ORIGINAL ARTICLE   **INFECTIOUS DISEASES**

Changes in the treatment of *Enterococcus faecalis* infective endocarditis in Spain in the last 15 years: from ampicillin plus gentamicin to ampicillin plus ceftriaxone

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Abstract

The aim of this study was to assess changes in antibiotic resistance, epidemiology and outcome among patients with *Enterococcus faecalis* infective endocarditis (EFIE) and to compare the efficacy and safety of the combination of ampicillin and gentamicin (A+G) with that of ampicillin plus ceftriaxone (A+C). The study was a retrospective analysis of a prospective cohort of EFIE patients treated in our centre from 1997 to 2011. Thirty patients were initially treated with A+G (ampicillin 2 g/4 h and gentamicin 3 mg/kg/day) and 39 with A+C (ampicillin 2 g/4 h and ceftriaxone 2 g/12 h) for 4–6 weeks. Increased rates of high-level aminoglycoside resistance (HLAR; gentamicin MIC ≥512 mg/L, streptomycin MIC ≥1024 mg/L or both) were observed in recent years (24% in 1997–2006 and 49% in 2007–2011; p 0.03). The use of A+C increased over time: 1997–2001, 4/18 (22%); 2002–2006, 5/16 (31%); 2007–2011, 30/35 (86%) (p <0.001). Renal failure developed in 65% of the A+G group and in 34% of the A+C group (p 0.014). Thirteen patients (43%) in the A+G group had to discontinue treatment, whereas only one patient (3%) treated with A+C had to discontinue treatment (p <0.001). Only development of heart failure and previous chronic renal failure were independently associated with 1-year mortality, while the individual antibiotic regimen (A+C vs. A+G) did not affect outcome (OR, 0.7; 95% CI, 0.2–2.2; p 0.549). Our study shows that the prevalence of HLAR EFIE has increased significantly in recent years and that alternative treatment with A+C is safer than A+G, with similar clinical outcomes, although the sample size is too small to draw firm conclusions. Randomized controlled studies are needed to confirm these results.

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Introduction

Enterococci are the third most common causal agent of infective endocarditis (IE) worldwide [1] and are becoming increasingly prevalent among the elderly [2], in patients with comorbidities [3,4], and when endocarditis is acquired in the healthcare setting [5,6]. The growing prevalence of enterococci is due to a progressive increase in the number of urogenital and abdominal procedures and an increase in the

number of cases of enterococcal catheter-related bacteraemia, thus highlighting the role of nosocomial acquisition, which is associated with higher mortality [6]. Enterococci produce predominantly left-sided IE, and a third of all cases of prosthetic valve (PV) IE [6–8]; approximately 90% of cases are due to *Enterococcus faecalis* and less than 5% are caused by *Enterococcus faecium* [3].

The mortality rate of enterococcal IE has not changed during the last three decades [9], but resistance to classic treatment options has emerged [10]. High-level aminoglycoside resistance (HLAR) in the case of *E. faecalis* endocarditis (EFIE) is particularly worrisome, because no randomized trials have provided high-quality data on alternatives to the classic combination of ampicillin plus an aminoglycoside (mainly gentamicin, A+G) to treat the disease. Ampicillin combined with an aminoglycoside has been the first choice for EFIE from the 1950s, when synergy was proven [11], and has been recommended in the AHA guidelines ever since [12]. However, this combination has disadvantages other than rising rates of HLAR, namely nephrotoxicity. A decade ago, Olaison and Schadewitz [13] proposed shortening the course of aminoglycoside to 2–3 weeks based on favourable results in a large series of 91 cases of EFIE. However, the most important advance in the last two decades has been the proven efficacy and safety profile of ampicillin plus ceftriaxone (A+C) [14]. Although A+C has been included in American and European guidelines as an alternative to treat HLAR EFIE [12,15], evidence from prospective studies comparing these two combinations is limited. Our objective was to assess changes in resistance to antibiotics, epidemiology and outcome of patients with EFIE during the last 15 years. We also compared the efficacy and safety of the combination of A+G and A+C for the treatment of EFIE.

Methods

Design

We performed a retrospective study of prospectively collected cases comprising a cohort who attended an urban tertiary care hospital with 850 beds. All consecutive enterococcal IE episodes diagnosed between January 1997 and December 2011 were collected in a specific database using a standardized case report form. The study population comprised patients with a definitive diagnosis of IE [16] caused by *E. faecalis* who were receiving treatment with A+G or A+C and whose antimicrobial sensitivity patterns were available. Outcomes were attributed to the initial treatment (intention-to-treat analysis). All survivors were followed for at least 1 year.

