an aminoglycoside for non-HLAR strains or with ceftriaxone for strains with or without HLAR [6]. In contrast to *E. faecalis*, over 90% of *E. faecium* clinical isolates are reported to be ampicillin-resistant; vancomycin combined with gentamicin is the recommended therapy in susceptible strains [7,8].

Teicoplanin has been proven to be effective for treating experimental EIE [9–13]. This drug has no associated renal toxicity and it is a given as a single-dose parenteral regimen. This implies undeniable benefits for patient quality of life, as they can be discharged with outpatient parenteral antimicrobial therapy (OPAT), as well as cost benefits for the publicly-funded healthcare system. However, to our knowledge, there is scarce clinical experience investigating teicoplanin use for Gram-positive IE, and enterococci are little represented in the available studies [14–17].

In our institution, teicoplanin is being used to treat *E. faecium* IE instead of vancomycin to avoid nephrotoxicity, and as salvage

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https://doi.org/10.1016/j.ijantimicag.2018.10.003
0924-8579/

Table 1
Demographic features, co-morbidities, aetiology, presumed source of infection and echocardiography findings in 22 episodes of enterococcal infective endocarditis (IE) treated with teicoplanin[a].

	Overall ($N = 22$)	First-line therapy ($N = 9$)	Salvage therapy ($N = 13$)
Demographics			
Age (years) [median (IQR)]	71.5 (58.3–78)	75 (64.5–83)	64 (53.5–74.5)
Male sex	17 (77.3)	7 (77.8)	10 (76.9)
Co-morbidities			
CCI [median (IQR)]	4.5 (3–7)	6 (4.5–8.5)	3 (2–6)
Chronic renal failure[b]	9 (40.9)	5 (55.6)	4 (30.8)
Diabetes mellitus	7 (31.8)	3 (33.3)	4 (30.8)
Transplantation	3 (13.6)	2 (22.2)	1 (7.7)
Neoplasm	3 (13.6)	2 (22.2)	1 (7.7)
Liver cirrhosis	1 (4.5)	1 (11.1)	0
HIV infection	1 (4.5)	1 (11.1)	0
Aetiology			
Enterococcus faecalis	14 (63.6)	1 (11.1)	13 (100)
Enterococcus faecium	8 (36.4)	8 (88.9)	0
Healthcare-associated infection	17 (77.3)	8 (88.9)	9 (69.2)
Presumed source of infection			
Gastrointestinal	8 (36.4)	5 (55.6)	3 (23.1)
Urinary tract	6 (27.3)	2 (22.2)	4 (30.8)
Unknown	6 (27.3)	2 (22.2)	4 (30.8)
Other[c]	2 (9.1)	0	2 (15.4)
Duration of symptoms (days) [median (IQR)]	16 (4.8–35.3)	16 (7.5–19.5)	23 (3–69)
Type of IE			
Native valve	16 (72.7)	6 (66.7)	10 (76.9)[d]
Prosthetic valve	5 (22.7)	2 (22.2)	3 (23.1)[e]
Non-valvular endocardium	1 (4.5)	1 (11.1)	0
Heart valve affected			
Aortic	8 (36.4)	4 (44.4)	4 (30.8)
Mitral	8 (36.4)	3 (33.3)	5 (38.5)
Aortic and mitral	4 (18.2)	1 (11.1)	3 (23.1)
Aortic, mitral, tricuspid and pulmonary	1 (4.5)	0	1 (7.7)
Vegetation size (mm) [median (IQR)]	8 (5.5–11)	7 (5–8)	9.5 (6.5–16.3)
Echocardiographic findings			
Moderate or severe valvular insufficiency	11 (50.0)	4 (44.4)	7 (53.8)
Valve perforation	4 (18.2)	1 (11.1)	3 (23.1)
Pseudoaneurysm	3 (13.6)	2 (22.2)	1 (7.7)
Periprosthetic leak	2 (9.1)	1 (11.1)	1 (7.7)
Perivalvular abscess	2 (9.1)	1 (11.1)	1 (7.7)
Valve chord rupture	1 (4.5)	1 (11.1)	0

