ORIGINAL ARTICLE

Infective Endocarditis in Argentina. Results of the EIRA 3 Study

Endocarditis infecciosa en la República Argentina. Resultados del estudio EIRA 3

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ABSTRACT

Background: The clinical and epidemiological characteristics of infective endocarditis (IE), a complex disease with high morbidity and mortality, have changed over time. Our country lacks updated information since the publication of the EIRA 1 and 2 studies (1992 and 2002).
Objective: The aim of this study was to analyze the epidemiology, clinical and microbiological characteristics and hospital outcome of patients with IE.
Methods: A prospective multicenter observational study of patients with definite IE was conducted according to the modified Duke criteria.
Results: A total of 502 patients were recruited from 48 centers (69.5% in the Buenos Aires Metropolitan Area). Mean age 60.7±19.3 years and 69.9% (n=351) were men]; 54.64% of patients (n=274) did not present underlying heart disease, 19.9% (n=100) had prosthetic valves and 38.1% (n=191) had history of a healthcare-related procedure. The diagnosis was made within one month after the first clinical manifestation in 73.3% of cases (n=368) [76.5% (n=384) in the native valve]. The aortic valve was the most commonly affected valve (45.96%; n=230), followed by mitral valve involvement (33%; n=150). The most common germs were *Staphylococcus spp* in 46.3% of patients (n=232), *Streptococcus spp* in 28.2% (n=141) and *Enterococcus* in 12.8% (n=64). Blood cultures were negative in 44 patients (8.76%). Complications: heart failure (30.9%; n=155), peripheral embolism (19.6%; n=98) and abscess (15.5%; n=78). Adequate empirical antibiotic treatment was administered to 62.4% (n=313) of the patients and 43.6% (n=219) underwent surgical treatment. Overall in-hospital mortality was 25.5% (n=128). Age, history of chronic kidney failure, mitral valve disease and heart failure were independent predictors of in-hospital mortality.
Conclusions: A high percentage of patients with IE do not present known prior heart disease. *Staphylococcus spp* was the most common microorganism. Mortality remains high and similar to the one observed in the EIRA 1 and 2 studies.

Key Words: Infective endocarditis- Epidemiology- Prosthetic cardiac valve- Hospital mortality.

RESUMEN

Introducción: La endocarditis infecciosa (EI) es una enfermedad compleja con elevada morbimortalidad, cuyas características clínicas y epidemiológicas han variado. Desde la realización de los Estudios EIRA 1 y 2 (1992 y 2002) no se dispone de información nacional actualizada.
Objetivo: Analizar la epidemiología, características clínicas, microbiológicas y evolución hospitalaria de los pacientes con EI.
Material y Métodos: Estudio observacional prospectivo multicéntrico de EI definidas según los criterios de Duke modificados.
Resultados: En 48 centros, (69.5% Área Metropolitana Buenos Aires), se registraron 502 pacientes; edad 60,7 ± 19,3 años, hombres 69,9% (N=351).
El 54,64% de los pacientes (N= 274) no presentó cardiopatía subyacente.
El 38,1% (N=191) tenía antecedentes de un procedimiento asociado al cuidado de la salud. En el 73,3% (N=368) se realizó el diagnóstico dentro del mes de la primera manifestación clínica. La localización más frecuente fue la aórtica, tanto en EI por válvulas nativas como protésicas (48,24%/N=233) seguida de mitral (25,88%/N=125). Los gérmenes más frecuentes fueron: *Staphylococcus spp* 46,3% (N=210), Streptococcus spp 28,2% (N=128) y *Enterococcus spp* 12,8% (N=58). En 9,56% (N=48) de los casos los hemocultivos fueron negativos. Complicaciones: insuficiencia cardíaca (30,9%/N=155), embolias periféricas (19,6%/N=98) y absceso (15,5%/N=78). El 62,4% (N= 313) recibió tratamiento antibiótico empírico adecuado y el 43,4% tratamiento quirúrgico (N= 218). Mortalidad hospitalaria global: 25,5% (N=128). La edad, el antecedente de insuficiencia renal, la afección de la válvula mitral y la presencia de insuficiencia cardíaca fueron predictores de mortalidad hospitalaria.
Conclusiones: Existe un elevado porcentaje de pacientes con EI sin enfermedad cardíaca previa conocida. El *Staphylococcus spp* fue el germen causal más frecuente. La mortalidad se mantiene elevada, y similar a la de los estudios EIRA 1 y 2.

