

Infective endocarditis: 10-year experience in a non-cardiovascular center

Endocarditis infecciosa: experiencia de 10 años en un centro no cardiovascular

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Abstract

Background and objective: Infective endocarditis (IE) is an infection with a poor prognosis, and an associated in-hospital mortality of at least 25%. Optimal therapy of IE requires long-term effective antibiotic therapy and valve surgery in many cases. The aim of this study was to review the demographics, bacteriology, and outcomes of patients with IE admitted to a tertiary referral center in Mexico City, over a 10-year period. **Methods:** Retrospective cohort study of patients admitted at Instituto Nacional Salvador Zubirán with a new diagnosis of IE over a 10-year period, from January 2009 to January 2019. Patients who met the definition for definitive diagnosis of infective endocarditis according to the modified Duke criteria were included in the study. **Results:** There were 62 patients (50.85 ± 17.46 years, 40.3% females) with IE. The culprit microorganism was identified in all cases, with *Staphylococcus aureus* being the most frequently found (34%). Valve surgery was performed in 58.1%, while 41.9% only received medical treatment. The mortality rate was 25.8% at 30 days and 41.9% at 12 months. Comparing the surgical and medical treatment groups, we found that 50% and 36% in each group, respectively, had died within 12 months of admission. **Conclusions:** Our center has a high prevalence of health care-associated endocarditis, mostly related to the presence of intravascular access devices. Most of the patients had a surgical indication. Patients with type 2 diabetes mellitus and decreased right ventricular systolic function had an increased mortality rate at 12 months.

Keywords: Infective endocarditis. Health care-associated endocarditis. Heart valve disease.

Resumen

Antecedentes y objetivo: La endocarditis infecciosa (EI) es una infección de mal pronóstico, con una mortalidad intrahospitalaria que va del 15-20%. La terapia óptima requiere antibioticoterapia efectiva por tiempo prolongado y cirugía valvular en algunos casos. El objetivo de este estudio fue revisar la epidemiología y desenlaces de pacientes con EI en un centro de referencia en la Ciudad de México. **Métodos:** Cohorte retrospectiva de pacientes admitidos al Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán con diagnóstico de EI en un periodo de 10 años, de enero de 2009 a enero de 2019. Se incluyeron a pacientes que cumplían la definición de diagnóstico definitivo de endocarditis infecciosa de acuerdo a los criterios modificados de Duke. **Resultados:** Se incluyeron a 62 pacientes (50.85 ± 17.46 años, 40.3% mujeres). Todos los

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casos tuvieron cultivos positivos, siendo *S. aureus* el microorganismo más frecuente (34%). El 58.1% de los pacientes recibió tratamiento quirúrgico y 41.9% recibió únicamente tratamiento médico. La mortalidad a 30 días fue de 25.8% y a 12 meses fue de 41.9%. Comparando los grupos de tratamiento médico y quirúrgico, se encontró que 50% y 36% de cada grupo, respectivamente, habían fallecido a los 12 meses. **Conclusiones:** Encontramos una alta prevalencia de EI asociada a los cuidados de la salud, principalmente en relación a accesos intravasculares. Casi todos los pacientes presentaban un criterio quirúrgico al momento del diagnóstico. Los pacientes con diabetes mellitus tipo 2 y función sistólica del ventrículo derecho disminuida presentaron una mayor mortalidad a 12 meses.

Palabras clave: Endocarditis infecciosa. Enfermedad valvular cardíaca. Endocarditis infecciosa asociada a los cuidados de la salud.

Introduction

Infective endocarditis (IE) is an infection of the cardiac endothelium that advances rapidly and can present with fever, sepsis, and systemic complications¹. Historically, it was diagnosed on the basis of classic findings of active valvulitis, embolic manifestations, and vascular immunologic phenomena, together with positive blood cultures. However, nowadays epidemiology has shifted towards health care-associated IE, which does not present with all the classic findings². Furthermore, this epidemiological change has led to an increase in the prevalence of *Staphylococcus aureus*³.

Despite advances in medical knowledge, technology, and antimicrobial therapy, the prognosis for IE continues to be poor, with an in-hospital mortality of at least 25%⁴.