Antimicrobial treatment

Antimicrobial treatment for non-HLAR EFIE was administered according to American and European recommendations [12,15]. Ampicillin was administered at a dose of 2 g/4 h and gentamicin at 3 mg/kg/24 h. Gentamicin levels were monitored following AHA guidelines [12]. A+C (ampicillin 2 g/4 h and ceftriaxone 2 g/12 h) was administered to patients with and without HLAR based on the favourable results obtained in an open-label non-randomized trial in Spain from 1995 to 2003 [14]. Ten of the patients who comprise the present cohort were included in that study. Length of standard treatment with both combinations was 28 days for non-complicated native valve (NV) IE and 42 days for PVIE or complicated IE.

Definitions

The variables analysed are depicted in Tables 1 and 2 and defined elsewhere [5].

Adverse events were considered related to treatment when renal failure or cochleo-vestibular toxicity developed with aminoglycosides and leukopenia or skin rash developed with betalactams. Renal failure was measured using creatinine, and the glomerular filtration rate (at baseline, at the end of admission, and in the case of treatment switch) was assessed according to the Modification of Diet in Renal Disease formula [18]. Acute renal impairment or failure was defined as a sudden increase (≤48 h) in serum creatinine of ≥0.3 mg/dL or an increase of ≥50% over baseline creatinine during a 7-day period or diuresis ≤0.5 mL/kg/h in 6 h [19], regardless of the presence or absence of previous chronic impairment (with the exception of patients undergoing haemodialysis, who were not included in this analysis). The definitions of ototoxicity related to aminoglycosides and side-effects of betalactams were those of previous studies [20,21].

Relapse was defined as a new episode of IE caused by the same microorganism during the 6 months after treatment. In-hospital mortality included death during the admission for the EFIE episode; 1-year mortality included death during the 365 days following the diagnosis of EFIE.

High-level aminoglycoside resistance for gentamicin, streptomycin or both was included in the epidemiological analysis during the study period. We used the variable high-level gentamicin resistance (HLGR) to analyse clinical outcomes, because no patients were treated with streptomycin and, therefore, high-level streptomycin resistance was assumed to have no impact on the type of antimicrobial regimen administered or on outcome.

The epidemiological analysis of the evolution of HLAR was performed and the type of antimicrobial therapy analysed according to three periods of time: 1997–2001, 2002–2006 and 2007–2011.

TABLE 1. Clinical characteristics and outcome of 69 episodes of *Enterococcus faecalis* infective endocarditis according to the presence or absence of HLGR