Palabras clave: Endocarditis, Epidemiología, Válvulas protésicas cardiacas, Mortalidad hospitalaria.

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Research Area and Council on Clinical Cardiology. Argentine Society of Cardiology.

Abbreviations

IE	Infective endocarditis	**TTE**	Transthoracic echocardiography
HF	Heart failure	**TEE**	Transesophageal echocardiography
ATB	Antibiotic		

INTRODUCTION

Infective endocarditis (IE) is a complex disorder that has always awakened great interest. (1) Although it is not a very common disease, it causes great impact on those who suffer from it, as more than 50% of the patients with IE experience some kind of severe complication in the course of the disease. Despite a better knowledge of the pathophysiology of the disease, the availability of more precise diagnostic tools, and more efficient antibiotics (ATB), the mortality of IE has not changed significantly over the past 40 years. Overall in-hospital mortality rate is 11-25% (and can be higher depending on the microorganism involved) and 30-40% at one year. (2, 3) In our country, mortality is still high, between 23.5% [EIRA (*Endocarditis Infecciosa en la República Argentina*) in 1993] (4) and 24.3% (EIRA 2 in 2002). (5)

The clinical characteristics and the epidemiology of IE have evolved over the past 50 years. (6,7) The factors contributing to these changes include the use of intravenous drugs, cardiovascular surgery, different types of heart valve prostheses and permanent catheters which may produce healthcare-associated IE.

There is limited information about the characteristics of IE in developing countries. The EIRA study was the first nationwide multicenter study analyzing the epidemiological profile of IE in our region. The study described the clinical characteristics, therapeutic management, and morbidity and mortality of the disease in Argentina in the early nineties. (4)

Thereafter, a new survey was conducted in 2002 (EIRA 2) (5) comparing the characteristics of IE and the changes that had occurred during the 10-year period between both studies, showing important differences as those observed in developed countries.

Our country lacks updated information since the publication of the EIRA 2 study. For this reason, and due to the high mortality rate and the changing profile of the disease, it is important to know its current status in a heterogeneous region as Argentina. The Council on Clinical Cardiology and Therapeutics "Tiburcio Padilla" and the Research Area of the Argentine Society of Cardiology decided to conduct a new registry of all the patients admitted with diagnosis of definite IE to public or private medical centers nationwide with working groups consisting of cardiologists and infectologists. The aim of this registry was: 1) to analyze the predisposing factors, clinical characteristics, diagnostic methods used, therapeutic approach and hospital outcome of the patients, and 2) to determine the predictors of morbidity and mortality.

METHODS

Selected prediction equations

A multicenter and prospective registry was designed for a cohort of patients with definite IE. Each center selected one cardiologist and one infectologist/bacteriologist as responsible of conducting the registry.

Eligible patients >18 years admitted with clinical diagnosis of definite IE according to the modified Duke criteria (8, 9) were enrolled in the study (Appendix 1).

Patients with confirmed or potential alternative diagnosis, possible IE and those without specific treatment for IE during initial hospitalization were excluded from the study.

Data were collected through the web using a specially designed electronic worksheet. Data on clinical history, predisposing factors, physical examination, complementary tests, microbiological tests and treatments were collected, as well as the information about procedures during hospitalization, hospital outcome and complications.

Definition of main events:

- Persistent fever: Persistent of intermittent fever ≥38 ºC after 1 (one) week of appropriate ATB treatment.
- Complications: Heart failure (HF), heart valve regurgitation, bleeding, embolism (location), cardiogenic or septic shock, systolic blood pressure ≤90 mmHg in the presence of adequate preload and in the absence of inotropic support; or systolic blood pressure ≤80 mmHg in the presence of adequate preload and inotropic support.
- Other complications: Acute myocardial infarction (presence of at least two of the following criteria: chest pain lasting 30 minutes or more, development of pathological Q waves - duration >0.4 sec or depth >1/3 R wave - or ST-segment elevation >1 mm lasting more than 30 minutes, and total CK or CK-MB values exceeding twice the upper reference limit), conduction disturbances and renal failure.
- All-cause mortality: In-hospital mortality due to cardiovascular and non-cardiovascular causes.

