MAJOR ARTICLE

Ampicillin Plus Ceftriaxone Is as Effective as Ampicillin Plus Gentamicin for Treating *Enterococcus faecalis* Infective Endocarditis

Nuria Fernández-Hidalgo,[1] Benito Almirante,[1] Joan Gavaldà,[1] Mercè Gurgui,[2] Carmen Peña,[3] Arístides de Alarcón,[4] Josefa Ruiz,[5] Isidre Vilacosta,[6] Miguel Montejo,[7] Nuria Vallejo,[8] Francisco López-Medrano,[9] Antonio Plata,[10] Javier López,[11] Carmen Hidalgo-Tenorio,[12] Juan Gálvez,[13] Carmen Sáez,[14] José Manuel Lomas,[15] Marco Falcone,[18] Javier de la Torre,[16] Xavier Martínez-Lacasa,[17] and Albert Pahissa[1]

[1]Servei de Malalties Infeccioses, Hospital Universitari Vall d'Hebron, and [2]Unitat de Malalties Infeccioses, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Department of Medicine, [3]Servei de Malalties Infeccioses, Hospital Universitari de Bellvitge, Barcelona, [4]Servicio de Enfermedades Infecciosas y Medicina Interna, Hospital Universitario Virgen del Rocío, Seville, [5]Unidad de Gestión Clínica de Enfermedades Infecciosas, Hospital Universitario Virgen de la Victoria, Málaga, [6]Instituto Cardiovascular, Servicio de Cardiología, Hospital Clínico San Carlos, Madrid, [7]Unidad de Enfermedades Infecciosas, Hospital Universitario de Cruces, Bizkaia, [8]Servicio de Cardiología, Hospital Germans Trias i Pujol, Barcelona, [9]Unidad de Enfermedades Infecciosas, Hospital Universitario 12 de Octubre, Madrid, [10]Servicio de Enfermedades Infecciosas, Hospital Universitario Carlos Haya, Málaga, [11]Instituto de Ciencias del Corazón (ICICOR), Hospital Clínico Universitario, Valladolid, [12]Servicio de Medicina Interna, Hospital Universitario Virgen de las Nieves, Granada, [13]Sección de Enfermedades Infecciosas, Hospital Universitario Virgen Macarena, Sevilla, [14]Sección de Enfermedades Infecciosas, Hospital Universitario de la Princesa, Madrid, [15]Unidad de Enfermedades Infecciosas, Hospital Juan Ramón Jiménez, Huelva, [16]Unidad de Enfermedades Infecciosas, Hospital Costa del Sol, Málaga, [17]Unitat de Malalties Infeccioses, Hospital Universitari Mútua de Terrassa, Barcelona, Spain; and [18]Department of Infectious Diseases, Policlinico Umberto I, Roma, Italy

(See the Editorial Commentary by Munita et al on pages 1269–72.)

Background. The aim of this study was to compare the effectiveness of the ampicillin plus ceftriaxone (AC) and ampicillin plus gentamicin (AG) combinations for treating *Enterococcus faecalis* infective endocarditis (EFIE).

Methods. An observational, nonrandomized, comparative multicenter cohort study was conducted at 17 Spanish and 1 Italian hospitals. Consecutive adult patients diagnosed of EFIE were included. Outcome measurements were death during treatment and at 3 months of follow-up, adverse events requiring treatment withdrawal, treatment failure requiring a change of antimicrobials, and relapse.

Results. A larger percentage of AC-treated patients (n = 159) had previous chronic renal failure than AG-treated patients (n = 87) (33% vs 16%, $P = .004$), and AC patients had a higher incidence of cancer (18% vs 7%, $P = .015$), transplantation (6% vs 0%, $P = .040$), and healthcare-acquired infection (59% vs 40%, $P = .006$). Between AC and AG-treated EFIE patients, there were no differences in mortality while on antimicrobial treatment (22% vs 21%, $P = .81$) or at 3-month follow-up (8% vs 7%, $P = .72$), in treatment failure requiring a change in antimicrobials (1% vs 2%, $P = .54$), or in relapses (3% vs 4%, $P = .67$). However, interruption of antibiotic treatment due to adverse events was much more frequent in AG-treated patients than in those receiving AC (25% vs 1%, $P < .001$), mainly due to new renal failure (≥25% increase in baseline creatinine concentration; 23% vs 0%, $P < .001$).