	HLGR[a] (N = 13)	Non-HLGR (N = 56)	p
Median age (IQR)	72.0 (65–80)	71.0 (64.5–77)	0.763
Male gender (%)	7 (54)	37 (66)	0.524
Year of diagnosis (%)			
1997–2001	1 (8)	17 (30)	0.018
2002–2006	1 (8)	15 (27)	
2007–2011	11 (84)	24 (43)	
Predisposing conditions and underlying diseases (%)			
Diabetes mellitus	5 (39)	18 (32)	0.748
Chronic renal failure	3 (23)	14 (25)	1.000
Haemodialysis[b]	1 (8)	4 (7)	1.000
History of cancer	4 (31)	12 (21)	0.481
HIV infection	0	1 (2)	1.000
Chronic liver disease	2 (15)	6 (11)	0.639
Chronic lung disease	3 (23)	12 (21)	1.000
Transplantation	0	1 (2)	1.000
History of infective endocarditis	2 (15)	7 (13)	0.674
Median Charlson comorbidity index (IQR)	2.0 (1–3)	3.0 (1–4)	0.221
Presumed mode of acquisition (%)			
Nosocomial	4 (31)	32 (57)	0.008
Non-nosocomial healthcare-associated	7 (54)	8 (14)	
Community-acquired	2 (15)	16 (29)	
Source of infection (%)			
Unknown	3 (23)	29 (52)	0.319
Catheter	1 (8)	3 (5)	
Urinary	5 (39)	13 (23)	
Abdominal/digestive tract	4 (31)	11 (20)	
Median days of symptoms until diagnosis (IQR)	7.0 (1.5–20)	15.0 (2–45)	0.197
Type of endocarditis (%)			
Native	8 (61)	37 (66)	0.735
Prosthetic valve	5 (39)	17 (30)	
Pacemaker lead[c]	2 (16)	2 (4)	
Valve involvement (%)			
Aortic valve	5 (39)	25 (45)	0.194
Mitral valve	2 (15)	20 (36)	
Pacemaker/intracardiac device lead	2 (15)	1 (2)	
Mitral + aortic	2 (15)	7 (13)	
Tricuspid + aortic	1 (8)	0	
Tricuspid + aortic + mitral	0	1 (2)	
Pulmonary	1 (8)	2 (3)	
Echocardiographic findings			
Presence of vegetation (%)	8 (62)	45 (80)	0.294
Vegetation size in mm, median (IQR)	14 (8–18)	10 (5–13)	0.593
Perivalvular abscess (%)	1 (8)	7 (13)	1.000
Complications (%)			
Heart failure	8 (63)	25 (45)	0.272
Systemic emboli	2 (15)	19 (34)	0.317
Relapses	1 (8)	4 (5)	1.000
Toxicity			
Baseline GFR in mL/min, median (IQR)	69.0 (39.5–99)	60.0 (44–86)	0.133
Baseline creatinine in mg/dL, median (IQR)	0.8 (0.7–1.4)	1.1 (0.9–1.4)	0.431
Occurrence of renal failure during treatment[d] (%)	3 (25)	27 (52)	0.092
GFR at the end of therapy, median (IQR)	46.0 (26–79)	49.0 (34–67)	0.553
Total GFR change during therapy; median (IQR)	−20.0, −12 to −28	−1.5, −19 to 15	0.088
Ototoxicity (%)	0	2 (4)	1.000
Vestibular toxicity (%)	0	1 (2)	1.000
Skin rash (%)	0	2 (4)	1.000
Myelotoxicity (%)	1 (8)	0	0.188
Median duration of treatment in days (IQR)	42.0 (28–42)	42.0 (28–42)	1.000
Median duration of aminoglycosides in days (IQR)	NA	28.0 (15–32)	–
Type of aminoglycoside regimen (%)			
QD	NA	1 (2)	–
BID		6 (11)	
TID		23 (41)	
Surgical treatment	4 (31)	26 (46)	0.305
Mortality (%)			
In-hospital mortality	2 (15)	15 (27)	0.390
1-year mortality	3 (23)	16 (29)	1.000

NA, not applicable.

[a]HLGR includes patients with high-level resistance to gentamicin (6) and patients with high-level resistance to both gentamicin and streptomycin (7). Non-HLGR includes 12 patients with high-level resistance to streptomycin.

[b]The five patients on haemodialysis are not included in the analysis of renal function and development of renal failure/toxicity.

[c]The two patients with intracardiac devices also had prosthetic valve IE.

[d]In all the patients who developed renal failure during treatment, baseline creatinine increased by ≥50% in ≤48 h.

Microbiological sample processing and definitions of HLAR

In all 69 cases with a diagnosis of EFIE, *E. faecalis* isolates were recovered and frozen in skimmed milk at −80°C. Strains were identified using the API Rapid ID32 STREP device (bioMérieux, Marcy l'Etoile, France). HLAR was assessed using the Etest following the manufacturer's recommendations (bioMérieux). HLAR was defined as follows: gentamicin MIC ≥512 mg/L, streptomycin MIC

TABLE 2. Clinical characteristics and outcome of 69 episodes of *Enterococcus faecalis* infective endocarditis according to the type of antimicrobial treatment administered