IQR, interquartile range; CCI, Charlson comorbidity index; HIV, human immunodeficiency virus.
[a] Data are *n* (%) unless otherwise stated.
[b] Three on haemodialysis (one in the first-line therapy group and two in the salvage therapy group).
[c] A catheter-related bloodstream infection and an infected abdominal aortic endoprosthesis.
[d] One patient also had an aortic abdominal endoprosthesis infection.
[e] One patient had a prosthetic aortic valve with an aortic root replacement.

therapy in *E. faecalis* IE because of adverse events with previous regimens or to enable continuation of therapy at home with a single daily dose. The objective of this study was to evaluate the effectiveness and safety of teicoplanin administered for the treatment of EIE.

2. Methods

This observational, retrospective, single-centre cohort study was performed at Vall d'Hebron University Hospital, a 1000-bed teaching hospital in Barcelona, Spain, that includes all major medical and surgical departments and is a referral centre for IE and cardiac surgery. All consecutive adult patients ≥18 years of age with a diagnosis of definite EIE and treated with teicoplanin as a first-line or salvage therapy at this centre from January 2000 through September 2017 were included.

Patients were retrospectively identified from the Infectious Diseases Registry where all episodes of IE are prospectively recorded [18]. Demographic data as well as clinical, diagnostic, treatment, destination at hospital discharge and follow-up data were obtained from the prospective endocarditis registry of the centre [18]. The reason for teicoplanin use and adverse events were obtained from the patients' medical charts and were entered in a database created specifically for this study.

The primary endpoint was all-cause mortality during treatment. Secondary endpoints were all-cause mortality over a 3-month follow-up period after finishing antimicrobial treatment, adverse events, interruption of teicoplanin due to adverse events, and relapse.

Quantitative variables are reported as the median (interquartile range) and qualitative variables are reported as the number and percentage. Statistical analyses were performed with IBM SPSS-PC+ v.22.0 (IBM Corp., Armonk, NY).

This study was approved by the Hospital Ethics Committee of Vall d'Hebron University Hospital and by the Spanish Drug Agency. Informed consent from patients was not required.

3. Results

3.1. Description of the overall series

A total of 22 patients received teicoplanin for EIE during the study period, including 9 (40.9%) as first-line therapy and 13 (59.1%) as salvage therapy. The demographic features, co-morbidities, aetiology, presumed source of infection and echocardiography findings are shown in Table 1. A total of 14 episodes (63.6%) were caused by *E. faecalis* (13 in the salvage therapy group) and 8 (36.4%) were caused by *E. faecium* (all in the first-line

Table 2
Complications, surgical treatment and outcomes of 22 episodes of enterococcal infective endocarditis (IE) treated with teicoplanin.