Statistical analysis

Qualitative variables are presented as frequency tables and percentages. Quantitative variables are expressed as mean ± standard deviation (SD), or median and interquartile range (IQR 25-75), according to their distribution,

Discrete variables were analyzed using contingency tables and for continuous variables, Student's t test, the Kruskall-Wallis test for unmatched groups, or the analysis of variance (ANOVA) were used, as applicable. The strength of the association between the variables was expressed as odds ratio (OR) with its corresponding 95% confidence interval (95% CI). The association of mortality (the dependent variable) with the independent variables (age, HF, sepsis, use of inotropic agents, among others) was analyzed using a univariate logistic regression model. Significant associations were studied using multivariate logistic regression analysis to estimate the probability of the association independently of other factors. A p value <0.05 was considered statistically

significant. All the calculations were performed using EpiInfo 7.2 and Stata/SE v13.0™ software package.

Ethical considerations

The study was approved by the Argentine Society of Cardiology Ethics Committee.

RESULTS

General characteristics

From September 2013 to March 2016, 502 patients from 48 centers of 13 Argentine provinces were included in the study (65.9% were from the Buenos Aires Metropolitan Area; 82.3% had cardiovascular surgery capabilities, 89.4% were able to perform automated blood cultures and 91.7% had TEE capabilities). Infective endocarditis was defined by 2 major criteria in 89.6% of the cases, by 1 major and 3 minor criteria in 4.6% and by histopathology in 5.8%. Mean age was 60.7±19.3 years and 69.9% were men. A history of underlying heart disease was present in 45.36% of the cases (Figure 1). Diabetes (23.5%) and chronic kidney failure (16.5%) were the most common underlying noncardiovascular conditions. Neoplasms were present in 12.1% of the patients, and 21.3% of these patients had metastasis. A predisposing event related to health care was found in 38.1% of the cases; among them, an endovascular procedure (31.9%) was the most common clinical situation associated with IE, followed by dental procedures (12.6%). Previous IE was reported by 8.96% of the patients.

Clinical and laboratory findings

Diagnosis of IE was made within 1 month after symptom onset in 73.3% of cases and after 6 months in 2.4%. Fever was preset in 88.4% of the patients admitted and 27.7% had clinical evidence of HF (Table 1). Petechiae were observed in 14.8% of the patients and 7.2% presented at least one immunologic phenomenon (Janeway lesions in 52.8 % of the cases) Mean erythrocyte sedimentation rate was 70.6±35.1 mm.

Echocardiographic findings and localization

Echocardiography was performed in 99.4% of the cases and 82.3% also underwent TEE. In 80% of the cases the investigators reported that TEE provided additional information and the examination had to be repeated at least once in 35.1% of the cases until evidence of IE was found. The main echocardiographic findings were: visible vegetations, 45.4% of aortic vegetations presenting with median size 8 (5-13) mm ×5 (3-8) mm and 31.2% of mitral vegetations with median size 10 (6-16) mm × 6 (3-9) mm; 41.7% aortic regurgitation (46.9% severe), 41.7% mitral regurgitation (31.6% severe); 19.4% annulus abscess; 14.4% valve perforation and 4.5% periprosthetic dehiscence (31.9% of the episodes on the prosthetic valve). Left ventricular systolic function was preserved in 75.2% of the patients. Table 2 details de distribution of IE localization.

Microbiological characteristics

Causative microorganisms were identified through blood cultures in 91.24% of the episodes, with the following distribution: 87.2% were gram positive cocci (*Staphylococcus spp* 53.0%, Streptococcus spp 32.3.2% and *Enterococcus* 14.6%), 7.9% gram negative bacili, 0.9% polymicrobial and 2% mycotic (Table 3).
Blood cultures were negative in 44 patients (8.76%).

Clinical course

Adequate empirical antibiotic treatment was administered to 62.4% of the patients. The most frequently observed complications are shown in Figure 2. Median hospital stay was 28 days (IQR 25-75: 15-45). During this period, surgery was indicated to 56.9% of the patients and 220 of them (43.6% of the total number of patients) underwent surgery (elective surgery in 67, emergency surgery in 33 and urgency procedure in 120). Surgery was not performed in 61 cases despite it was indicated.

