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Original article

Changing Epidemiology of Native Valve Infective Endocarditis

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ABSTRACT

Introduction and objectives: The aim of our study is to assess changes in the epidemiologic features of patients with native valve infective endocarditis.
Methods: We analyzed a prospective series of 228 cases of native valve infective endocarditis in non-intravenous drug users attending our center between 1987 and 2009. We compared three subperiods: 1987-1994 (67 cases), 1995-2002 (74 cases) and 2003-2009 (87 cases).
Results: The mean age of patients has progressively increased (38 ± 22 years in the first subperiod vs 60 ± 16 years in the third; $P < .001$), as has the proportion of cases without predisposing heart disease (25%, 46% and 67%; $P < .001$). Incidence of mitral valve prolapse remained stable (12%, 18% and 11%). Percentages of patients with predisposing heart disease and who were aware of their condition have fallen in recent years (45%, 27% and 21%; $P < .001$). A portal of entry for the infection could not be identified in 64%. Overall, *Staphylococcus aureus* is the most frequent causative organism (26%) whereas the percentage of cases caused by *Streptococcus viridans* remains unaltered (22%, 20% and 24%).
Conclusions: We found significant changes in the epidemiology of native valve infective endocarditis. The incidence of patients without predisposing heart disease has increased significantly and staphylococci are the most frequent causative organisms.

Cambios epidemiológicos de la endocarditis infecciosa sobre válvula nativa

Palabras clave:
Endocarditis
Epidemiología
Válvula nativa

RESUMEN

Introducción y objetivos: El objetivo de nuestro estudio es evaluar los cambios producidos en los aspectos epidemiológicos de la endocarditis sobre válvula nativa.
Métodos: Estudiamos una serie prospectiva de 228 casos con endocarditis sobre válvula nativa en pacientes no usuarios de drogas por vía parenteral atendidos en nuestra institución desde 1987 hasta 2009, y comparamos tres periodos de estudio: 1987-1994 (67 casos), 1995-2002 (74 casos) y 2003-2009 (87 casos).
Resultados: La media de edad de los pacientes ha aumentado progresivamente (38 ± 22 años en el primer periodo frente a 60 ± 16 años en el tercero; $p < 0{,}001$), así como la proporción de casos sin cardiopatía predisponente (el 25, el 46 y el 67%; $p < 0{,}001$). La incidencia de prolapso valvular mitral ha permanecido estable (el 12, el 18 y el 11%). La tasa de pacientes portadores de una cardiopatía predisponente y conocedores de ella se redujo significativamente en los últimos años (el 45, el 27 y el 21%; $p < 0{,}001$). No se pudo identificar una puerta de entrada a la infección en el 64% de los casos. En general, *Staphylococcus aureus* es el germen causal más frecuente (26%), mientras que la proporción de casos por *Streptococcus viridans* no se ha modificado (el 22, el 20 y el 24%).
Conclusiones: Se han producido cambios significativos en la epidemiología de la endocarditis infecciosa sobre válvula nativa. La incidencia de casos de endocarditis sin cardiopatía predisponente está aumentando significativamente y en ella los estafilococos siguen siendo los más frecuentes.

Abbreviations

IE: infective endocarditis
IVDU: intravenous drug users

INTRODUCTION

Historically, infective endocarditis (IE) affected patients with predisposing valvular heart conditions caused by rheumatic disease, and streptococcus of the *viridans* type were the most frequent pathogens.[1] This continues to be the principal form of presentation in emerging countries where prevalence of rheumatic diseases remains high. In the developed world, mitral valve prolapse is currently considered the most frequent predisposing illness in patients with IE.[2,3] Many recent studies point to

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Staphylococcus aureus as the most frequent causative organism in IE.[4–7] However, these clinical observations come from tertiary centers and may not reflect the real changes affecting IE epidemiology.

The objective of our study is to analyze the clinical, epidemiologic and microbiologic characteristics of patients with native valve IE over a long period and the changes that occur.