	A+G (N = 30)	A+C (N = 39)	p
Median age in years (IQR)	75.0 (68–77)	70.0 (63–78)	0.289
Male gender (%)	22 (73)	22 (56)	0.147
HLAR[a] (%)	7 (23)	18 (46)	0.051
Year of diagnosis (%)			<0.001
1996–2001	14 (47)	4 (10)	
2002–2006	11 (37)	5 (13)	
2007–2011	5 (17)	30 (77)	
Predisposing conditions and underlying diseases (%)			
Diabetes mellitus	11 (37)	12 (31)	0.606
Haemodialysis	4 (13)	1 (3)	0.159
History of cancer	7 (23)	9 (23)	0.980
HIV infection	0	1 (3)	1.000
Chronic liver disease	1 (3)	3 (18)	0.125
Chronic lung disease	7 (23)	8 (21)	0.778
Transplantation	0	1 (3)	1.000
History of infective endocarditis	2 (7)	7 (18)	0.281
Median Charlson score (IQR)	2.0 (1–3)	3.0 (1–4)	0.766
Presumed mode of acquisition (%)			
Nosocomial	19 (63)	17 (44)	0.207
Non-nosocomial healthcare-associated	4 (13)	11 (28)	
Community-acquired	7 (23)	11 (28)	
Type of endocarditis (%)			
Native valve	20 (67)	25 (64)	1.000
Prosthetic valve	9 (30)	13 (33)	
Pacemaker lead	1 (3)	1 (3)	
Valve involvement (%)			
Aortic valve	19 (63)	25 (64)	0.394
Mitral valve	9 (30)	13 (33)	
Right-sided/intracardiac device	2 (7)	1 (3)	
Echocardiographic findings			
Presence of vegetation	25 (84%)	28 (72%)	0.260
Vegetation size in mm, median (IQR)	10 (5–14)	9.5 (6–13)	0.659
Perivalvular abscess	5 (17%)	3 (8%)	0.281
Complications (%)			
Heart failure	13 (43)	20 (51)	0.512
Renal failure	17 (65)	13 (34)	0.014
Systemic emboli	8 (27)	13 (33)	0.551
Persistent bacteraemia	2 (4)	7 (10)	0.690
Toxicity[b]			
Renal failure at baseline	8 (27%)	9 (23%)	0.732
Baseline GFR in mL/min, median (IQR)	58.5 (44–81)	61.0 (44–92)	0.112
Baseline creatinine in mg/dL, median (IQR)	1.2 (0.9–1.7)	1.0 (0.8–1.3)	0.171
GFR at unplanned termination of treatment in mL/min, median (IQR)	21.0 (9–28)	65 (NA)[c]	0.020
Creatinine at discontinuation/end of treatment, median (IQR)	2.8 (2.2–5.7)	1.0 (NA)[c]	0.242
Ototoxicity	2 (7%)	0	0.185
Vestibular toxicity	1 (3%)	0	0.435
Skin rash	0	2 (5%)	0.501
Haematological abnormalities	0	1 (3%)	1.000
Change from A+G to A+C[d]	13 (43%)	1 (3%)	<0.001
Surgical treatment	15 (50%)	15 (39%)	0.338
Mortality (%)			
In-hospital mortality	8 (27)	9 (23)	0.732
1-year mortality	9 (30)	10 (26)	0.688
Relapses	2 (3)	3 (8)	1.000

[a]The seven patients in the A+G arm had high-level resistance to streptomycin only; among the HLAR[a] patients treated with A+C, five presented high-level resistance to streptomycin only, six to gentamicin only, and seven to both aminoglycosides.
[b]Patients on haemodialysis were excluded from the assessment of renal function and toxicity.
[c]NA, not applicable. Only one patient treated with A+C had to discontinue treatment.
[d]Two patients with HLAR (to streptomycin only) and 11 with non-HLAR strains switched from A+G to A+C during treatment (p 0.113). Median duration of the aminoglycoside course did not differ between the groups (23.9 and 26.8 days, respectively; p 0.984). One patient treated with A+C had to discontinue treatment owing to severe skin rash.

≥1024 mg/L, or both gentamicin MIC ≥512 mg/L and streptomycin MIC ≥1024 mg/L.

Statistical analysis

Comparisons between groups were performed according to three main variables: type of endocarditis (NV vs. PV/pacemaker), type of initial antimicrobial treatment (A+G vs. A+C), and the presence or absence of HLGR. Categorical variables are summarized as percentages. Continuous variables are summarized as median and interquartile range (IQR). Categorical variables were compared using the chi-square test (or Fisher's exact test when necessary). The Mantel–Haenszel test for trend was applied to find significant differences in HLAR throughout the study. We used Kaplan–Meier survival analysis to analyse 1-year mortality and treatment discontinuation according to the regimen taken. Curves were compared using the log-rank test. Predictors with a p value <0.30 were included in the logistic regression analysis, which was performed using a likelihood ratio-based backward exclusion method. A two-sided p <0.05 was considered to be statistically significant. The statistical analysis was performed using SPSS version 16.0 (SPSS Inc, Chicago, IL, USA).

Results

Epidemiological and clinical characteristics of EFIE

During the study period, we diagnosed 80 episodes of enterococcal IE, which accounted for 13% of the 620 cases of IE diagnosed at our institution. Eleven of these cases were excluded from the analysis (two cases of *E. faecium* IE, five treated with combinations other than A+G or A+C, two because of lack of data (early death), and two cases of polymicrobial IE). Twenty patients (29%) were referred from other centres. Median time of follow-up was 392 days (IQR, 118.5–792.0). The clinical characteristics and outcome of these 69 cases are summarized according to the presence or absence of HLGR in Table 1. Forty-six cases (67%) were NVIE, 21 (30%) were PVIE and two (3%) had pacemaker-related infections. There were five relapses (7%).