Optimal IE therapy requires long-term effective antibiotic therapy and valve surgery in some cases. According to the European College of Cardiology (ESC) guidelines, surgical indications include heart failure secondary to valve dysfunction, uncontrolled infection, and prevention of septic embolisms⁵. Heart failure is the most frequent complication of IE and represents the most common indication for surgery⁶.

The purpose of our study was to review the demographics, bacteriology, and outcomes of patients with IE admitted to a tertiary referral center in Mexico City, over a 10-year period.

Methods

We conducted a retrospective cohort study of patients admitted at Instituto Nacional Salvador Zubiran with a new diagnosis of IE over a 10-year period, from January 2009 to January 2019. Patients who met the definition for definitive diagnosis of infective endocarditis according to the modified Duke criteria were included in the study. Both written and electronic patient records were reviewed. A total of 145 records were

reviewed, of which only 62 met the inclusion criteria. Included cases were followed for up to 12 months.

Demographic, clinical, and biochemical data recorded at the time of initial assessment were collected. Isolates in blood culture and/or biopsy were recorded. Diagnostic imaging tests were recorded, including the most important echocardiographic data.

For each case, it was evaluated whether they met surgical criteria according to the 2015 ESC guidelines. If so, the indication and the level of recommendation for each of these indications were included in the study.

Finally, the length of stay, antibiotic days, 30-day mortality, 12-month reinfections, 12-month readmissions, and 12-month mortality were recorded.

The cases were categorized as community acquired or health care-associated. Health care-associated endocarditis was defined as IE developing in a patient hospitalized for more than 48 h before onset of signs/symptoms or as IE diagnosed within 48 h of admission in patients with close contact with health services as reflected by any of the following criteria: (1) receipt of intravenous therapy, wound care, or specialized nursing care at home within the 30 days before the onset of IE; (2) attendance at a hospital or hemodialysis clinic or receipt of intravenous chemotherapy within the 30 days before the onset of IE; (3) hospitalization in an acute care hospital for 2 or more days in the 90 days before the onset of IE; or (4) residence in a nursing home or long-term care facility.

For the analysis, patients were divided in two groups: patients with medical treatment only and patients with surgical treatment. Categorical variables were expressed as percentages. Continuous variables were expressed as means \pm standard deviation. Groups were compared by performing Chi-square test for the categorical variables and Student's t-test for the continuous variables. A two-sided $p < 0.05$ was considered statistically significant. All analyses were performed using the SPSS version 22 (SPSS for Mac; IBM, Chicago, Illinois, USA).

Table 1. Clinical and demographic data

	Values
Number of patients, n (%)	62 (100)
Age, years*	50.85 ± 17.46
Gender	
Female, n (%)	25 (40.3)
Male, n (%)	37 (59.7)
Type 2 diabetes mellitus, n (%)	22 (35.5)
Systemic arterial hypertension, n (%)	34 (54.8)
Liver cirrhosis, n (%)	7 (11.3)
Cigarette smoking, n (%)	18 (29)
Cancer, n (%)	13 (21.3)
Chronic kidney disease, n (%)	24 (39.3)
Dental disease, n (%)	8 (12.9)
Hemodialysis, n (%)	23 (37.1)
Intravenous drugs use, n (%)	1 (1.6)
Surgery in the past 30 days, n (%)	11 (17.7)
Intravenous access device, n (%)	29 (46.8)
Pacemaker, n (%)	3 (4.8)
Cardiopathy, n (%)	3 (4.8)
Heart valve disease, n (%)	15 (24.2)
Prosthetic heart valve, n (%)	5 (8.1)
Immunosuppression, n (%)	13 (21)
Human immunodeficiency virus, n (%)	1 (1.6)

*Data expressed as mean ± standard deviation.