Median time from hospital admission to surgery was 12 (5-21) days and 75 patients (34.1%) were operated on before day 7. The most common causes to indicate surgery were: valve regurgitation (138 patients, 49.5%), HF (68 patients, 24.4%), annulus abscess (66 patients, 23.7%), mobile vegetation (56 patients, 23,7%) and embolism (50 patients, 17.9%). Heart failure (54.5%) was the main indication of early surgery (before day 7), followed by valve regurgitation (45.5%). The surgical procedures were: on the aortic valve, and consisted of valve replacement with bioprosthesis (61 patients) and mechanical prosthesis (56 patients), homograft (9 patients) and aortic valve repair (3 patients); on the mitral valve, procedures were

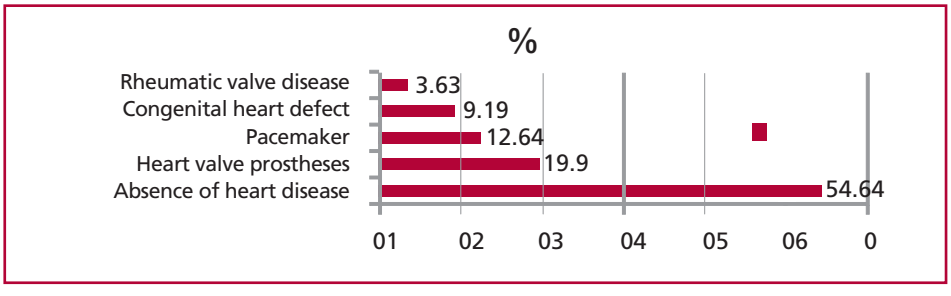

Fig. 1. Distribution of underlying cardiac diseases

valve replacement with bioprosthesis (20 patients) and mechanical prosthesis (30 patients), and mitral valve repair (14 patients); tricuspid valve repair (8 patients); and pacermaker or implantable cardioverter defibrillator removal (44 patients). The Ross procedure was not performed in any case. Thirteen patients underwent valve surgery combined with coronary artery bypass grafting.

Global mortality was 25.5%. Univariate analysis of mortality is presented in Table 4. Mortality was 27.4% in patients with heart valve disease and 10.5% in those with cardiac device-related IE (p=0.03). Conversely, mortality was 22.0% in patients undergoing surgery and 59.0% in those with indication of surgery who were not operated on. In patients without indication of surgery mortality was 20.7%.

The independent predictors of hospital mortality were: age > 65 years, history of chronic kidney failure, mitral valve compromise and HF on admission or during hospitalization (Table 5).

Table 1. Clinical data at admission

	n	%
Fever	443	88.4
Sepsis	233	46.5
Severe sepsis	80	16.0
Septic shock	56	11.1
Heart failure	139	27.7
Petechiae	74	14.8
Immunologic phenomena	36	7.2
Osler's nodes	15	41.7
Janeway lesions	19	52.8
Roth's spots	9	25.0
Embolism	154	30.7
Spleen enlargement	54	10.8
New murmur	160	31.9
Worsening murmur	65	13.0
Conduction disturbances	45	9.0
Arrhythmias	52	10.4

Table 2. Location of IE

	N (483)	%
Native valve	333	68.94
Aortic	153	45.96
Mitral	110	33.03
Aortic and mitral	28	8.40
Tricuspid	40	12.01
Pulmonary	2	0.60
Prosthetic valve	103	21.32
Aortic	80	77.68
Mitral	15	14.56
Aortic and mitral	6	5.82
Tricuspid	0	
Pulmonary	2	1.94

DISCUSSION

The EIRA 3 study represents the largest series of cohort studies of patients with definite IE in our country and Latin America.

Unlike other cardiovascular diseases, IE is a condition with low incidence that still has elevated mortality and severe complications despite improvements in diagnosis and treatment.

For this reason, it is important to carry out registries and to know the information of our country, as the situation of the disease under study may emerge from these registries. Effectively, this registry demonstrates that the high-risk profile of the patients and the frequency of the most pathogenic microorganisms as *Staphylococcus aureus* are increasing, and could be the reason of the high mortality observed. (3, 6)