METHODS

In our center, 331 consecutive cases of IE in non-intravenous drug users (IVDU) were diagnosed between January 1987 and December 2009. Our hospital is a tertiary center which during the study period was the referral center for cardiovascular surgery in the Spanish provinces of Córdoba and Jaén (the area includes 2 regional hospitals in Córdoba and 4 hospitals in Jaén). At our center, patients diagnosed with IE are traditionally admitted to the cardiology service only. Patients enrolled in this study came from the emergency room, internal medicine, or echocardiography. Thirty patients (9%) were referred from other hospitals. The incidence of patients from other centers remained constant during the study period. We excluded 23 IVDU patients, 7% of all those diagnosed with IE, because their characteristic clinical profile has a greater proportion of tricuspid valve IE, an infection usually caused by *S. aureus*; their prognosis tends to be more positive than that of other native valve IE patients; and in most cases cardiac surgery is not required. Until 1994, IE diagnosis was based on criteria described by Von Reyn et al.[8] Post-1994, criteria proposed by Durack et al.[9] were used and, later, modified Duke criteria.[10] Since 2004, we have applied the European Cardiology Society's new diagnostic criteria.[2] In this series, 228 patients had native valve IE and these were selected for analysis in the present study. Diagnosis of predisposing heart disease (rheumatic, congenital, or degenerative) was obtained from clinical case histories and was essentially based on echocardiography. To analyze variation in clinical and epidemiologic profiles, we arbitrarily divided the 23-year study period into 3 more or less equal subperiods (including 8, 8, and 7 years, respectively): 1987-1994 with 67 cases, 1995-2002 with 74 cases, and 2003-2009 with 87 cases. To analyze trends in variables over time, we needed at least 3 comparison periods. We decided to use this minimum number because 4 or more would have made the number of cases in each subgroup very small. Transesophageal echocardiography has been available in our center since 1990. We considered hospitalization for antibiotic treatment, which generally lasted 4 weeks, as the active phase of the illness. Indications for surgery during the active phase (early surgery) were the appearance of severe heart failure due to valve or prosthesis dysfunction; persistent sepsis despite correct antibiotic treatment; appearance of local complications such as abscesses, pseudoanaeurysms and fistulas; repeated embolisms; and cases caused by aggressive organisms that generally did not respond to antibiotics, such as fungi, *Coxiella* spp, and *Brucella* spp. Indications for surgery did not differ over the study period. We defined urgent surgery as that which could not be postponed > 24 h without putting the patient's life at risk, and elective surgery as that which could be delayed a few days without increasing the risk to the patient's life. Early death was defined as that occurring inhospital, prior to discharge. Deaths following discharge were considered as late.

Statistical Analysis

All baseline and follow-up data were recorded in an SPSS 17.0 (SPSS Inc.; Chicago, Illinois, United States) database. Normal distribution of quantitative data was confirmed with the Kolmogorov-Smirnov test. Continuous variables with a normal distribution are expressed as mean $\pm$ standard deviation. Qualitative variables are expressed as number (percentage). Comparisons between subperiods were with analysis of variance, with linear polynomial contrast for quantitative variables, and chi squared for trend (linear-by-linear association) in qualitative variables. We established $P < .05$ as significant.

RESULTS

During the study period, 228 non-IVDU patients with native valve IE were diagnosed and treated at our center. Figure 1 shows the number of patients with IE in the study period. The principle clinical characteristics of the cohort are shown in Table 1; 150 patients (66%) were men and 78 (34%) women, with a male:female ratio of 1.9:1. Mean age increased from 38 $\pm$ 22 years in the first subperiod to 60 $\pm$ 16 years in the third ($P < .001$).