	n (%)		
	Overall ($N=22$)	First-line therapy ($N=9$)	Salvage therapy ($N=13$)
Complications			
Patients with ≥1 complication	15 (68.2)	7 (77.8)	8 (61.5)
Heart failure	10 (45.5)	5 (55.6)	5 (38.5)
New renal failure	5 (22.7)	3 (33.3)	2 (15.4)
Symptomatic embolism	4 (18.2)[a]	1 (11.1)	3 (23.1)
Paravalvular complication	4 (18.2)	2 (22.2)	2 (15.4)
Stroke	2 (9.1)	1 (11.1)	1 (7.7)
Surgery indicated	13 (59.1)	6 (66.7)	7 (53.8)
Indications for surgery (two patients had >1 indication)			
Heart failure	8/13 (61.5)	3/6 (50.0)	5/7 (71.4)
Locally uncontrolled infection	4/13[b] (30.8)	2/6 (33.3)	2/7 (28.6)
Severe valve regurgitation without heart failure	2/13 (15.4)	0/6	2/7 (28.6)
Persisting positive blood cultures despite appropriate antibiotic therapy	1/13 (7.7)	1/6 (16.7)	0/7
Surgery performed during the active phase of infection (if indicated)	4/13 (30.8)	1/6 (16.7)	3/7 (42.9)
Reasons for no surgery, if indicated			
High-risk patient	4/9 (44.4)	3/5 (60.0)	1/4 (25.0)
Critical status	2/9 (22.2)	2/5 (40.0)	0/4
Good outcome without surgery	2/9 (22.2)	0/5	2/4 (50.0)[c]
Active intravenous drug use	1/9 (11.1)	0/5	1/4 (25.0)
Mortality during treatment			
Overall	5 (22.7)	4 (44.4)	1 (7.7)
Without indication for surgery	1/5 (20.0)	1/4 (25.0)[d]	0/1
Surgery indicated and performed	–	–	–
Surgery indicated and not performed	4/5 (80.0)	3/4 (75.0)[e]	1/1 (100)[f]
Hospital discharge			
OPAT	12/17 (70.6)	3/5 (60.0)	9/12 (75.0)
Transferred to another hospital	3/17 (17.6)	1/5 (20.0)	2/12 (16.7)
Home	2/17 (11.8)	1/5 (20.0)	1/12 (8.3)
Death during 3 months follow-up	2/17 (11.8)	1/5 (20.0)[g]	1/12 (8.3)[h]
Surgery during follow-up[i]	2/17 (11.8)	0/5	2/12 (16.7)
Relapse	0	0	0

OPAT, outpatient parenteral antimicrobial therapy.
[a] Two in the spleen, one in the lungs and one in the spine.
[b] Two patients with a pseudoaneurysm, one with a pseudoaneurysm and a perivalvular abscess and one with a perivalvular abscess.
[c] Indication for surgery of the two patients with good outcome without surgical intervention was severe valvular insufficiency according to 2004 guidelines.
[d] This was a cirrhotic patient who died due to massive haematemesis and hepatic encephalopathy after 12 days of treatment.
[e] Two patients died due to refractory septic shock after 5 days and 9 days of treatment, and one due to heart failure after 52 days.
[f] Died due to refractory heart failure with repeatedly negative blood cultures after 32 days of treatment.
[g] Unknown cause of death.
[h] Died secondary to nosocomial pneumonia with unknown aetiology acquired during the hospitalisation for IE.
[i] Two mitral valvuloplasties.

therapy group). All eight *E. faecium* isolates were susceptible to vancomycin and teicoplanin. All 14 *E. faecalis* isolates were susceptible to ampicillin, vancomycin and teicoplanin, and 5 had HLAR according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) recommendations. Surgery was indicated based on the clinical guidelines in use at the time of the diagnosis in 13 patients (59.1%) but was only performed during the active phase of infection in 4 (30.8%) of them.

3.2. Outcomes

Of the 22 patients, 5 (22.7%) died during treatment (4 in the first-line therapy group and 1 in the salvage therapy group) (Table 2). Of the four patients in the first-line therapy group, one did not have an indication for surgery and the other three patients had a surgery indication but they were not operated due to their critical clinical status and high surgical risk (Table 3). The single patient who died in the salvage therapy group had a surgery indication due to heart failure but was not operated because of active intravenous drug abuse. Two additional patients died before completing 3 months of follow-up: one in the first-line therapy group with an indication for surgery but not operated, and one in the salvage therapy group without a surgery indication.

All-cause mortality at 90 days was 31.8% (7 patients). The median length of follow-up in survivors was 43.2 (22.1–69.1) months. There were no relapses, and two mitral valvuloplasty procedures were performed in the salvage therapy group during follow-up.