Table 2. Clinical presentation

	Values
Symptoms at presentation:	
Fever, n (%)	56 (90)
Chills, n (%)	40 (64.5)
Diaphoresis, n (%)	11 (17.7)
Weight loss, n (%)	19 (30.6)
Malaise, n (%)	53 (85.5)
Headache, n (%)	7 (11.3)
Arthralgias, n (%)	10 (16.1)
Abdominal pain, n (%)	16 (25.8)
Dyspnea, n (%)	11 (17.7)
Chest pain, n (%)	2 (3.2)
Signs at presentation:	
New cardiac murmur, n (%)	36 (58.1)
Altered mental status, n (%)	10 (16.1)
Focal neurological deficit, n (%)	6 (9.7)
Petechiae, n (%)	4 (6.5)
Splenomegaly, n (%)	22 (35.5)
Janeway lesions, n (%)	6 (9.7)
Osler nodes, n (%)	0 (0)
Roth spots, n (%)	7 (11.3)
Complications:	
Heart failure, n (%)	19 (30.6)
Septic emboli, n (%)	34 (54.8)
Metastatic infection, n (%)	8 (12.9)
Glomerulonephritis, n (%)	1 (1.6)
Embolic stroke, n (%)	14 (22.6)
Laboratory findings:	
Hemoglobin, g/dL*	10.13 ± 2.5
Platelets, ×109/dL*	184.05 ± 119.5
Leucocytes, ×109/dL*	12.76 ± 5.96
Creatinine, mg/dL*	3.87 ± 4.11
Bilirubin, mg/dL*	1.33 ± 1.42
ALT, U/dL*	30.2 ± 39.18
AST, U/dL*	38.4 ± 35.7
Albumin, g/dL*	2.75 ± 0.8
C reactive protein, mg/dL*	12.5 ± 6.8
Erythrocyte sedimentation rate, mm/hour*	53.3 ± 33.8

*Data expressed as mean ± standard deviation.

Results

A total of 62 patients were included, of whom 25 were women and 37 were men, with a mean age of 50.85 ± 17.46 years. The baseline characteristics of the patients are presented in table 1, while the clinical characteristics are presented in table 2. Forty-four (70.9%) patients had left IE. Of the total of patients, 35 (56.5%) were classified as health care-associated IE, the most frequent cause of this being the presence of intravenous access device in 29 (46.8%) of them. Patients with congenital heart defects were not included. Only 5 (8.1%) patients had IE associated with a prosthetic valve.

Within the diagnostic approach, 35 (56.5%) underwent an abdominal CT scan, 24 (38.7%) a head MRI, and 6 (9.7%) underwent a nuclear medicine test. In

those who underwent an MRI, a stroke was observed in 14 (22.6%). Meanwhile, 50 (80.6%) patients underwent transthoracic echocardiography and 54 (87.1%) underwent transesophageal echocardiography. The echocardiographic findings at diagnosis are described in table 3. The most frequently affected valve was the mitral valve (29%) followed by the aortic valve (22.6%) and the mitro-aortic complex (19.4%). Valvular vegetation was found in 59 (95%) of the patients and 7 (11.3%) of them presented non-valvular vegetation. The mean size of the vegetations was 16.5 ± 6.3 mm. Furthermore, an abscess was found in 10 patients (4 valvular and 6 perivalvular).

Blood cultures were requested from all patients and microbiological isolation was found in 57 (91.9%) of

Table 3. Echocardiographic findings

	Values
Left ventricle ejection fraction, %*	59.8 ± 9.7
Left ventricle global longitudinal strain, %*	18.5 ± 4.3
Pulmonary artery systolic pressure, mmHg*	44.7 ± 19.8
Tricuspid annular plane systolic excursion, mm*	22.3 ± 4.9
Affected valve, n (%)	
Mitral	18 (29.5)
Aortic	14 (23)
Tricuspid	9 (14.8)
Pulmonary	1 (1.6)
Aortic and mitral	12 (19.7)
Tricuspid and mitral	1 (1.6)
Right atrium involvement, n (%)	5 (8.2)
Valvular vegetation, n (%)	59 (95)
Non-valvular vegetation, n (%)	7 (11.3)
Number of vegetations ^a	1.68 ± 1
Maximal vegetation size, mm ^a	16.5 ± 6.3
Mobile vegetation, n (%)	37 (59.7)
Papillary muscle rupture, n (%)	5 (8.1)
Abscess, n (%)	10 (16)
Valvular	4 (6.5)
Perivalvular	6 (9.7)
Valvular perforation, n (%)	8 (12.9)
Valvular dysfunction, n (%)	53 (85)
Severe regurgitation	35 (56)