Conclusions. AC appears as effective as AG for treating EFIE patients and can be used with virtually no risk of renal failure and regardless of the high-level aminoglycoside resistance status of *E. faecalis*.

Keywords. *Enterococcus faecalis*; infective endocarditis; ampicillin plus ceftriaxone; gentamicin; outcome.

Received 27 August 2012; accepted 27 November 2012; electronically published 7 February 2013.

Presented in part: 52nd Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, California, 9–12 September 2012. Abstract K-938.

Correspondence: Nuria Fernández-Hidalgo, MD, Servei de Malalties Infeccioses, Hospital Universitari Vall d'Hebron, Passeig de la Vall d'Hebron 119-129, 08035 Barcelona, Spain (nufernan@gmail.com).

Clinical Infectious Diseases 2013;56(9):1261–8

DOI: 10.1093/cid/cit052

Enterococcus species are the third most frequent cause of infective endocarditis (IE) in developed countries, after staphylococci and streptococci, and account for 10%–14% of all IE episodes [1–3]. *Enterococcus faecalis* is the most frequently isolated of these microorganisms. Few contemporary studies have focused on the subgroup of patients with IE due to enterococci, and they have some limitations, such as a small sample size or retrospective design [4–6].

International guidelines on IE recommend 4–6 weeks of penicillin or ampicillin plus an aminoglycoside for treating β-lactam– and gentamicin-susceptible enterococcal IE [7, 8]. Since the publication of an observational, nonrandomized, multicenter clinical trial in 2007 [9], the ampicillin plus ceftriaxone (AC) combination has been recognized as a viable alternative for treating *E. faecalis* IE (EFIE) caused by isolates with high-level aminoglycoside resistance (HLAR) [8]. In daily practice, this combination has also been used for treating non-HLAR EFIE. There are, however, no studies comparing AC and ampicillin plus gentamicin (AG) for treating EFIE. Thus, the aim of this study was to compare the safety and effectiveness of these 2 antimicrobial combinations for treating this disease.

METHODS

Design, Settings, and Patients

This observational, nonrandomized, comparative multicenter cohort study was performed at 17 hospitals located in 5 different geographical areas of Spain, and 1 center in Rome, Italy. All but 3 of the Spanish centers were referral hospitals for cardiac surgery.

All consecutive adult patients (≥18 years of age) with a diagnosis of EFIE treated from January 2005 through December 2011 were enrolled in the study. Patients were prospectively identified from the Infectious Diseases, Internal Medicine, Neurology, Cardiology, and Cardiac Surgery (when present) departments, the Microbiology Department's blood culture registry, and the Echocardiography Laboratory of each participating hospital. All patients in each center were evaluated by the same staff medical team during the entire study period.

Definitions

IE was defined as definite or possible according to the modified Duke criteria [10]. Healthcare-associated IE [11] and catheter-related bacteremia [12] have been defined elsewhere. The Charlson comorbidity index [13] was used at admission to stratify overall comorbidity. The indication for surgery was established according to current guidelines [7, 8].

Right-sided IE was defined as isolated infection of the tricuspid or pulmonary valves without involvement of the left-sided valves or any implantable cardiac device. Prosthetic valve IE was defined as involvement of at least 1 prosthetic valve, regardless of the presence of infection in the other native valves. Pacemaker IE was defined as lead infection plus endocardial involvement.

We classified a patient as having received AC or AG if, once the etiology of IE was known, a 4- to 6-week course was planned with any of these antimicrobial combinations (for AG, at least 2 weeks of planned gentamicin [14]) and oral antimicrobial suppressive therapy was not administered at the end of this time period. Otherwise, patients were classified as having received other antimicrobial therapies. Three patients receiving penicillin plus gentamicin were assigned to the AG group.

Ampicillin was administered intravenously at 2 g every 4 hours (adjusted according to renal function when necessary), ceftriaxone intravenously at 2 g every 12 hours, and gentamicin at 3 mg/kg/day (adjusted according to renal function when necessary). Gentamicin was administered in 1, 2, or 3 divided doses according to the criteria of the attending physician and renal function at diagnosis. Use of AC, AG, or other antibiotic combinations was decided by the attending physician based on local protocols. Gentamicin trough levels were monitored in the referral centers according to local protocols, with a target of 0.5–1 mg/L for multidose administration.