3.3. Use of teicoplanin

The median length of antimicrobial therapy was 43.5 (38.8–56.3) days overall and 53 (42.5–61) days in survivors. The median length of teicoplanin therapy was 23 (12.8–41.3) days overall and 27 (17–41.5) days in survivors, with a median dose of 10 (10–10.8) mg/kg/day following an induction dose of twice-daily dosing the first day of treatment in all cases. Reasons for teicoplanin use were antimicrobial resistance to β-lactams (9 patients; 40.9%), adverse events with previous regimens (7; 31.8%) and OPAT (6; 27.3%).

In the first-line therapy group, the reason for teicoplanin use was β-lactam resistance in all 9 patients: 8 *E. faecium* isolates and 1 *Enterococcus* initially identified as resistant to ampicillin. This last organism was confirmed to be ampicillin-susceptible *E. faecalis* 8 days after starting teicoplanin, at which time blood cultures tested negative; treatment was then changed to ampicillin plus ceftriaxone. The median length of antimicrobial treatment in survivors in this group was 42.5 (38.3–55.5) days and the median duration of teicoplanin was 42 (24.5–57.5) days. Three patients required prolonged treatment due to septic complications (Table 3).

In the salvage therapy group ($n=13$), the reasons for teicoplanin use were adverse events with previous regimens in

Table 3
Characteristics and outcome of nine enterococcal infective endocarditis (IE) episodes treated with teicoplanin as first-line therapy.

Sex/age (years)	Main co-morbidities (CCI)	Aetiology	Type of infection	Complication(s)	Surgery indicated /performed	Length of treatment (days) (teicoplanin/overall)	Death during treatment(cause)	Death during 3-mo follow-up (cause)	Relapse (follow-up)
M/48	Diabetes, renal insufficiency cirrhosis, HIV infection (5)	*E. faecium*	Native aortic valve	Renal insufficiency	No/No	12/12	Yes (haematemesis and hepatic encephalopathy)	–	–
M/87	Renal insufficiency, urothelial carcinoma (8)	*E. faecalis*	Native mitral valve	Heart failure	Yes/No	8/30	No	No	No (3.7 months)
M/73	Renal insufficiency (6)	*E. faecium*	Prosthetic mitral valve	Stroke, splenic abscess	No/No	60/60[a]	No	No	No (4.2 years)
M/75	Diabetes, colon adenocarcinoma (6)	*E. faecium*	Native aortic valve	Heart failure	Yes/Yes	42/42	No	No	No (3.2 years)
M/92	(3)	*E. faecium*	Native mitral valve	Heart failure	Yes/No	41/41	No	Yes (unknown)	–
F/56	Hepatic transplantation, renal insufficiency (7)	*E. faecium*	Non-valvular endocardium	Septic shock	Yes/No	9/9	Yes[b] (multi-organ failure)	–	–
M/73	Hepatic transplantation (9)	*E. faecium*	Native aortic and mitral valve	Heart failure, perivalvular complication, renal insufficiency, septic shock	Yes/No	5/5	Yes (refractory septic shock)	–	–
F/79	Diabetes, renal insufficiency (9)	*E. faecium*	Prosthetic aortic valve	Heart failure, paravalvular complication, renal insufficiency	Yes/No	52/52[c]	Yes (refractory heart failure)	–	–
M/79	(4)	*E. faecium*	Native aortic valve	No	No/No	55/55[d]	No	No	No (5.5 months)

CCI, Charlson comorbidity index; HIV, human immunodeficiency virus.

[a] Treated for 60 days due to splenic abscess.

[b] Patient with hepatic cirrhosis admitted due to hepatic encephalopathy and bacteraemic spontaneous bacterial peritonitis. After antimicrobial treatment, she underwent liver transplantation with a torpid post-op, septic shock and respiratory distress. Six days after transplantation she had persistent bacteraemia due *to E. faecium* and after transoesophageal echocardiography was diagnosed with non-valvular endocarditis (vegetation in the left atrium). Blood cultures persisted positive despite 5 days of antibiotic treatment with teicoplanin, thrombophlebitis was ruled out, and the patient died due to multi-organ failure at 9 days of treatment.

