Original article

Reassessment of Blood Culture-Negative Endocarditis: Its Profile Is Similar to That of Blood Culture-Positive Endocarditis

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ABSTRACT

Introduction and objectives: Left-sided infective endocarditis with blood culture-negative has been associated with delayed diagnosis, a greater number of in-hospital complications and need for surgery, and consequently worse prognosis. The aim of our study was to review the current situation of culture-negative infective endocarditis.

Methods: We analyzed 749 consecutive cases of left-sided infective endocarditis, in 3 tertiary hospitals from June 1996 to 2011 and divided them into 2 groups: group I (n=106), blood culture-negative episodes, and group II (n=643) blood culture-positive episodes. We used Duke criteria for diagnosis until 2002, and its modified version by Li et al. thereafter.

Results: Age, sex, and comorbidity were similar in both groups. No differences were found in the proportion of patients who received antibiotic treatment before blood culture extraction between the 2 groups. The interval from symptom onset to diagnosis was similar in the 2 groups. The clinical course of both groups during hospitalization was similar. There were no differences in the development of heart failure, renal failure, or septic shock. The need for surgery (57.5% vs 55.5%; *P*=.697) and mortality (25.5% vs 30.6%; *P*=.282) were similar in the 2 groups.

Conclusions: Currently, previous antibiotic therapy is no longer more prevalent in patients with blood culture-negative endocarditis. This entity does not imply a delayed diagnosis and worse prognosis compared with blood culture-positive endocarditis. In-hospital clinical course, the need for surgery and mortality are similar to those in patients with blood culture-positive endocarditis.

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Revaluación de la endocarditis con hemocultivos negativos: su perfil es similar al de la endocarditis con hemocultivos positivos

RESUMEN

Introducción y objetivos: La endocarditis con hemocultivos negativos se ha asociado a retraso en el diagnóstico, mayor número de complicaciones y necesidad de cirugía; en definitiva, a un peor pronóstico. Nuestro objetivo es revisar la situación actual de la endocarditis con hemocultivos negativos. *Métodos:* Analizamos 749 casos consecutivos de endocarditis izquierda recogidos en tres hospitales terciarios entre junio de 1996 y 2011, y los dividimos en dos grupos: grupo I (n = 106), episodios con hemocultivos negativos; grupo II (n = 643), episodios con hemocultivos positivos. El diagnóstico de endocarditis se realizó según los criterios de Duke hasta 2002 y utilizando la versión modificada por Li et al. desde esa fecha.

Resultados: La edad, el sexo y la presencia de comorbilidades fueron similares en ambos grupos. No hubo diferencias significativas en la proporción de sujetos que habían recibido tratamiento antibiótico antes de la extracción de los hemocultivos. El periodo desde el inicio de los síntomas hasta el diagnóstico fue similar en ambos grupos. No hubo diferencias significativas respecto a aparición de insuficiencia cardiaca, insuficiencia renal o shock séptico. No se encontraron diferencias en la necesidad de cirugía (el 57,5 frente al 55,5%; p = 0,697) ni tampoco en la mortalidad (el 25,5 frente al 30,6%; p = 0,282). Conclusiones: Actualmente, la administración previa de antibióticos no es más frecuente en la endocarditis con hemocultivos negativos. Tampoco supone un retraso en el diagnóstico ni en el inicio del tratamiento adecuado. La evolución clínica intrahospitalaria, la necesidad de cirugía y la mortalidad son similares a las de los pacientes con hemocultivos positivos.

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Abbreviations

BCN-E: blood culture-negative endocarditis BCP-E: blood culture-positive endocarditis

IE: infective endocarditis

TEE: transesophageal echocardiogram

INTRODUCTION

Blood cultures are a fundamental tool in the diagnosis and treatment of infective endocarditis (IE). Blood culture-negative imply the loss of a microbiological reference which might guide the therapy and diagnosis of the disease. Blood culture-negative endocarditis (BCN-E) has been associated with a delay in diagnosis, a greater number of intrahospital complications, greater need for surgery and, in short, a worse prognosis. ¹⁻⁶ According to published data, the main cause of BCN-E has classically been prior administration of antibiotics. ^{5.7-12}

In the last decade, a series of changes has occurred in the epidemiological factors and microorganisms causing IE (higher patient age, predominance of *Staphylococcus aureus*, increased incidence of nosocomial IE, etc.). 8,13–17 Furthermore, in recent years, the use of transesophageal echocardiogram (TEE) in patients with suspected IE is increasingly frequent and early. All these changes have modified some diagnostic and prognostic aspects of this disease. The aim of our study was to review the current situation of BCN-E.