IE complications were defined as the development of any of the following conditions: (1) congestive heart failure (new condition or worsening of a known condition), (2) paravalvular complication (diagnosed by echocardiography or during surgery), (3) stroke, (4) symptomatic systemic embolism other than stroke, and (5) acute renal failure, established as a 25% increase in the baseline creatinine concentration.

Outcomes

Adverse effects recorded in patients receiving AC and AG included leukopenia (total white blood cell count <4000 cells/mm^3), fever (axillar temperature ≥38.3°C), new renal failure (defined above), and vestibular toxicity. These were considered adverse effects after excluding other potential causes, such as uncontrolled infection. Interruption of antimicrobial treatment due to adverse events was left to the physician's criteria.

Treatment failure requiring a change of antimicrobials was defined as a change of antimicrobial therapy based on detection of new vegetations, septic paravalvular complications, or persistently positive blood cultures to *E. faecalis* in a patient still undergoing treatment.

Mortality was defined as death from any cause while on antimicrobial treatment or up to 3 months of follow-up. Follow-up was defined as the period between the day after completing antimicrobial therapy to death or the last clinical control. A minimum of 3 months' follow-up was required in each case. Relapse was established on documentation of positive blood cultures caused by the same microorganism as the initial endocarditis within the first 3 months after completing antimicrobial treatment.

Data Collection

Demographic, clinical, treatment, and follow-up data were obtained by detailed chart abstraction with use of standardized reporting forms and were entered in a database created specifically for the purposes of the study (Microsoft Access 2000).

Starting in October 2010, data were prospectively collected in 14 hospitals. Before that time, and for the entire study period in the remaining 4 hospitals, data were retrospectively collected. Nonetheless, all centers have broad experience in treating IE patients and consolidated IE databases in which the information is prospectively collected. This study was conducted with the approval of the ethics committees of all the participating centers, and informed consent from patients was not required.

Statistical Analysis

Quantitative variables are reported as the median (interquartile range [IQR]), and qualitative variables are reported as percentages. The χ^2 test was used to compare the distribution of categorical variables, and the Student *t* test for comparison of continuous variables. For variables with a nonnormal distribution, we used the Mann-Whitney test. Differences were considered statistically significant at a *P* value of <.05. All outcomes were estimated using an intent-to treat analysis. All tests were 2-sided, with a 95% confidence interval. Statistical analyses were performed with SPSS-PC+, version 15.0 (SPSS, Chicago, Illinois).

RESULTS

Epidemiological, Clinical, and Outcome Characteristics of the Complete EFIE Series

During the study period, 291 episodes of EFIE were treated in 291 patients: 159 (55%) with AC, 87 (30%) with AG, and 45 (15%) with other antimicrobial combinations. Among the total, 272 (94%) episodes were diagnosed as definite IE according to the modified Duke criteria. Seventy-two (25%) *E. faecalis* strains showed HLAR.

Overall, EFIE patients had a median age of 69.9 years (IQR, 60.1–76.6 years), and 206 (71%) were men. The median score on the Charlson index was 2 points (IQR, 1–4 points). Ninety-eight patients (34%) had diabetes mellitus, 85 (29%) chronic renal failure (21 of them undergoing hemodialysis), 42 (14%) cancer, and 21 (7%) liver cirrhosis; 10 (3%) were transplant recipients, and 10 (3%) had HIV infection. One hundred fifty-two (52%) patients acquired the infection in the healthcare setting. The known origins of infection were urologic (80 [28%]), catheter-related bacteremia (37 [13%]), gastrointestinal (34 [12%]), previous cardiac surgery (19 [7%]), and others (17 [6%]). In 104 (36%) patients, the source of infection could not be identified.

EFIE affected native valves in 186 (64%) cases, prosthetic valves in 102 (35%), and implanted cardiac devices in 3 (1%). Eleven (4%) episodes were exclusively right-sided.

The median interval from symptoms onset to the start of antimicrobial treatment was 16 days (IQR, 5–44 days). At least 1 complication was diagnosed in 226 (78%) patients; 166 (57%) had congestive heart failure, 106 (36%) acute renal failure, 65 (22%) septic paravalvular complications, 49 (17%) symptomatic embolisms other than stroke, and 45 (16%) stroke.

