

Infectious endocarditis without intracardiac devices or underlying structural heart disease

Endocarditis infecciosa sin dispositivos intracardiacos ni cardiopatía estructural subyacente

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Abstract

Objective: To describe clinical, microbiological and echocardiographic aspects of endocarditis in a specific group of patients without intracardiac devices or underlying structural heart disease. **Method:** Retrospective study, clinical records and echocardiographic reports were reviewed during the period 1997 to 2020. Duke's modified criteria were applied. Statistical analysis: univariate expressed in frequencies, using measures of dispersion and central tendency. **Results:** 30,000 echocardiographic reports were reviewed, only 1350 had infectious endocarditis as a reason for sending, of which 248 cases were selected. The mean age was 48.1 ± 16.7 years. 140 men (56%) and 108 women (44%). The most frequent echocardiographic sign was vegetation, in 278 (93.60%), and most common location was mitral (35.55%), with a higher number of cases in the right ventricle than expected. The most common systemic disease was kidney disease, in 135 (41.08%). A case of *Streptococcus thoraltensis* not previously reported in Mexico was identified. **Conclusions:** The presence of infectious endocarditis has increased due to invasive in-hospital and drug procedures. Due to their complexity, multidisciplinary teams are indispensable.

Keywords: Endocarditis. Infectious endocarditis. Vegetation.

Resumen

Objetivo: Describir aspectos clínicos, microbiológicos y ecocardiográficos de endocarditis en un grupo específico de pacientes sin dispositivos intracardiacos ni cardiopatía estructural subyacente. **Método:** Estudio retrospectivo en el que se revisaron expedientes clínicos y reportes ecocardiográficos durante el periodo de 1997 a 2020. Se aplicaron los criterios modificados de Duke. Se describió la muestra por edad, sexo, enfermedad sistémica, vegetaciones y agente microbiológico. Se excluyeron pacientes con cardiopatía estructural o Libman-Sacks. Análisis estadístico: univariado expresado en frecuencias, utilizando medidas de dispersión y tendencia central. **Resultados:** Se revisaron 30,000 reportes ecocardiográficos, de los cuales solo 1350 tenían como motivo de envío endocarditis infecciosa, y de estos se seleccionaron 248 casos. La edad promedio fue de 48.1 ± 16.7 años. Hubo 140 hombres (56%) y 108 mujeres (44%). El signo ecocardiográfico más frecuente fue la vegetación, en 278 (93.60%), y la ubicación más común fue mitral (35.55%), con un número mayor de casos en el ventrículo derecho de lo esperado. La enfermedad sistémica más común fue la enfermedad renal, en 135 (41.08%). Se identificó un caso de *Streptococcus thoraltensis* no reportado previamente en México.

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Conclusiones: *La presencia de endocarditis infecciosa ha aumentado debido a procedimientos invasivos intrahospitalarios y fármacos. Por su complejidad, los equipos multidisciplinarios son indispensables.*

Palabras clave: *Endocarditis. Endocarditis infecciosa. Vegetación.*

Introduction

Infective endocarditis (IE) is a multisystemic infection that typically results from an infection, often caused by bacteria, on the heart endocardial surface. IE is categorized based on its location, clinical presentation, mode of acquisition, infectious agent, or presence of underlying structural heart disease^{1,2}. The mortality rate of IE that can vary between countries but remains consistently over 30% within 30 days. The estimated incidence rate of IE is 3 to 10 cases per 100 000 people per year^{2,3}. However, contemporary reviews have indicated a gradual increase in its epidemiology, from 0.32 up to 0.75 cases per 100 000 people in the United States alone⁴, being 30% of the cases associated with the health care provided⁵.

In 2011, expert consensus in Europe already raised concerns on the predisposing factors for developing IE⁶, as demonstrated by other meta-analyses such the one conducted by Rigau et al.⁷ who showed variations in clinical presentation, treatment, prognosis, and mortality when patients were stratified based on vegetation location and predisposing factors such as intracardiac devices, use of IV drugs, or underlying structural heart disease (whether rheumatic, degenerative, congenital, or ischemic). Other proposed risk groups include patients on hemodialysis, immunosuppressive therapy, non-cardiac surgery, and elderly patients^{8,9}.

