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

J. M. Pericas[1], C. Cervera[1], A. del Rio[1], A. Moreno[1], C. Garcia de la Maria[1], M. Almela[2], C. Falces[3], S. Ninot[4], X. Castañeda[1], Y. Armero[1], D. Soy[5], J. M. Gatell[1], F. Marco[2], C. A. Mestres[4], J. M. Miro[1] and The Hospital Clinic Endocarditis Study Group[†]

1) *Infectious Diseases Service, Hospital Clínic, Institut d'Investigacions Biomèdiques August Pi i Sunyer,* 2) *Microbiology Service, Hospital Clínic, Institut d'Investigacions Biomèdiques August Pi i Sunyer,* 3) *Cardiology Service, Hospital Clínic, Institut d'Investigacions Biomèdiques August Pi i Sunyer,* 4) *Department of Cardiovascular Surgery, Hospital Clínic, Institut d'Investigacions Biomèdiques August Pi i Sunyer and* 5) *Pharmacy Service, Hospital Clínic, Institut d'Investigacions Biomèdiques August Pi i Sunyer, University of Barcelona, Barcelona, Spain*

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.

Keywords: Ampicillin plus ceftriaxone, antimicrobial treatment, *Enterococcus faecalis*, high-level aminoglycoside resistance, infective endocarditis, outcomes
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Corresponding author: J. M. Miro, Infectious Diseases Service, Hospital Clínic, Villarroel 170, 08036-Barcelona, Spain
E-mail: jmmiro@ub.edu

[†]Members of the Hospital Clínic Endocarditis Study Group are listed in Appendix 1

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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 ($\leq$48 h) in serum creatinine of $\geq$0.3 mg/dL or an increase of $\geq$50% over baseline creatinine during a 7-day period or diuresis $\leq$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.