Surgery was indicated in 174 (60%) cases, with the most common indications being refractory heart failure (112/174 [64%]) and septic paravalvular complication (54/174 [31%]). However, surgery was ultimately performed in only 104 of 174 (60%) cases, a median of 10 days (IQR, 4–22 days) after the start of treatment. In 89 of 104 (86%) patients, valve culture was carried out. The median duration of treatment before surgery was 22 days in the 39 patients with negative valve culture (IQR, 10–38 days), and 8 days (IQR, 3–15 days) in the 50 patients with positive valve culture ($P < .001$).

In the total series, 224 (77%) patients remained alive at the end of antimicrobial treatment, after a median of 42 days (IQR, 37–45 days) of antibiotics, and 212 (73%) patients remained alive at discharge. Median follow-up was 11.1 months (IQR, 4.4–22.5 months) in the 224 patients alive at the end of antimicrobial therapy. During that time period, 10 patients (5%) relapsed at a median of 37 days (IQR, 25–55 days) after completing antimicrobial treatment, and 12 patients (5%) underwent surgery at a median follow-up of 78 days (IQR, 48–109 days) after completion of antimicrobial treatment.

Comparative Findings in the AC Versus AG Treatment Groups

The demographic and clinical features of 246 EFIE episodes treated with AC (n = 159) or AG (n = 87) are shown in Table 1. In 51 (32%) episodes of EFIE treated with AC, the causal strains showed HLAR. The 2 treatment groups were comparable, except for the fact that AC patients had a greater incidence of chronic renal failure (33% vs 16%, $P = .004$), neoplastic disease (18% vs 7%, $P = .015$), transplantation (6% vs 0%, $P = .040$), and infection acquired in the healthcare setting (59% vs 40%, $P = .006$).

The antimicrobial treatment received, complications, surgeries, and in-hospital mortality of the 2 treatment groups is shown in Table 2. Of note, patients in the AG group presented new renal failure more often than did AC patients (46% vs 33%, $P = .051$).

Last, the outcomes of patients treated with the AC or AG combinations are summarized in Table 3. Between AC- and AG-treated EFIE patients, there were no differences in mortality while on antimicrobial treatment (22% vs 21%, $P = .81$), mortality at 3 months of follow-up (8% vs 7%, $P = .72$), treatment failure requiring an antimicrobial change (1% vs 2%,

Table 1. Demographic and Clinical Features in 246 Episodes of *Enterococcus faecalis* Infective Endocarditis Treated With Ampicillin Plus Ceftriaxone or Ampicillin Plus Gentamicin

Variable	Ampicillin + Ceftriaxone (n = 159)	Ampicillin + Gentamicin (n = 87)	*P* Value
Demographics			
Age, y, median (IQR)	70.4 (62.9–77.4)	69.8 (57.9–74.6)	.187
Male sex	114 (72%)	62 (71%)	.94
Definite IE (modified Duke criteria)	146 (92%)	84 (97%)	.151
Underlying condition			
CCI, median (IQR)	2 (2–4)	2 (1–4)	.053
Diabetes mellitus	53 (33%)	31 (36%)	.72
Chronic renal failure	53 (33%)	14 (16%)	.004
Neoplasm	29 (18%)	6 (7%)	.015
HIV infection	2 (1%)	6 (7%)	.017
Liver cirrhosis	13 (8%)	4 (5%)	.29
Hemodialysis	12 (8%)	3 (3%)	.199
Transplantation	10 (6%)	…	.040
Healthcare-associated infection	93 (59%)	35 (40%)	.006
Source of infection			.35
Unknown	49 (31%)	37 (43%)	
Urologic	53 (33%)	18 (21%)	
Catheter-related bacteremia	20 (13%)	12 (14%)	
Gastrointestinal	17 (11%)	10 (12%)	
Valve surgery	11 (7%)	5 (6%)	
Other	9 (6%)	5 (6%)	
Duration of symptoms, d, median (IQR)			
Overall	17 (5–44)	19 (7–36)	.36
Healthcare-associated IE	11 (4–45)	19 (7–31)	.47
Community-acquired IE	17 (5–58)	21 (8–40)	.89
Type of IE			.51
Native valve IE	98 (62%)	57 (66%)	
Prosthetic valve IE	59 (37%)	30 (34%)	
Pacemaker IE	2 (1%)	…	
Heart valve affected			.73
Aortic alone	73 (46%)	37 (43%)	
Mitral alone	46 (29%)	32 (37%)	
Aortic and mitral	30 (19%)	14 (16%)	
Tricuspid	5 (3%)	2 (2%)	
Aortic, mitral, and tricuspid	3 (2%)	…	
Mitral and tricuspid	1 (1%)	1 (1%)	
Unknown	1 (1%)	1 (1%)	
Vegetation size, mm, median (IQR)	10 (6–15)	10 (7–16)	.50