The registry also shows that the age of the popula-

Table 3. Microbiology

	Global (n=454) n (%)	Native valve IE (n=310) N (%)	Prosthetic valve IE (n=94) N (%)
Streptococcus spp	128 (28.2)	97 (31.3)	21 (22.3)
- *Viridans*	82 (64.1)	60 (61.9)	14 (66.7)
- *Bovis*	26 (20.3)	22 (22.7)	3 (14.3)
- Others	20 (15.6)	15 (15.5)	4 (19.0)
Enterococcus spp	58 (12.8)	37 (11.9)	18 (19.1)
Staphylococcus spp	210 (46.3)	145 (46.8)	37 (39.4)
- *S. Aureus*	148 (70.5)	119 (82.1)	14 (37.8)
- Coagulase-negative	56 (26.7)	22 (15.2)	23 (62.2)
HACEK	9 (2.0)	5 (1.6)	4 (4.3)
Other Gram-negative	27 (5.9)	14 (4.5)	7 (7.4)
Polymicrobial	4 (0.9)	4 (1.3)	0
Mycotic	9 (2.0)	5 (1.6)	2 (2.1)
Others	9 (2.0)	3 (1.0)	5 (5.3)

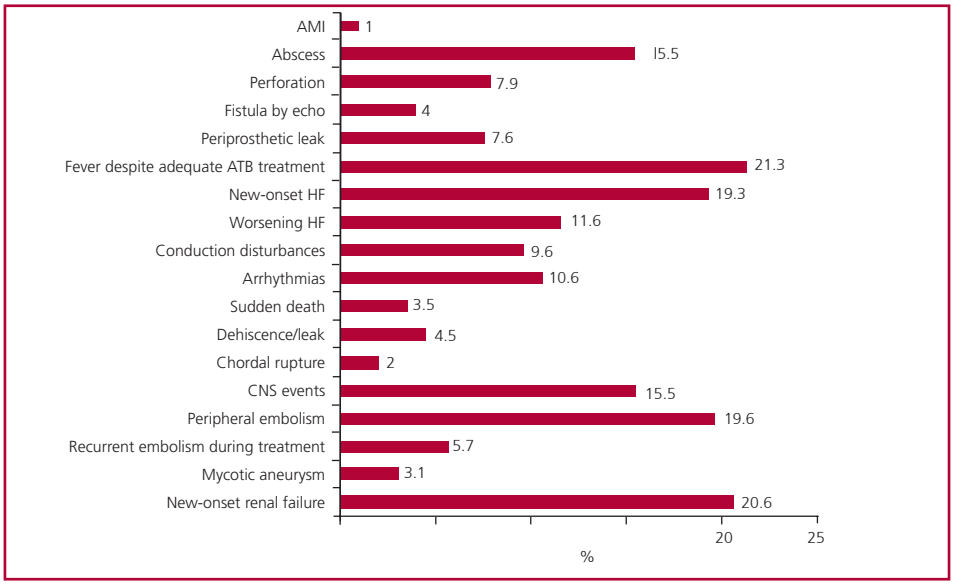

Fig. 2. Incidence of complications during hospitalization. AMI: Acute myocardial infarction. Echo: Echocardiogram. ATB: Antibiotic. HF: Heart failure. CNS: Central nervous system).

Table 4. Univariate analysis of in-hospital mortality

Variable	Alive (n=374) (74.5%) n	%	Dead (n=128) (25.5%) n	%	OR	IC95%	p
Male sex	261	72.5	80	62.5	0.63	0.41 – 0.97	0.034
Age	59.8 ± 18.7		65.2 ± 18.5				0.004
Age >65 years	165	46.3	75	58.6	1.64	1.08 – 2.47	0.017
Diabetes	87	24.4	29	23.0	0.92	0.57 – 1.49	0.75
COPD	40	12.0	13	11.1	0.92	0.47 – 1.78	0.79
CKF	48	13.4	32	25.8	2.25	1.36 – 3.73	0.001
Coronary artery disease	68	19.9	18	16.1	0.77	0.43 –1.36	0.36
Previous HF	50	14.0	31	26.1	2.16	1.29 – 3.58	0.002
Previous IE	31	8.7	12	9.4	1.10	0.55 – 2.21	0.79
Malignancy	39	11.1	22	17.5	1.70	0.96 – 2.99	0.06
Previous congenital heart defect	39	10.9	8	6.3	0.56	0.25 – 1.22	0.14
Previous native valve disease	150	46.0	52	50.0	1.17	0.75 – 1.83	0.48
Previous device or heart valve replacement	127	35.3	43	33.6	0.93	0.60 – 1.42	00.73
Previous hospitalization	199	56.1	78	60.9	1.22	0.81 – 1.85	0.34
Previous moderate-to-severe LV dysfunction	34	9.7	19	16.1	1.78	0.97 – 3.26	0.059
Fever on admission	322	89.9	111	88.1	0.83	0.44 – 1.57	0.56
HF on admission	85	23.6	51	39.8	2.14	1.39 – 3.29	0.0004
Aortic valve disease	195	54.6	71	55.9	1.05	0.70 – 1.58	0.80
Mitral valve disease	108	30.1	56	43.8	1.81	1.19 – 2.74	0.004
Abscess by ecocardiography	68	19.0	29	19.5	1.04	0.62 – 1.73	0.89
Positive blood cultures	319	91.7	110	90.9	0.90	0.44 – 1.88	0.79
New-onset HF	46	12.8	48	37.8	4.12	2.56 – 6.62	<0.0001
Worsening HF	29	8.1	28	22.6	3.29	1.87 – 5.80	<0.0001
HF on admission or during hospitalization	102	28.3	74	57.8	3.46	2.28 – 5.27	<0.0001