In Mexico, IE started being reported back in 1976, primarily in native vs prosthetic valves, microbiology, embolic complications, and medical vs surgical therapy^{10,11}. However, little is known on the predisposing factors, clinical presentation, microbiological agents, and complications in patients with systemic disease, without intracardiac devices, or underlying structural heart disease^{11,12}. This study aimed to identify the clinical aspects and predisposing factors of this group of patients.

Method

This was a retrospective study involving the review of all echocardiographic studies conducted at the Cardiology Department of UMAE "Dr. Bernardo Sepúlveda Gutiérrez" Hospital de Especialidades within Centro Médico Nacional Siglo XXI of the IMSS, Mexico City,

Mexico. The study only included patients who met the absolute or possible modified Duke criteria for IE¹³. Patients with IE in prosthetic valves, those with pacemakers, a history of underlying structural heart disease, or non-infectious Libman-Sacks endocarditis were all excluded.

Echocardiographic studies were performed using commercially available echocardiographic equipment (iE33®, Philips Medical System, Andover, MA, United States). Two-dimensional and M-mode images were acquired from parasternal and apical approaches while the patient remained in the left lateral decubitus position. Measurements followed the recommendations established by the American Society of Echocardiography¹⁴. The echocardiographic criteria for diagnosing IE were based on the European Society of Cardiology clinical practice guidelines, including the definitions for vegetation, abscess, aneurysm, pseudoaneurysm, perforation, fistula, and valvular aneurysm¹⁵.

Descriptive statistics was used and expressed as means and standard deviations for the quantitative variables and percentages for the dichotomous ones. The incidence rate was calculated considering the total number of cases and studies conducted per year. The SPSS Statistics version 22.0 software was utilized for data analysis.

Results

A total of 30 000 patient studies conducted at the Cardiology Department were reviewed from January 1997 through December 2020. Of these, 248 cases met the inclusion criteria for IE with a mean annual incidence of 5 cases of IE per 1000 echocardiographic studies. A 35.9% increase in cases within the last year was reported vs the previous one (12.8 vs 8.2) for a total of 140 men, 108 women, and a mean age of 48.1 ± 16.7 years (Fig. 1).

A total of 207 (83.20%) patients had 1 or more systemic diseases. Chronic kidney disease (CKD) was the most widely reported in 54.43% of the patients (135 cases), followed by endocrine diseases in 27.41% of the patients (diabetes mellitus, 43; hypothyroidism, 18; dyslipidemia, 7), rheumatological diseases in 7.25% (systemic lupus erythematosus, 8; rheumatoid arthritis,

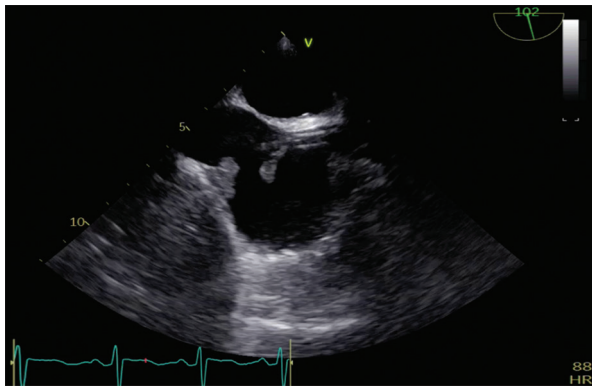


Figure 1. Right atrial endocarditis. The bicaval view of the transesophageal echocardiogram reveals the presence of a vegetation attached to the distal end of the hemodialysis catheter and another one at the inferior vena cava junction.

4; vasculitis, 3; dermatomyositis, 2; fibromyalgia, 1), solid tumors in 5.18% (17), hematological diseases in 3.62% (leukemias, 6; aplastic anemia, 2; amyloidosis, 1), neurological disorders in 1.20% (multiple sclerosis, 1; Guillain-Barré syndrome, 1; stroke, 1), and GI diseases with only 2 cases reported of ulcerative colitis (0.60%). Predisposing factors were identified in 157 patients (63.30%). Among the 196 cases with predisposing factors, the most common one was the presence of a catheter for hemodialysis in 96 patients, while only 6 cases with a past medical history of dental extraction within the 12 months prior to developing IE were reported (Table 1).