METHODS

We analyzed all consecutively recorded cases of IE in 3 tertiary hospitals occurring between June 1996 and June 2011. The episodes were recorded on a datasheet and were added to a general database prospectively and consecutively, in an orderly fashion, following the guidelines defined by the group of participating researchers and evaluated in annual meetings. Of the 896 IE episodes included in this period, only patients with left endocarditis (n=749) were selected, which composed our study group. Episodes of right endocarditis were excluded due to their different epidemiological, microbacteriological, clinical and prognostic profiles.

Episodes of left endocarditis were classified into 2 groups: group I (n=106), episodes of BCN-E, and group II (n=643), blood culture-positive (BCP-E) episodes. The diagnosis of endocarditis was performed according to the classic criteria of Duke University¹⁸ until 2002. From that date onwards, we used the modified version by Li et al.¹⁹ Of group I episodes, 74.5% (n=79) met the criteria for definite IE and 25.5% (n=27) for possible IE. Within this latter group, most episodes (n=24) showed a major criterion, determined by echocardiographic findings and 2 minor criteria. Only 3 episodes were diagnosed as possible IE with 3 minor criteria.

The information obtained from each patient was prospectively entered into our database following a standardized protocol for the 3 participating centers, which included performing at least 3 blood cultures at the time of admission and 48 h after the start of antibiotic treatment. In most episodes, the antibiotic treatment was initiated empirically after blood cultures had been taken, following the recommendations of clinical practice guidelines. ^{20,21} Later, the antibiotic treatment was adjusted according to the results of the blood cultures. Three pairs of blood cultures were

taken at each extraction and were incubated for up to 4 weeks. In all patients, the material obtained during surgery (valve tissue, prosthetic material, abscesses, peripheral embolisms, etc.) was delivered to the microbiology department. In BCN-E episodes, as well as in many other cases, some of this material was sent to the pathology department for histological evaluation with special dyes (Gram, silver, etc.). In episodes in which the blood cultures remained negative 72 h after admission, serology was systematically requested for *Brucella*, *Legionella*, *Coxiella*, *Mycoplasma* and *Chlamydia* and, in later years, *Bartonella*.

To study the evolution of IE within our cohort and determine the possible effect of the time factor on the microbacteriological profile and its influence on the disease's behavior, we performed a series of subanalyses, dividing the study period into 3 intervals of similar lengths (period 1: 1996-2001; period 2: 2002-2005; period 3: 2006-2011). We also studied the microbacteriological profile within each of the defined intervals.

Situations or procedures that held a risk of bacteremia and occurred 2 months before symptom onset were considered possible entry sites. Previous antibiotic treatment was considered relevant in episodes that occurred 15 days prior to blood culture extraction.

A transthoracic echocardiogram and a TEE were performed in all patients. The echocardiographic criteria used to define the presence of vegetations, abscesses, pseudoaneurysms and fistulas has been described in other publications.^{22,23} The size of vegetations was determined by measuring their largest diameter, and in cases with more than 1 vegetation, the largest was used.

Indications for surgery during the active phase of the disease were established at the beginning of the study by means of a consensus among the researchers and included heart failure refractory to medical treatment, signs of persistent infection (defined as persistence of bacteremia or fever lasting more than 7 days after the start of appropriate antibiotic treatment, and exclusion of secondary or metastatic sources of the infection), fungal infection, and recurrent embolism despite appropriate antibiotic treatment. In patients who did not undergo surgery despite its being indicated, the reason was the patient's refusal or excessive surgical risk according to the EuroSCORE scale after 1999, and before that date, the decision made by a multidisciplinary team which included at least 1 clinical cardiologist and a cardiac surgeon.

A total of 62 epidemiological, clinical, electrocardiographic, radiological, echocardiographic, microbiological and prognostic variables were recorded.

Statistical Analysis

The data are expressed as absolute frequencies or as percentages in the case of qualitative variables. The quantitative variables are described as mean (SD) and the median and the interquartile range in the case of asymmetry. To compare qualitative variables, either the chi-square or Fisher's exact test were used, as indicated. The quantitative variables were compared using Student t test and its non-parametric equivalent, the Mann-Whitney U test. Statistical significance was set at P<.05. The software package used for the analysis was SPSS version 15.0 for Windows (SPSS, Inc., Chicago, Illinois, United States).

RESULTS

Epidemiology and Clinical Presentation

The mean age of our population (n=749) was 61 (16) years. Some 63.2% were men and 38.5% were from other centers. In 40% of

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