Abbreviations: CCI, Charlson comorbidity index; HIV, human immunodeficiency virus; IE, infective endocarditis; IQR, interquartile range.

$P = .54$), or relapse (3% vs 4%, $P = .67$). However, AG had to be discontinued much more often than AC owing to adverse events (25% vs 1%, $P < .001$), mainly new renal failure (23% vs 0%, $P < .001$).

In the comparisons of the subgroup of patients with EFIE caused by non-HLAR strains (108 patients treated with AC and 87 patients treated with AG), similar results were found (data not shown). The only difference was a higher percentage of patients with septic paravalvular complications in the AC group (40% vs 26%, $P = .050$).

Gentamicin Use in Patients With EFIE Caused by Non-HLAR Strains

In 31 patients, gentamicin was administered as long as ampicillin. In 34 patients (39%), gentamicin was stopped before completing antimicrobial treatment as had been previously

Table 2. Treatment and In-Hospital Mortality According to Antimicrobial Combination in 246 Episodes of *Enterococcus faecalis* Infective Endocarditis Treated With Ampicillin Plus Ceftriaxone or Ampicillin Plus Gentamicin

Variable	Ampicillin + Ceftriaxone (n = 159)	Ampicillin + Gentamicin (n = 87)	*P* Value
Duration of antimicrobial treatment, d, median (IQR)			
Overall, in survivors	42 (39–46)	42 (35–44)	.122
Days until surgery	11 (6–22)	9 (3–22)	.34
Adverse events			
Overall	14 (9%)	38 (44%)	<.001
Overall obliging to withdraw treatment	2 (1%)	22 (25%)	<.001
Drug stopped due to rash/fever	1 (0.6%)	0	.46
Drug stopped due to leukopenia	1 (0.6%)	0	.46
Drug stopped due to new renal failure	0	20 (23%)	<.001
Drug stopped due to vestibular toxicity	0	2 (2%)	.055
Complications			
Any complication	120 (76%)	72 (83%)	.187
Heart failure	87 (55%)	54 (62%)	.27
New renal failure	53 (33%)	40 (46%)	.051
Paravalvular complication	36 (23%)	22 (25%)	.64
Stroke	25 (16%)	14 (16%)	.94
Embolism other than stroke	28 (18%)	10 (12%)	.20
Surgery indicated	92 (58%)	54 (62%)	.52
Indications for surgery			
Heart failure	56/92 (61%)	37/54 (69%)	.35
Paravalvular complication	34/92 (37%)	14/54 (26%)	.171
Severe valve regurgitation without heart failure	23/92 (25%)	9/54 (17%)	.24
Vegetation size	9/92 (10%)	3/54 (6%)	.37
Uncontrolled infection	4/92 (2%)	5/54 (9%)	.23
Valve thrombosis	2/92 (2%)	…	.28
Pacemaker infection	2/92 (2%)	…	.28
Surgery performed during the active phase of infection (if indicated)	53/92 (58%)	35/54 (65%)	.39
Reasons for no surgery, if indicated			.37
High-risk patient	12/39 (31%)	9/19 (47%)	
Critical status	9/39 (23%)	4/19 (21%)	
Age[a]	7/39 (18%)	1/19 (5%)	
Patient rejected	4/39 (10%)	2/19 (11%)	
Surgeon rejected	3/39 (8%)	1/19 (5%)	
Hemorrhagic stroke	2/39 (5%)	…	
Other	2/39 (5%)	2/19 (11%)	
Surgery during follow-up	4/117 (3%)	6/69 (9%)	.094
In-hospital death			
Overall	42 (26%)	22 (25%)	.85
Without indication for surgery	8/67 (12%)	4/33 (12%)	.98
Operated	10/53 (19%)	10/35 (29%)	.29
Not operated (with indication)	24/39 (62%)	8/19 (42%)	.163

Abbreviation: IQR, interquartile range.