COPD: Chronic obstructive pulmonary disease. CKF: Chronic kidney failure. HF: Heart failure. LV: Left ventricular.

	OR	95% CI	p
HF on admission or during hospitalization	3.39	2.19 – 5.23	<0.0001
Chronic kidney failure	2.08	1.22 – 3.56	0.007
Mitral valve disease	1.76	1.13 – 2.75	0.013
Age > 65 years	1.56	1.01 – 2.42	0.046

Table 5. Multivariate logistic regression analysis of mortality

tion has increased across the different EIRA studies, from 51.3 years in the EIRA 1 (4) to 58.1 in the EIRA 2 (5) and 60.4 years in the current registry. This trend is consistent with other more recent registries. (3) In accordance with other findings, our registry confirmed male predominance in the incidence of IE with a ratio of 2:1. This could be due to the protective effect of circulating estrogens in women of childbearing age. (10) In addition, as women develop cardiovascular disease later than men, the onset of degenerative disease would be delayed over time.

The classic description made by Osler more than a century ago has been left behind, when most of the patients presented rheumatic valve disease as a predisposing factor with community-acquired bacteremia. In this sense, almost half of the patients did not present known structural cardiac disease while one third presented IE as consequence of a medical procedure (healthcare-associated IE), emphasizing the importance of prevention in this new scenario. Degenerative disease is the most common predisposing factor, whereas the role of rheumatic valve disease in our country is becoming less frequent. (7). There is also an increasing trend in the episodes of prosthetic valve IE compared with the previous registries and in agreement with international records (3) (EIRA 1: 8.5% (4), EIRA 2: 19.2% (5), EIRA 3: 20.7%).

In most cases (71.36%), the diagnosis was made within the first month, probably due to the high incidence of acute IE with more evident manifestations. In addition, the greater use of TEE could also contribute to the early diagnosis, as this method provided definite information for the diagnosis in 80% of the patients. However, the high clinical suspicion of the disease motivated repeated echocardiograms in 35.1% of the cases until the presence of IE was confirmed.

In Argentina, *Staphylococcus aureus* is still the most common microorganism involved as in the EIRA 2 study, (5) but the difference with Streptoccocus viridans is even more marked in the present study. Probably, this could be due to the high incidence of health care-associated IE and to exposure to invasive procedures predisposing to this type of infections caused by microorganisms as *Staphylococcus aureus*, which, in contrast with Streptococci, do not need the presence of preexistent heart valve disease (11) and infect patients without predisposing structural heart disease.

In the same sense, *Enterococcus* is the microorganism involved in almost 13% of the cases and, as *Staphylococcus aureus*, is associated with invasive procedures, nosocomial infections and involvement of weakened older adults or with comorbidities. This scenario has also been observed in other series reported. (12)

Blood cultures were negative in 8.6% of the IE episodes, below the values reported in both the ICE-PCS (11.1%) (3) and the EIRA 2 (10.8%) (5) studies but above those reported by Fournier et al. (5%). (13) Despite IE with negative blood cultures could have greater long-term mortality, we have not found differences in the outcome of these patients, in agreement with the publication of Ferrera et al. (13)

During hospitalization, the incidence of complications as HF, persistent sepsis and embolism was high, with a trend toward indication of early surgery in the active stage of the disease. (14-16) More than 40% of the patients underwent surgical treatment. This percentage is similar to the one observed in other international registries and represents one of the differences with the EIRA 2 study in which only 24% of the patients underwent surgery. (5) However, not all the patients with indication of surgery were operated on, similar to what happens in other parts of the world, and this fact could contribute to greater mortality. (17)

In-hospital mortality is still high, similar to the one observed in the previous registries (23.5%, 24.3% and 25.5% in EIRA 1, EIRA 2 and EIRA 3, respectively; p=0.87) despite better management, and in contrast with other cardiovascular diseases.