Evolution of HLAR over time and influence on prognosis

Twenty-five isolates presented HLAR (36%). A trend towards higher total HLAR rates was observed in more recent years (p 0.095) (Fig. 1a). High-level resistance to gentamicin, streptomycin and both aminoglycosides increased between 1997–2006 and 2007–2011: 6% vs. 31% (p 0.007), 21% vs. 34% (p 0.203) and 24% vs. 49% (p 0.030), respectively. Patient characteristics, antibiotic treatment and outcome according to the presence or absence of HLGR in the strains causing EFIE

are shown in Table 1. IE cases produced by HLGR strains were more frequently diagnosed in the latter period of the study (p 0.018) and in healthcare-associated cases (p 0.008), while no other relevant differences between groups were found.

Effect of antimicrobial treatment on outcome

No differences in baseline characteristics were detected in the general clinical characteristics and outcome of the cohort according to the type of treatment. However, an overwhelming increase in the use of A+C was detected over time (Fig. 1b), in parallel with the HLAR rate. No differences were detected between patients receiving A+G and those receiving A+C with respect to clinical presentation, severity of IE or surgery rates. The Kaplan–Meier survival analysis in Fig. 2b shows that 1-year mortality was not significantly different between those patients initially treated with A+G and those treated with A+C (29% vs. 26%, respectively). In-hospital mortality was 27% in the A+G group and 23% in the A+C group (p 0.732). The relapse rate was very low, with no statistically significant differences between the groups (three relapses in the A+C group and two in the A+G group; p 1.000). Due to the multiple changes introduced in the manuscript along the several revisions performed, we consider

that Supplementary Material referring to relapses management is not necessary.

Patients receiving A+G presented a higher incidence of renal failure during treatment (65% vs. 34%; p 0.014), although no differences were found in other types of treatment-induced toxicity. In the A+C group, only one patient had to discontinue treatment owing to a severe skin rash. Two patients in the A+C group presented *C. difficile*-associated diarrhoea that did not require discontinuation of treatment. In both cases, treatment with oral vancomycin was sufficient to achieve a cure.

More A+G patients than A+C patients had to discontinue treatment owing to toxicity (43% and 3%, respectively; p 0.001) (Fig. 2a). Thirteen patients switched from A+G to A+C a median of 18 days after initiation of A+G (range, 5–30 days; IQR, 15–24.5 days). The reason for switching was impaired renal function in 10 cases and persistent bacteraemia in the remaining three patients. Among these 10 patients initially treated with A+G who had to discontinue treatment owing to renal failure and switched to A+C, GFR improved by a median of 15.0 mL/h (IQR, 7.5–34.5), and serum creatinine decreased by 1.3 mg/dL (0.8–3.8). At the end of treatment, GFR and serum creatinine were 37.0 mL/h (22.0–53.8) and 1.8 mg/dL (1.1–1.98), respectively. Four of these patients died, three during admission (at days 5, 23 and 44 after switching treatment).

Aminoglycosides were administered QD in 3% of patients, BID in 23% and TID in 74%. Treatment duration was not statistically different between patients initially treated with A+G and those treated with A+C (median of 42 days in both groups). Length of treatment with A+C did not reach 8 weeks in any of our patients. We did not find worse outcomes (relapses and mortality) in patients treated with A+C for 6 weeks than in those treated with 4 weeks of A+G.