[a] Median age of these 8 patients was 84.9 years (IQR, 83.1–85.9 years).

scheduled, but not because of adverse events, after a median of 23 days (IQR, 14–34 days). In the 22 patients in whom gentamicin was withdrawn due to adverse events, no other antimicrobial was added in 10 cases (median length of gentamicin, 14 days [IQR, 12–20 days]), gentamicin was switched to ceftriaxone in 10 others (median length of gentamicin,

Table 3. Outcomes of 246 Episodes of *Enterococcus faecalis* Infective Endocarditis Treated With Ampicillin Plus Ceftriaxone or Ampicillin Plus Gentamicin

Variable	Ampicillin + Ceftriaxone (n = 159)	Ampicillin + Gentamicin (n = 87)	*P* Value
Failures			
Death during treatment	35 (22%)	18 (21%)	0.81
Death during 3-mo follow-up	13 (8%)	6 (7%)	0.72
Adverse effects requiring treatment withdrawal	2 (1%)	22 (25%)	<0.001
Treatment failure requiring change of antimicrobials	2 (1%)	2 (2%)	0.54
Relapse	3/124 (3%)	3/69[a] (4%)	0.67

[a] These patients had received 28, 36, and 42 days of ampicillin plus gentamicin, respectively.

15 days [IQR, 7–17 days]), AG was switched to daptomycin in 1 patient after 14 days, and AG was switched to linezolid plus levofloxacin in the last patient after 10 days.

Monitoring of gentamicin plasma levels was performed in 52 of 87 patients (60%). In 80 patients (92%), data on gentamicin administration schedule were obtained. In 37 patients, gentamicin was administered once a day, in 6 twice a day, and in 37 three times a day.

DISCUSSION

In this observational, nonrandomized, comparative multicenter cohort study, the AC combination was as effective as AG for treating *E. faecalis* infective endocarditis. Although AC-treated patients in the present series were in poorer general condition before acquiring the infection than AG patients, there were no differences in mortality between the treatment groups. However, AG patients experienced a high rate of adverse events related to antimicrobial therapy and, for this reason, antibiotics had to be withdrawn in 25% of cases.

To our knowledge, this is the most extensive published report on EFIE to date, including a large number of reference centers, a fact that lends strength to the results. Although *E. faecalis* is now the third most frequent cause of IE [1–3], there are few contemporary studies on this subject. This lack of findings is particularly important because of the continuous epidemiologic changes IE has undergone over the last few years [15]. It is noteworthy that >50% of patients in the present study acquired the infection by close contact with the healthcare system. The nosocomial origin of a considerable percentage of enterococcal bacteremia and endocarditis cases has been pointed out by Fernández-Guerrero et al [5, 16]. In consequence, the median age in this cohort of patients and the percentage of previous comorbid conditions is particularly high, in keeping with findings from previous studies [4–6, 14].

The lack of comparative clinical studies on antimicrobial therapy for EFIE has prompted various in vitro and animal experiments to be carried out with several antimicrobial combinations [17–21]. In one recently published study, gentamicin proved to be the most effective aminoglycoside for treating EFIE in a rabbit model, with best efficacy at 6 mg/kg/day [21]. Nonetheless, bearing in mind that EFIE often affects frail elderly patients with, or at risk of, renal failure, the recommendation of 4–6 weeks of penicillin or ampicillin plus an aminoglycoside for treating β-lactam– and gentamicin-susceptible enterococcal IE is a matter of concern. This situation has motivated publication of a study evaluating the length of aminoglycoside administration for this purpose, in which it was concluded that 2–3 weeks of aminoglycoside treatment might suffice [14].