The most common clinical sign at hospital admission was fever (52.54%), followed by hypotension (6.77%), dyspnea (5.93%), and weight loss (4.23%). Splinter hemorrhages, pharyngeal abscess, and bradycardia were less common, accounting for 7.61% of the cases. Complications occurred in 23 patients (9.23%): 12 cerebral embolisms (52.7%), 6 pulmonary embolisms (26.06%), 4 osteomyelitis (17.39%), and 1 mycotic pseudoaneurysm (4.34%).

Echocardiography was the most widely used imaging modality (100%) for diagnosing IE. Transesophageal echocardiography was used in 36% of the cases of persistent IE. Other imaging modalities included computed tomography in 12 patients and scintigraphy with ciprofloxacin in 9 (3.62%).

A total of 301 images consistent with IE were identified, including 282 vegetations (93.60%), 7 cases (2.35%) of valve perforation, 7 cases (2.35%) of aneurysm/pseudoaneurysm, and 5 cases (1.68%) suggestive of abscess on the echocardiogram. The mean maximum diameter of vegetations was $16.81 \text{ mm} \pm 11 \text{ mm}$, with a minimum mean of $10 \text{ mm} \pm 8.9 \text{ mm}$. Regarding transplant

Table 1. Predisposing factors, clinical presentation, and complications of infective endocarditis

	n	%
Systemic disease	248	100
Chronic kidney disease	135	54.43
Systemic arterial hypertension	51	20.56
Diabetes mellitus	43	17.33
Other	99	39.91
Predisposing factors	196	100
Hemodialysis	96	48.95
Immunosuppressive drugs	27	13.78
IV drug use	19	9.69
Central catheter	25	12.76
Organ transplant	9	4.59
Peritoneal dialysis	8	4.08
Dental extraction	6	3.06
Tissue infection	6	3.06
Clinical presentation		
Fever	118	52.54
Purulent secretion	62	15.25
Neurological: delirium, seizures, stroke	18	7.66
Other	9	24.55

recipients (8 renal and 1 marrow), the mean vegetation size was 10 mm, with no differences being reported compared to the general mean (Table 2).

The most frequent location of IE was the left heart in 175 cases (58.13%), with the mitral valve as the most commonly damaged one in 107 cases (35.55%), followed by the aortic valve in 65 (21.59%), the left atrium in 2 (0.66%), and the left ventricle in 1. Right heart IE was described in 126 (41.86%) echocardiograms, being the right atrium the most common location in 61 (20.27%) cases, followed by the tricuspid valve in 46 (15.28%), the superior vena cava in 11 (3.65%), the pulmonary valve in 5 (1.66%), and the right ventricle in 3 (Fig. 2).

Regarding blood cultures, a total of 113 results (45.56%) tested positive, being *Staphylococcus aureus* the most frequently isolated agent in 49 cases (42.61%), followed by *Staphylococcus epidermidis* in 19 cases (16.52%). *Streptococcus thoraltensis* isolation was confirmed through histopathological examination. Fungal agents (5.26%) included 1 case of *Histoplasma capsulatum* and 5 cases of *Candida albicans*, but they were rare findings. The antibiogram reported 26.53% of oxacillin-resistant *S. aureus* isolates, and only 1 case of vancomycin-resistant *Enterococcus gallinarum* (Fig. 3).

Discussion

IE without pre-existing structural heart disease ranges from 2% up to 58% in the case series reported¹⁶.

Table 2. Echocardiographic findings and location of infective endocarditis

Echocardiographic findings of IE	No. of images suggesting IE (n = 301)	%
Vegetations	282	93.68
1	215	71.42
2	58	19.26
3	9	2.99
Perforation	7	2.32
Pseudoaneurysm	7	2.32
Abscess	5	1.66
Location of echocardiographic findings	No. of images suggesting IE (n = 301)	%
Left heart chambers	175	58.13
Mitral valve	107	35.54
Aortic valve	65	21.59
Left atrium	2	0.66
Left ventricle	1	0.33
Right heart chambers	126	41.86
Right atrium	61	20.26
Tricuspid valve	46	15.28
Inferior vena cava	11	3.65
Pulmonary valve	5	1.66
Right ventricle	3	0.99

IE: infective endocarditis.