Again, as in the EIRA 2 study, the outcome of the disease can be determined at the patient's bedside. Age and HF are still independent predictors of mortality, with the addition of history of chronic kidney failure and mitral valve disease in this study. Early identification of patients with these risk factors may help with early contact or referral of these patients to tertiary centers with multidisciplinary and specialized "endocarditis team" as recommended by the latest EI guidelines. (7, 18-22)

Study limitations

The EIRA studies are observational registries in which the main limitations are the collection bias and the type of centers incorporated to the investigation.

Serological tests that could have clarified those cases with negative blood cultures were not performed.

Although this registry does not pretend to be representative of the complete reality of IE in Argentina, it offers elements of analysis that could help to im-

prove the identification and management of the disease. We believe it is a very important stimulus for all the investigators interested in knowing the reality of this disease in order to improve its management.

CONCLUSIONS

Throughout the decades, patients with IE have high clinical risk and are increasingly older. *Staphylococcus aureus* is the most common microorganism, followed by *Streptococcus viridans*. Despite improvements in diagnosis and treatment, mortality is still high and similar to the one observed in previous registries. The identification of independent predictors of in-hospital mortality, as history of chronic kidney failure, mitral valve compromise and the development of HF could help establish strategies to improve the results.

Conflicts of interest

None declared. (See authors' conflicts of interest forms on the website/Supplementary material).

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APPENDIX 1

Duke Infective Endocarditis Criteria

Major criteria

a. Positive blood cultures

- Typical microorganisms for IE from two separate blood cultures: *Streptococcus viridans*, *Streptococcus bovis*, HACEK group, *Staphylococcus aureus*, or community-acquired *Enterococcus*, in the absence of a primary focus; or
- Persistently positive blood culture, defined as recovery of a microorganism consistent with IE from at least two blood cultures drawn more than 12 hours apart or from three blood cultures or a majority of four or more blood samples, with first and last drawn at least 1 hour apart.
- Single positive blood culture for *Coxiella burnetti* or IgG antibody titer >1:800

b. Evidence of endocardial involvement

- Echocardiogram consistent with IE: 1) oscillating intracardiac mass, on valve or supporting structures, in the path of regurgitant jets, or on implanted material, in the absence of an alternative explanation; or 2) myocardial abscess; or 3) new partial dehiscence of a prosthetic valve.
- New valvular regurgitation (increase or change in pre-existing murmur not sufficient).

Minor criteria

a. Predisposition (predisposing heart condition or intravenous drug abuse)
b. Fever >38.0 C
c. Vascular phenomena (major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhage, Janeway lesions)
d. Immunologic phenomena (glomerulonephritis, Osler's nodes, Roth's spots, rheumatoid factor)
e. Microbiological evidence (positive blood culture not meeting major criteria* or serologic evidence of active infection with organisms consistent with IE)

* Excluding single positive cultures for coagulase-negative *Staphylococcus* or organisms not causing endocarditis

Definition of infective endocarditis according to Duke modified criteria:

Definite IE

a. Pathologic criteria:
- Microorganisms demonstrated by culture or histologic examination of a vegetation, a vegetation that has embolized, or in an intracardiac abscess; or
- Pathologic lesions: vegetations or intracardiac abscesses confirmed by histology showing active endocarditis.

b. Clinical criteria:

- major criteria
- major criterion and 3 minor criteria
- minor criteria

Possible IE

- major criterion and 1 minor criteria
- minor criteria

Rejected IE

- Firm evidence of alternative diagnosis to IE; or
- Resolution of IE symptoms with ATB therapy for ≤4 days; or
- No pathologic evidence of IE at surgery or autopsy, with antibiotic therapy for ≤4 days; or
- Does not meet criteria for possible IE

a) Additional minor criteria for NV EI:

- New splenomegaly
- Petechiae
- Splinter hemorrhages
- Elevated erythrocyte sedimentation rate (>30 mm/h in patients <60 years and >50 mm/h in those >60 years)
- Elevated C-reactive protein level >100 mg/l
- Microscopic hematuria

b) Additional minor criteria for PV EI

- New onset HF
- New conduction disturbances

APPENDIX 2

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