Since publication of an observational, nonrandomized, multicenter clinical trial in this line [9], the AC combination has been recognized as an alternative for treating EFIE due to HLAR isolates [8]. However, this combination can be used in both HLAR and non-HLAR EFIE, and administration of these agents is neither limited by, nor a cause of, renal failure. Although the present study was not a randomized trial, AC proved to be as effective as AG, even though patients treated with this combination were in a poorer general condition at baseline (prior to acquiring the infection) than patients in the AG group. Moreover, acute renal failure occurred more frequently in patients receiving gentamicin. However, AC can be used with no risk of renal failure and regardless of the HLAR status of *E. faecalis*.

In our study, relapse occurred in 5% of all EFIE cases, 3% in the AC group, and 4% in AG-treated patients. The relapse rate for the overall series was similar to the reported rate of 7% of relapses in a retrospective Spanish study [5] of 47 episodes of EFIE, but far from the 0% reported by Wilson et al in 1984 [22]. However, both studies are not comparable owing to the relevant changes in the epidemiology this disease has suffered in the last decades [1, 15]. Focusing on patients treated with AC, our previous study showed a relapse risk of 5% [9]. Although the information about relapses in recent studies is scarce, a recent report described 2% of relapses in a general contemporary series of left-sided infective endocarditis [1].

The present study has several limitations, the most important being retrospective collection of many of the cases. However, all the participating centers have extensive experience in managing IE patients and all maintain local databases with prospectively collected, standard variables, and our previous experience has proven that the populations are comparable. Second, although it is a comparative study, it was not randomized because the use of different antimicrobial combinations for treating EFIE was center-dependent. Some hospitals always use AC in EFIE; others administer AG for non-HLAR and AC for HLAR EFIE; and, in the remaining centers, the choice between AC and AG treatment depends on the baseline renal function and/or the risk of new renal failure. Thus, there may have been some selection bias, in which patients in poorer clinical condition at baseline would be included in the AC group, as evidenced in the overall series by a higher percentage of patients with chronic renal failure receiving this treatment (33% vs 16%, $P = .004$) and in the non-HLAR subgroup by a higher percentage of septic paravalvular complications in patients receiving AC (40% vs 26%, $P = .050$). Third, due to its observational, nonrandomized nature, interruption of gentamicin due to adverse events was left to the discretion of the attending physician. Moreover, gentamicin levels were not determined in all centers because this technique was not available in the few participating community hospitals. These factors may have introduced some bias in the study toward significantly greater toxicity in the AG group. Nonetheless, these considerations also highlight the difficulties encountered when treating *E. faecalis* IE with gentamicin in actual clinical practice: it can be a difficult antimicrobial to manage, especially in patients with some degree of renal failure at the start of treatment. Another limitation of this multicenter study is the lack of molecular analysis of *E. faecalis* strains, because of which it was unknown whether there was a clonal cluster of cases in patients with healthcare-associated acquisition. Finally, the relatively small sample of non-HLAR EFIE patients treated with AG limited the statistical power of some of the comparisons with AC-treated non-HLAR EFIE patients.

In conclusion, in our cohort of *E. faecalis* infective endocarditis patients, treatment with the AC combination was found to be as therapeutically similar to treatment with AG. However, discontinuation of AG was often required because of acute renal failure. AC can be used with no risk of renal failure and regardless of the HLAR status of *E. faecalis*. A randomized controlled trial should be performed to further confirm these observations.

Notes

Acknowledgments. We thank Celine Cavallo for English-language support.

Financial support. This work was supported by the Ministerio de Sanidad y Consumo (Spanish Ministry of Health and Consumer Affairs), Instituto de Salud Carlos III–FEDER, Spanish Network for the Research in Infectious Diseases (REIPI RD06/0008). The funding source had no role in the study.