Prognostic factors of EFIE

Table 3 shows the predictive variables associated with 1-year mortality. The only variables selected for logistic regression analysis were year of diagnosis, presence of diabetes and chronic renal failure, median Charlson score, occurrence of heart failure during treatment, and surgical treatment of EFIE. As mean Charlson score was collinear with diabetes and chronic renal failure, this variable was not included in the model. Table 4 shows the results of the logistic regression analysis to find independent risk factors for 1-year mortality. Only heart failure (OR, 4.3; 95% CI, 1.2–15.4; p 0.024) and chronic renal failure (OR, 4.3; 95% CI, 1.2–14.7; p 0.021) were independently associated with mortality. Neither the type of antimicrobial regimen (OR, 0.7; 95% CI, 0.2–2.2; p 0.549 after forcing its inclusion in the model) nor the period of diagnosis affected mortality.
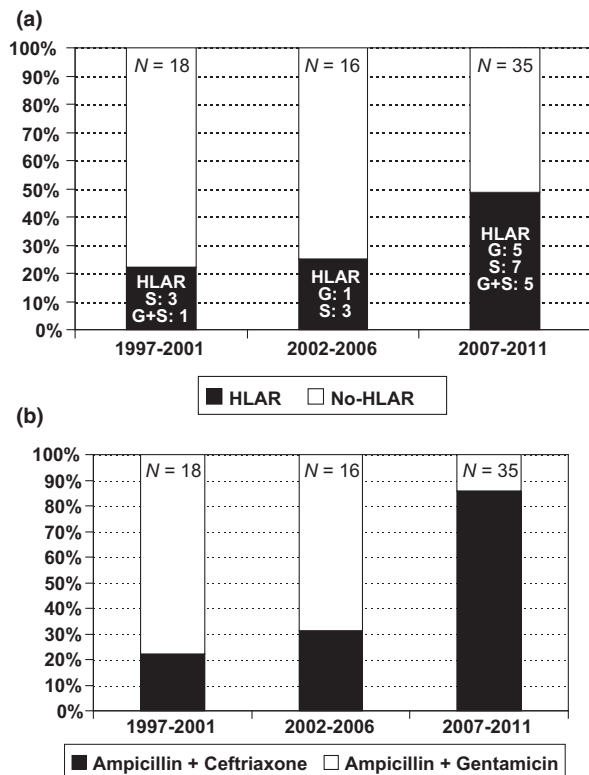
FIG. 1. Evolution of HLAR and treatment of EFIE over time. (a) Evolution of HLAR over time. (b) Evolution of EFIE antibiotic treatment over time.
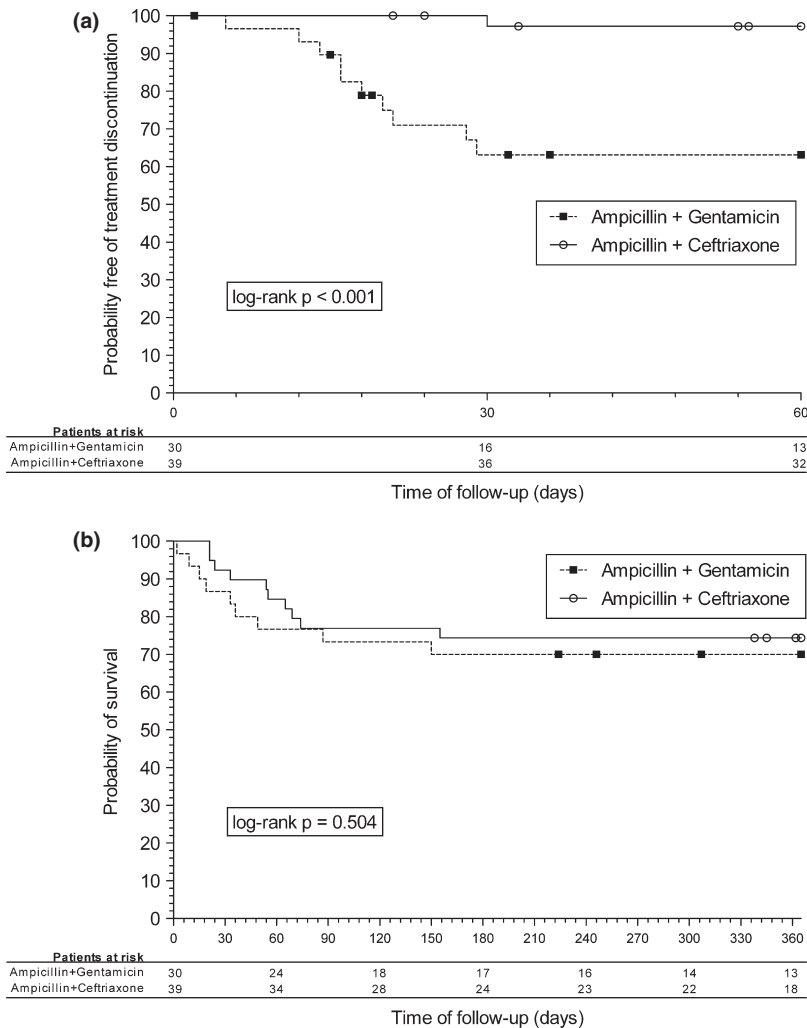
FIG. 2. Kaplan–Meier survival analysis curves. (a) Treatment discontinuation at 60 days. (b) 1-year mortality.

Discussion

The general features of our cohort did not differ from those of other EFIE cohorts described in global series and guidelines [1,7,12,15]; namely, 13% prevalence of IE episodes, older patients with comorbidities, need for surgery in fewer than half of the patients (44%), 7% frequency of relapses, and around 30% mortality. The high percentages of healthcare-acquired EFIE (75%) [1,5] and PVIE (33%) [8] are consistent with the findings of other previous studies.