*Data expressed as mean ± standard deviation.

them, while 15 of heart valve cultures were positive. Two microorganisms were found in 3 patients. Overall, the culprit organism was identified in all patients: *Staphylococcus* in 28/62 (*S. aureus* in 21, *S. epidermidis* in 6, and *Staphylococcus saprophyticus* in 1), *Streptococcus* in 16/62 (*S. gallolyticus* in 4, *S. viridans* in 1, *S. mitis* in 2, *S. agalactiae* in 2, *S. sp* in 2, *S. sanguis* in 2, *S. parasanguinis* in 1, *S. pyogenes* in 1, and *Granulicatella adiacens* in 1), *Enterococcus faecalis* in 8/62, Gram-negative bacilli in 3/62 (*E. coli* in 2 and *Acinetobacter baumannii* in 1), fungi in 6/62 (*C. glabrata* in 1, *C. albicans* in 2, *C. parapsilosis* in 2, and *C. tropicalis* in 1), *Corynebacterium jeikeium* in 3/62, and *Lactobacillus sp.* in 1/62.

Regarding treatment, 36 (58.1%) received surgical treatment, while 26 (41.9%) received medical treatment only. In the surgical treatment group, valve replacement was performed in 33 patients, while the remaining 3

patients underwent vegetectomy. The median time between diagnosis and surgery was 5.5 days (IQR 3-12.5). Of the prosthetic valves employed during surgery, 63.6% were mechanical and the remaining 36.4% were biological valves. One of the patients died in the operating room. Only 2 patients in the surgical treatment group required surgical reintervention 30 days after the initial procedure.

The median length of hospital stay was 34 days (IQR 24.5-52.5) and the median length of antibiotic therapy was 42 days (IQR 28-42). In the 30-day follow-up, 16 (25.8%) patients died, the most frequent cause being septic shock. When the medical and surgical treatment groups were compared, it was found that 30.7% (8/26) and 22.2% (8/36) of each group, respectively, had died within 30 days, but this difference was not statistically significant ($p = 0.44$). Regarding the 12-month outcomes, reinfection was found in 5 and rehospitalization in 8, and 26 (41.9%) had died in that period of time. At 12 months, it was found that 13/26 (50%) and 13/36 (36%) of the medical and surgical group, respectively, had died, but this difference was not statistically significant ($p = 0.27$).

The mean left ventricular ejection fraction was 60.2 ± 11.9% and 59.3 ± 6.6% in the group that survived and died at 12 months, respectively. On the other hand, the mean tricuspid annular plane systolic excursion was 23.9 ± 5.15 mm and 20.7 ± 4.34 mm in the group that survived and died at 12 months, respectively, with this difference being statistically significant ($p = 0.026$).

Regarding the comorbidities of the patients, it was found that type 2 diabetes mellitus was associated with a higher mortality at 12 months ($p = 0.01$). When these patients with diabetes mellitus ($n = 22$) were separated by age, the 12-month mortality rate was 63.6% (7/11) in both those under and above 60 years of age.

When evaluating whether the patients had surgical intervention criteria according to ESC guidelines, it was found that 54 (87%) of them had an indication for surgery. Of these, 28 (51.9%) had an indication with class of recommendation I, 18 (33.9%) with class of recommendation IIa, and 8 (14.8%) with class of recommendation IIb. The most frequent indications were: (1) severe valve dysfunction with vegetation >10 mm in the mitral or aortic valve in 16 (25.8%), (2) severe valve regurgitation with symptoms of heart failure in 15 (24%), (3) vegetation >15 mm in 8 (12.9%), and (4) presence of an abscess in 10 (16%) patients. In those who had a surgical indication and did not undergo surgery, a

12-month mortality of 52% (10/19) was found against a 37% (13/35) mortality in those who had an indication and did undergo surgery, but this difference did not turn out to be statistically significant ($p = 0.4$).