[c] Treated for 52 days for perivalvular abscess but inoperable due to co-morbidities.

[d] Treated for 55 days due to pancreatic abscesses.

7 patients (53.8%) after 27 (21–28) days of antibiotics, and OPAT in 6 patients (46.2%) after 35 (29–59) days of hospitalisation, with continuation of antimicrobial treatment for 17 (14.5–37.5) days. All adverse events occurred in patients undergoing treatment with ampicillin plus ceftriaxone. Five patients presented leukopenia attributable to β-lactams after a median of 27 (25–33.5) days, which resolved by changing the treatment to teicoplanin. One patient developed *Clostridium difficile* infection after 21 days of ampicillin plus ceftriaxone, which went well after switching to teicoplanin and starting oral vancomycin. One patient presented β-lactam-related fever after 21 days that resolved with therapy switch to teicoplanin. The median length of antimicrobial treatment in survivors was 54 (43–83) days and the median duration of teicoplanin was 23 (15.5–29.3) days. Three patients required prolonged treatment due to septic complications.

Overall, in both groups OPAT with teicoplanin could be performed for 17.5 (14.3–29.3) days in 12 (66.7%) of the 18 patients who survived after 35 (29–53) days of hospitalisation. Adverse events secondary to teicoplanin occurred in 2 patients (9.1%) in the salvage therapy group, requiring withdrawal in both cases. One patient with native-valve IE due to *E. faecalis* treated with ampicillin plus ceftriaxone presented leukopenia at 28 days of treatment. Therapy was changed to teicoplanin 12 mg/kg/day but the patient had fever and a skin reaction 13 days later. Treatment was then switched to vancomycin 15 mg/kg every 12 h but the rash persisted and 2 days later therapy was changed to daptomycin 6 mg/kg/day for 19 days with a favourable outcome. The second patient experiencing an adverse event had *E. faecalis* IE of the prosthetic aortic valve and aortic root replacement treated with ampicillin plus ceftriaxone. The patient developed leukopenia and after 29 days of treatment therapy was changed to teicoplanin 9.2 mg/kg/day, with resolution of leukopenia. However, after 35 days of teicoplanin, leukopenia reappeared; treatment was changed to vancomycin 14 mg/kg/day and was maintained for 25 days with a good outcome.

4. Discussion

In this study, teicoplanin was mainly given as salvage therapy for *E. faecalis* because of adverse events with other regimens or to facilitate hospital discharge. In a smaller number of patients it was used as the first-line therapy for *E. faecium* IE. Mortality during treatment occurred in 5 patients (22.7%), including 4 in the first-line therapy group; in 4 of the 5 patients who died, surgery had been indicated but was not performed. All-cause mortality at 90 days was 31.8% (7 patients) and there were no relapses. Adverse events secondary to teicoplanin occurred in 2 patients (9.1%) in the salvage therapy group and required withdrawal in both cases.

Teicoplanin is a glycopeptide antibiotic widely used in the treatment of various Gram-positive infections, including some difficult-to-treat infections such as osteoarticular enterococcal infection, with good outcomes when used in monotherapy [19]. However, experience with its use for the treatment of IE is very limited [14,17,20]. Teicoplanin can be used in *E. faecalis* IE as a sequential treatment for patients experiencing adverse effects with other regimens or to allow OPAT. Adverse events have been reported with ampicillin plus ceftriaxone or gentamicin [5,6] and, according to the current results, teicoplanin may be a safe alternative in these cases. Several factors support the use of teicoplanin in OPAT programmes as (i) this antibiotic has a long elimination half-life that enables once-daily dosing, (ii) serious side effects are uncommon and (iii) monitoring serum concentrations is not well established in daily clinical practice. Although teicoplanin was associated with an increased risk of OPAT failure in one study because of IE decompensation or adverse events, the population included had IE of several aetiologies, not only enterococci [21]. In our experience, this agent is a good option for EIE in selected patients, with a rate of adverse events and relapses similar to that of other regimens [6].