Interestingly, we found an increase in HLAR rates in recent years, mainly because of the increased prevalence of HLGR. Rates from the first two periods (1997–2006) are consistent with those described by the European Centre for Disease Prevention and Control for the period 2001–2007 [22], but are clearly higher in the third period (2007–2011). While evidence from randomized trials evaluating antimicrobial

therapy for EFIE is lacking, rates of resistance to classic treatment options continue to increase [23,24]. The largest multicentre cohort studies considering the characteristics and evolution of EFIE do not generally include the effect of HLAR on outcome [3], although this has traditionally been considered one of the major determinants of EFIE management, relapses and mortality [25,26]. In this regard, no study has assessed the development of HLAR in EFIE over time, although there is some evidence of a clear increase in the prevalence of HLAR strains [4,27–30]. While almost no relapses were described in EFIE treated with A+G in the 1980s [17], most recent series reported relapse rates of 7–10% [4,14]. However, we found no statistically significant differences in the requirement for surgery, relapses or mortality according to HLGR. We hypothesize that this may be because of the efficacy of A+C against HLGR strains.

The *in vitro* efficacy of double beta-lactam therapy was first described in the mid-1990s [31] and has since been proved in

TABLE 3. Univariate analysis of risk factors associated with 1-year mortality in endocarditis due to *Enterococcus faecalis*

	One-year mortality (N = 19)	Alive (N = 50)	p
Mean age (SD) in years	70.1 (11.2)	69.6 (12.1)	0.979
Male gender (%)	12 (63)	32 (64)	0.948
Year of diagnosis (%)			
1997–2006	13 (68)	21 (42)	0.050
2007–2011	6 (32)	29 (58)	
HLGR	3 (16)	10 (20)	1.000
Predisposing conditions and underlying diseases (%)			
Diabetes mellitus	9 (47)	14 (28)	0.127
Chronic renal failure	8 (42)	9 (18)	0.059
Haemodialysis	2 (11)	3 (6)	0.611
History of cancer	6 (32)	10 (20)	0.347
HIV infection	1 (5)	0	0.275
Chronic liver disease	3 (16)	5 (10)	0.675
Chronic lung disease	2 (11)	13 (26)	0.206
Transplantation	0	1 (2)	1.000
History of infective endocarditis	1 (5)	8 (16)	0.427
Mean Charlson score (SD)	3.0 (2.0)	2.2 (1.5)	0.035
Healthcare acquisition (%)	16 (84)	36 (72)	0.363
Type of endocarditis (%)			
Native valve	13 (68)	32 (64)	0.446
Prosthetic valve	5 (26)	17 (34)	
Pacemaker lead	1 (5)	1 (2)	
Valve involvement (%)			
Aortic[a]	12 (63)	32 (64)	0.312
Mitral	5 (26)	17 (34)	
Right-side[b]	2 (11)	1 (2)	
Complications (%)			
Heart failure	13 (68)	20 (40)	0.035
Renal failure	10 (53)	20 (40)	0.344
Systemic emboli	7 (37)	14 (28)	0.476
Perivalvular abscess	3 (16)	3 (6)	0.429
Persistent bacteraemia	3 (16)	3 (6)	0.334
Surgical treatment (%)	6 (32)	24 (48)	0.219
Treatment groups (%)			
A+G	9 (47)	21 (42)	0.788
A+C	10 (53)	29 (58)	

[a]Patients with aortic IE had concurrent infection of their intracardiac device (two patients), mitral native valve (nine cases), mitral plus tricuspid native valve (one case) and tricuspid native valve (one case).
[b]Right-sided IE consisted of intracardiac device infection (two cases) and pulmonary native valve infection (one case). A+G, ampicillin plus gentamicin; A+C, ampicillin plus ceftriaxone.

TABLE 4. Multivariate analysis of risk factors associated with 1-year mortality in endocarditis due to *Enterococcus faecalis*

	Univariate analysis			Multivariate analysis		
	OR	95% CI	p	OR	95% CI	p
Year of diagnosis 2007–2011 vs. 1997–2006	0.2	0.4–1.0	0.05	–	–	–
Diabetes mellitus	2.5	0.7–9.3.	0.155	–	–	–
Chronic renal failure	2.6	0.6–10.4	0.191	4.3	1.2–15.4	0.024
Heart failure	7.5	1.8–31.6	0.006	4.3	1.2–14.7	0.021
Surgical treatment	0.5	0.1–1.6	0.226	–	–	–
Treatment groups[a]						
A+C vs. A+G	1.5	0.3	6.4	0.7	0.2–2.2	0.549

[a]The variable A+C vs. A+G was forced into the final regression model for theoretical reasons.

animal models [32,33] and in a small non-randomized clinical trial performed in Spain [14]. On the basis of this evidence, the combination A+C was included in the 2005 American and 2009 European guidelines as an option for HLAR or multiresistant strains [12,15]. As stated above, A+C almost completely replaced A+G in our cohort during the study period.