Our study represents the largest reported case series of IE in patients with systemic disease and without pre-existing structural heart disease, or intracardiac devices in Mexico. The mean annual incidence in this cardiology unit was 5 cases for every 1000, with a peak of 27 cases back in 2017, which, compared to other published case series, indicates a higher incidence (10.4 vs 6-9/100 000 inhabitants)¹⁷. Over the past 5 years, a 45.5% increase vs the previous 5 years (2001-2005) was reported. This increase is consistent with the current trend observed in high-income countries, such as Germany, where Zahn et al.¹⁸ reported more cases and a high in-hospital mortality rate (21.96%), which does not seem to drop despite advances made in diagnostic and surgical treatment.

The mean age of our study population was 48.1 ± 16.7 years, which is similar to the findings made by Wu et al. in their study¹⁹ One possible explanation

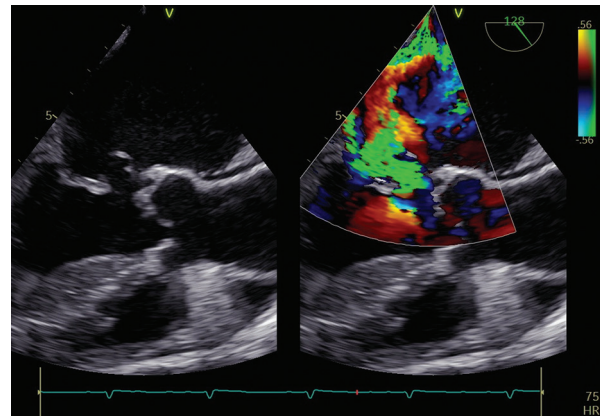


Figure 2. Mitral valve endocarditis. Long-axis view of the left ventricle on the transesophageal echocardiogram. A perforation of the mitral valve A2 segment can be seen (left image), resulting in regurgitant flow (right image). The mechanism of regurgitation is consistent with type I in Carpentier's functional classification.

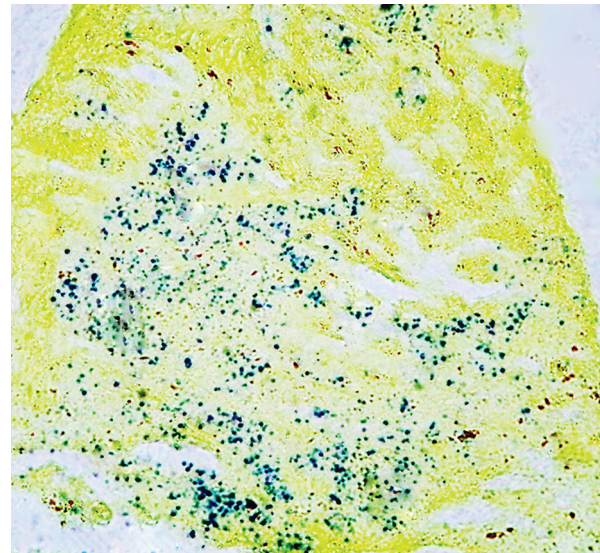


Figure 3. Aortic valve endocarditis. Gram staining revealed gram-positive cocci (blue dots), which was consistent with the presence of *S. thoraltensis* in blood cultures.

is the exclusion of cases with degenerative valvular heart disease, which is associated with older age²⁰. Unlike other series reported, IE was more common in men vs women, with a male-to-female ratio of 1.33:1, which is quite different to other reports with ratios as high as 9:1²¹.