Potential conflicts of interest All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Fernández-Hidalgo N, Almirante B, Tornos P, et al. Immediate and long-term outcome of left-sided infective endocarditis. A 12-year prospective study from a contemporary cohort in a referral hospital. Clin Microbiol Infect **2012**; 18:E522–30.
2. Selton-Suty C, Célard M, Le Moing V, et al. Preeminence of *Staphylococcus aureus* in infective endocarditis: a 1-year population-based study. Clin Infect Dis **2012**; 54:1230–39.
3. Murdoch DR, Corey GR, Hoen B, et al. International Collaboration on Endocarditis-Prospective Cohort Study (ICE-PCS) Investigators. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the International Collaboration on Endocarditis–Prospective Cohort Study. Arch Intern Med **2009**; 169:463–73.
4. Martínez-Marcos FJ, Lomas-Cabezas JM, Hidalgo-Tenorio C, et al. Enterococcal endocarditis: a multicenter study of 76 cases. Enferm Infecc Microbiol Clin **2009**; 27:571–9.
5. Fernández-Guerrero ML, Goyenechea A, Verdejo C, Roblas RF, de Górgolas M. Enterococcal endocarditis on native and prosthetic valves: a review of clinical and prognostic factors with emphasis on hospital-acquired infections as major determinant of outcome. Medicine (Baltimore) **2007**; 86:363–77.
6. McDonald JR, Olaison L, Anderson DJ, et al. Enterococcal endocarditis: 107 cases from the international collaboration on endocarditis merged database. Am J Med **2005**; 118:759–66.
7. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: endorsed by the Infectious Diseases Society of America. Circulation **2005**; 111:e394–434.
8. Habib G, Hoen B, Tornos P, et al. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the International Society of Chemotherapy (ISC) for Infection and Cancer. Eur Heart J **2009**; 30:2369–413.
9. Gavaldà J, Len O, Miró JM, et al. Brief communication: treatment of *Enterococcus faecalis* endocarditis with ampicillin plus ceftriaxone. Ann Intern Med **2007**; 146:574–9.
10. Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis **2000**; 30:633–8.
11. Fernandez-Hidalgo N, Almirante B, Tornos P, et al. Contemporary epidemiology and prognosis of health care-associated infective endocarditis. Clin Infect Dis **2008**; 47:1287–97.
12. Raad I, Hanna H, Maki D. Intravascular catheter-related infections: advances in diagnosis, prevention, and management. Lancet Infect Dis **2007**; 7:645–57.
13. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis **1987**; 40:373–83.

14. Olaison L, Schadewitz K. Swedish Society of Infectious Diseases Quality Assurance Study Group for Endocarditis. Enterococcal endocarditis in Sweden, 1995–1999: can shorter therapy with aminoglycosides be used? Clin Infect Dis **2002**; 34:159–66.
15. Fernández-Hidalgo N, Almirante B. Infective endocarditis in the XXI century: epidemiological, therapeutic, and prognosis changes [in Spanish]. Enferm Infecc Microbiol Clin **2012**; 30:394–406.
16. Fernández-Guerrero ML, Herrero L, Bellever M, Gadea I, Roblas RF, de Górgolas M. Nosocomial enterococcal endocarditis: a serious hazard for hospitalized patients with enterococcal bacteraemia. J Inter Med **2002**; 252:510–5.
17. Mainardi JL, Gutmann L, Acar JF, Goldstein FW. Synergistic effect of amoxicillin and cefotaxime against *Enterococcus faecalis*. Antimicrob Agents Chemother **1995**; 39:1984–7.
18. Gavaldà J, Torres C, Tenorio C, et al. Efficacy of ampicillin plus ceftriaxone in treatment of experimental endocarditis due to *Enterococcus faecalis* strains highly resistant to aminoglycosides. Antimicrob Agents Chemother **1999**; 43:639–46.
19. Gavaldá J, Onrubia PL, Gómez MT, et al. Efficacy of ampicillin combined with ceftriaxone and gentamicin in the treatment of experimental endocarditis due to *Enterococcus faecalis* with no high-level resistance to aminoglycosides. J Antimicrob Chemother **2003**; 52:514–7.
20. Farina C, Russello G, Chinello P, et al. In vitro activity effects of twelve antibiotics alone and in association against twenty-seven *Enterococcus faecalis* strains isolated from Italian patients with infective endocarditis: high in vitro synergistic effect of the association ceftriaxone-fosfomycin. Chemotherapy **2011**; 57:426–33.
21. Dubé L, Caillon J, Jacqueline C, Bugnon D, Potel G, Asseray N. The optimal aminoglycoside and its dosage for the treatment of severe *Enterococcus faecalis* infection. An experimental study in the rabbit endocarditis model. Eur J Clin Microbiol Infect Dis **2012**; 31: 2545–7.
22. Wilson WR, Wilkowske CJ, Wright AJ, Sande MA, Geraci JE. Treatment of streptomycin-susceptible and streptomycin-resistant enterococcal endocarditis. Ann Intern Med **1984**; 100:816–23.