This change did not lead to lower mortality over time, although a significantly lower treatment discontinuation rate was detected with A+C (p 0.001). A+C has been shown to be a safer option in terms of renal impairment during treatment. This is a valuable feature for a combination whose target population is at high risk of nephrotoxicity. Some of our main findings coincide with those of Fernandez-Hidalgo *et al.* [34], who recently found similar outcomes with A+C and A+G for EFIE.

The guidelines of the AHA (2005) [12] and of the ESC (2009) [15] recommend 4 weeks of A+G for patients with uncomplicated NVIE and 6 weeks for patients with PVIE and patients with a > 3-month history of symptoms before diagnosis. In the case of A+C, which is considered an option for HLAR strains, 8 weeks is always recommended in both guidelines. Length of treatment with A+C did not reach 8 weeks in any of our patients. However, 6 weeks of treatment with A+C did not lead to poorer outcomes than those obtained with the standard A+G regimen for non-HLAR EFIE. Because the number of patients treated with 4 weeks of A+C is small, we cannot recommend the 4-week A+C regimen until further data on its efficacy are available. Nevertheless, based on the results of our group and those of Fernandez-Hidalgo *et al.* [34], a recommended duration of 6 weeks of A+C seems sufficient.

Dahl *et al.* [35] recently demonstrated equivalent efficacy and reduced nephrotoxicity of ampicillin plus short-course gentamicin (2 weeks) and the standard regimen in a cohort of 84 patients with non-HLAR EFIE. They also demonstrated the same efficacy for both the QD regimen and the TID regimen, which is the recommended option in the AHA guidelines [12]. Median duration of aminoglycosides in our cohort was 28 days (IQR, 15–32 days), and most patients received treatment TID. The sample size is too small to detect relevant differences between regimens. In our cohort, renal toxicity was recorded and aminoglycosides withdrawn after a median of 18 days; this supports the conclusion of Dahl *et al.* that 2 weeks of aminoglycosides might be preferable to 4–6 weeks. As we recently stated elsewhere, currently available evidence leads us to conclude that, in cases of HLAR, A+C should be the first choice [36]. Furthermore, the results of both the Fernández-Hidalgo study [34] and our study support the finding that A+C has similar efficacy to A+G and is safer in EFIE patients without HLAR treated with A+G for 4–6 weeks. The question of which approach (ampicillin plus short-term gentamicin (2 weeks) or A+C) is best for these patients remains unanswered. A randomized controlled study is needed to provide more conclusive data [36].

Our study has several limitations. First, it is not randomized. Second, statistical power is limited owing to the small sample size. Third, in contrast to other studies, referral bias probably

led us to include non-standard EFIE patients, namely, younger subjects with a high likelihood of surgical management, higher prevalence of healthcare-associated infection (75%), and antibiotic treatment at the time of referral. Fourth, we considered that renal failure in patients receiving aminoglycosides was at least partially attributable to aminoglycoside toxicity, which involves a risk of overestimation. Fifth, aminoglycoside trough levels and data on concomitant use of nephrotoxic agents are not provided. And finally, a possible historical bias leading to better results in the A+C group due to significantly later and improved general medical care could have affected some results.

In conclusion, the efficacy of A+C administered for 6 weeks appears similar to and safer than that of A+G administered for 4–6 weeks according to AHA and ESC recommendations for the treatment of EFIE. A+C is the preferred regimen for HLAR strains. This combination presents lower rates of discontinuation due to toxicity than a 4–6-week course of A+G in patients with non-HLAR EFIE. Although HLAR rates have increased over time, HLGR EFIE did not have a worse prognosis than non-HLGR EFIE. As a consequence, the treatment of EFIE in Spain has shifted from A+G to A+C in recent years.

Transparency Declaration

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Authorship

All the authors listed in the contributors' affiliations meet ICMJE Authorship Criteria, meaning that they substantially contributed to the conception and design of the study, acquisition of data, writing of the article, and critical revision and final approval of the manuscript.

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Appendix 1

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