Enterococcus faecium infection is related to healthcare assistance as it develops in the context of antibiotic pressure. In some geographical areas the incidence of nosocomial infection caused by multidrug-resistant *E. faecium* isolates is increasing [22], but in Spain there are few cases of vancomycin-resistant enterococcal infections. The current European Society of Cardiology and American Heart Association endocarditis guidelines recommend vancomycin use for β-lactam-resistant *E. faecium* strains [7,8], although there is no optimal established treatment for *E. faecium* IE. As this infection often affects elderly patients with co-morbidities, treatment with vancomycin may be risky; teicoplanin could be a useful alternative in situations where there are few safer options available. In the same way that ampicillin plus ceftriaxone has been used to reduce the toxicity of treatment for *E. faecalis* IE, teicoplanin was used as first-line therapy in 5 patients (55.6%) with chronic renal failure. Of note, none of the patients receiving teicoplanin for the entire IE treatment experienced adverse events requiring withdrawal of the drug.

Analysis of the patients treated with teicoplanin as first-line therapy in comparison with a relatively contemporary multicentre cohort of patients with *E. faecalis* IE treated with ampicillin plus ceftriaxone or ampicillin plus gentamicin may provide some additional insights into teicoplanin use in this scenario [6]. The percentage of patients with an indication for surgery was similar in the two cohorts, but the percentage that underwent surgery was much lower in the current series [1/6 (16.7%) vs. 88/146 (60.3%)] and mortality was higher [4/9 (44.4%) vs. 53/246 (21.5%)], with death mainly occurring in patients with an indication for surgery that was not performed. Although in the current study the percentage of surgeries performed when indicated was lower, there were no relapses. Viewing this set of results from the two studies, we believe that the higher mortality rate in this cohort of *E. faecium* IE is attributable to the poorer clinical status of the patients, who were frail after several admissions and unable to undergo surgery, and not to the effectiveness of the treatment. The fact that none of the survivors relapsed further supports this interpretation.

Novel drug combinations (i.e. daptomycin + ceftaroline) are being investigated to improve the effectiveness of antimicrobial strategies for EIE and to avoid the risk of vancomycin-resistant *E. faecium* colonisation with current treatments [23]. Until additional studies and clinical trials are available regarding the best treatment for *E. faecium* IE, teicoplanin may be a useful option in selected cases.

The main limitations of this study are its retrospective single-centre design and the small sample size. However, it also has some strengths. Although identification of patients was retrospective, inclusion in the hospital Infectious Diseases Registry was prospective, which ensured that all patients treated with teicoplanin were included. To the best of our knowledge, this is the largest series of *E. faecium* IE patients treated with teicoplanin.

5. Conclusions

No optimal safe treatment has been established for *E. faecium* IE episodes due to susceptible strains. These results in a limited sample indicate that teicoplanin can be used as an alternative first-line treatment in *E. faecium* IE and may be valuable as a salvage therapy in selected patients with *E. faecalis* IE experiencing adverse events with standard regimens and to enable OPAT.

Acknowledgment

The authors thank Celine Cavallo for English language support.

Funding

This work was supported by Plan Nacional de I+D+i 2013–2016 and Instituto de Salud Carlos III, Subdirección General de Redes y Centros de Investigación Cooperativa, Ministerio de Economía, Industria y Competitividad, Spanish Network for the Research in Infectious Diseases [REIPI RD16/0016/0003]—co-financed by the European Development Regional Fund 'A way to achieve Europe', Operative program Intelligent Growth 2014–2020.

Competing interests

None declared.

Ethical approval

This study was approved by the Hospital Ethics Committee of Hospital Universitari Vall d'Hebron (Barcelona, Spain) and by the Spanish Drug Agency [approval NFH-TEI-2017-01]. Informed consent from patients was not required.

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