Regarding the recommended time for surgery, 49 (91%) had a recommendation to perform the surgery urgently (in the next 7 days) and 5 (9%) to perform it electively (in 1-2 weeks). Only 20 (37%) underwent surgery in the time recommended by the ESC. In those who did not undergo surgery in the recommended time, the mortality rate at 12 months was 27.8% (15/54), against a mortality rate of 14.3% (8/54) in those who did undergo surgery in the indicated time, but this difference was not statistically significant ($p = 0.76$).

Discussion

We report the results of a retrospective cohort, in which we evaluated the clinical characteristics and outcomes of adults with IE in a third-level non-cardiovascular center.

This series found a predominance of Gram-positive microorganisms (90% of cases), with *S. aureus* being the most frequently isolated microorganism (34%), of which 33.3% were methicillin-resistant. This is similar to what was reported in the study of the International Collaboration on Endocarditis (ICE)⁷. However, we found 6 (9.6%) cases of yeast, 3 (5%) of gram-negative bacilli, 3 (4.8%) of *Corynebacterium jeikeium*, and 1 (1.6%) case of *Lactobacillus*, which differs from what was published in other series. The ICE study, for example, reported a yeast frequency of 1.6% globally and 1.1% in South American countries⁷. It is possible that the isolates found in our series respond to the large proportion of patients with health care-associated IE (56.5%) and the large proportion of patients with intravascular accesses (46.8%).

Even with diagnostic and therapeutic advances, IE is associated with a poor prognosis, with an in-hospital mortality rate that ranges from 15 to 25% and a 12-month mortality of approximately 40%⁸⁻¹¹. However, Botelho-Nevers et al. demonstrated a reduction in mortality with the implementation of a medical and surgical treatment protocol, achieving a 12-month mortality of 8.2%¹².

Valve surgery has been shown to be a predictor of a good prognosis in IE, and today, around 40-50% of patients with IE are taken to surgery^{7,13-15}. In a prospective cohort study involving patients with native-valve infective endocarditis, a multivariable analysis with adjustment for coexisting conditions showed that an

indication for surgery without performance of the surgery was an independent predictor of death¹⁶. The study published by Botelho-Nevers et al. – during the period that found a reduction in mortality – reported an adherence of 92% to the surgical protocol¹². Meanwhile, we found that, despite the fact that only 66% of patients who had a surgical indication (of any kind) underwent valve surgery, this resulted in a surgery ratio of 58.1%. This proportion is higher than that reported in a systematic review of the global burden of endocarditis, in which a mean proportion of valve surgery of 32.4% was found globally and of 41.3% in Latin American countries⁴. Even though mortality rates were lower in the surgical group at 30 days and 12 months, this difference was not statistically significant. It is possible that the surgical treatment group obtained a good long-term result because the ventricular (both left and right) function parameters were preserved, which is a predictor of a good post-operative prognosis¹⁷.

Our study had several limitations. First, it is a retrospective review of a single center. Despite having included all cases in a 10-year period, the sample size was relatively small. This relatively small sample could explain why some of our comparisons did not result in significant differences, despite having a clear numerical difference. Furthermore, some of the presentation variables had to be removed from the analysis due to the absence of complete data in the clinical records. For example, it was not possible to include cardiac biomarkers at patient admission, nor was it possible to calculate APACHE or SOFA for all patients. Being a national reference center, we cannot rule out a selection bias and the data presented here may not reflect the general epidemiology of Mexico.

Conclusions

Our center has a high prevalence of health care-associated IE, and this was associated with a low presentation of the classic clinical characteristics of IE; the index of suspicion should be high, particularly in patients who have intravascular access devices.

Patients with IE that had a former diagnosis of type 2 diabetes mellitus and those with decreased right ventricular systolic function at the time of diagnosis had an increased mortality rate at 12 months.

Most of the patients had surgical criteria at the time of diagnosis, but not all had surgery, nor was this intervention performed in the recommended time in all. Therefore, we believe that institutional protocols should be implemented in order to promote valve surgery in

patients with surgical indication and to ensure that this is performed within the recommended time by international guidelines.

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Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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