The risk of developing IE depends on various factors related to the host as well as external factors, such as surgical or therapeutic procedures causing transient bacteremia. Factors such as poor oral hygiene, chronic alcoholism, systemic lupus erythematosus, diabetes

mellitus, and chronic kidney disease (CKD) can increase the risk²². At least 1 systemic disease was present in 207 (83.20%) patients, being CKD the most widely reported, which is similar to reports coming from various studies. The most significant predisposing factor was hemodialysis in 96 patients, which was higher vs other series²³. However, we should mention that our hospital serves as a tertiary referral center for patients with CKD, meaning that there can be a bias of overrepresentation. Nonetheless, our case review spanned 23 years, which is longer compared to other studies of patients with CKD with only 4 years of income observation and fewer patients²⁴. Another strength of our study was the ability to identify multiple predisposing factors, as patients without, at least, 1 predisposing factor accounted for only 36.7% (91 out of 248 patients), which is a much lower rate than the one reported by Castillo et al.²⁵ at 68% (33 out of 49 patients).

Regarding clinical presentation, fever was present in 52.54% of the population, which was a less common finding vs other studies (80% to 94%). One possible explanation is the immunosuppression observed in some patients, as suggested by DeSimone et al.²⁶, where 46% of the patients with IE did not exhibit fever associated with immunosuppression.

Among the systemic complications associated with IE, the neurological ones were the most frequent, occurring in over 30% of the cases. However, we cannot rule out that they occur more frequently due to limited screening with tomographic or magnetic resonance imaging studies in our setting, as other reviews have found rates > 30%, even up to 60%^{27,28}. In our study, the mean size of vegetations was 13.2 mm, which is a smaller size compared to other reported cases (14.2 mm), possibly due to the low frequency of this complication (4.8%)²⁸. Another embolic complication in the study associated with left-sided IE was 1 mycotic pseudoaneurysm and 1 case of osteomyelitis.

Left-sided heart involvement is the most frequent location for IE, with incidence rates of up to 80%. In our study, the mitral valve was the most impacted one (50% of the cases), followed by the aortic valve (both valves with incidence rates from 10% to 25%)²⁹. The most common site of left-sided IE was the mitral valve (64%), followed by the aortic valve (37%), which similar to other cohorts^{29,30}.

Right-sided IE represents between 5% and 10% of the general population but it can be as high as 90% in IV drug users. According to former studies, only 10% occur in patients with intravascular catheters for

hemodialysis, chemotherapy, vascular or intracardiac devices³⁰. However, in our study, 3 times more echocardiographic images were found in the right heart, with 107 (35.54%) non-IV drug users. Therefore, in our setting, invasive treatments could play a more relevant role in the development of IE than previously described³¹. Also, right heart lesions were more present in the right atrium vs the tricuspid valve (20.27% vs 15.28%), as expected by the research group, since the latter has been reported in up to 90% of right heart lesions found, which may be associated with the invasive nature of hemodialysis³².

S. aureus was the most widely isolated agent, which is similar to what former studies have reported in this regard. Streptococci were less commonly isolated compared to the study conducted by Castillo et al.³³ (4.38% vs 34%). However, we should mention the isolation of *S. thoraltensis*, a rare agent for IE (reported in Vietnam in 2020 in 1 patient with mechanical valve IE). Therefore, compared to the medical literature currently available, this would be the very first case of IE in a native valve, and the very first case ever reported Mexico caused by this agent, which was associated with aortic valve perforation and septic embolism to the central nervous system³⁴. A case of *Histoplasma capsulatum* was identified in the fungal group, which had previously been reported by researchers from this hospital³⁵. Unfortunately, no follow-up of these EI cases was possible.

Conclusions

In this 23-year case review conducted in our hospital, the presence of IE associated with systemic disease was found in 248 patients, with an incidence of 5 cases for every 1000. The most widely reported systemic disease was CKD (in 135 patients), and the most common predisposing factor was the presence of hemodialysis catheters in 96 patients. The most common location for the IE was the mitral valve in 107 patients, but the frequency of right-sided IE was 3 times higher than the one reported in the literature. The most common complication was embolism to the central nervous system (4.8%). *S. thoraltensis* was isolated in 1 case. The most frequently isolated agent was *S. aureus*.

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Conflicts of interest

None declared.

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 have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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