Table 2 summarizes the distribution of predisposing heart disease and risk factors for infection. During the study period, incidence of predisposing rheumatic heart disease fell significantly, from 24% of patients in the first subperiod to 3% in the third ($P < .001$). Incidence of congenital heart disease also fell, from 28% to 7% ($P < .001$). However, incidence of degenerative heart disease showed no difference: 22% in the first subperiod, 24% in the second, and 23% in the third ($P = .95$). Mitral valve prolapse was

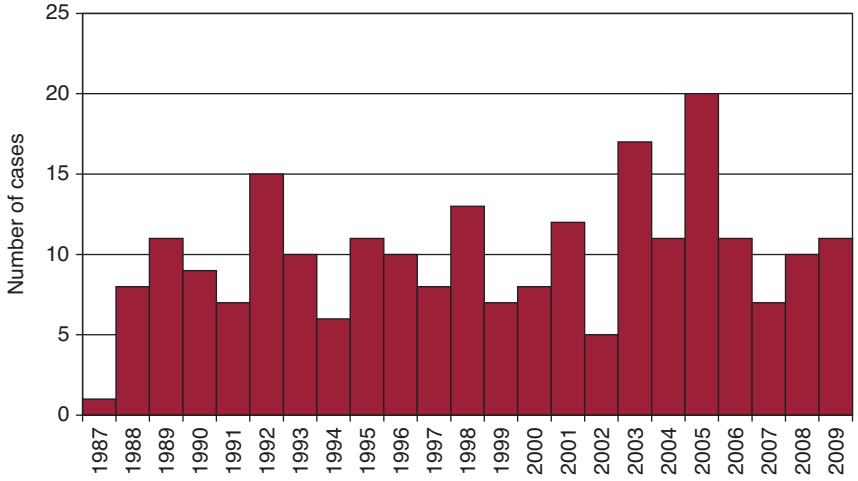

Figure 1. Distribution of the number of cases of native valve infective endocarditis in non-intravenous drug users during the study period.

Table 1
Clinical and Demographic Characteristics of 228 Patients With Native Valve Infective Endocarditis

Age (years)	50 ± 20
Sex (male/female)	1.9/1
Site of infection	
Mitral	100 (44)
Aortic	89 (39)
Tricuspid	24 (10)
Pulmonary	6 (3)
Other	9 (4)
Vegetation size (mm)	12 ± 6
Vegetations in TTE	180 (79)
Vegetations in TOE[a]	165 (97)

TOE, transesophageal echocardiography; TTE, transthoracic echocardiography.
Data are expressed as n (%) or mean ± standard deviation.
[a] Performed on 170 patients.

the most frequent predisposing heart condition (13%) but was not statistically significant (12%, 18%, and 11%; $P = .69$). The percentage of patients with IE and aortic valve disease fell (30%, 16% and 11% respectively; $P = .05$). The percentage of patients with no predisposing heart disease increased considerably, rising from 17 (25%) in the first subperiod to 34 (46%) in the second and 58 (57%) in the third ($P < .001$).

The proportion of patients who were aware they had a heart disease predisposing them to IE fell significantly: from 45% in the first subperiod to 21% in more recent years ($P < .001$).

We identified a possible entry portal for infection in 82 patients (36%). Dental origin of infection was similar in the 3 sub-periods (10%). The trend towards a greater number of IE cases with a possible digestive portal of entry increased in the later subperiods ($P < .067$). Variation in genitourinary cause of infection was not statistically significant.

Table 3 summarizes the causative organisms of infection during the study. Streptococcus was the cause in 40% of cases and staphylococcus in 37%. *S. aureus* was isolated in 59 patients (26%) and was the most frequent organism, followed by *Streptococcus viridans* in 51 patients (23%). Infection caused by *S. viridans, S. aureus*, or enterococcus did not vary significantly over the 3 subperiods but infection caused by *Staphylococcus epidermidis* did increase significantly (from 4.5% in the first subperiod to 17% in the last; $P < .01$).

Vegetation size increased significantly from 10 ± 2 mm in the first subperiod to 12 ± 5 mm in the second and 15 ± 7 mm in the third ($P < .001$).

More than half of the patients with IE underwent active phase interventions. Over the 24 year period period, the rate of active phase surgery increased significantly, from 45% in the first subperiod to 65% in the last ($P < .01$), even though the rate of severe complications during the active phase remained stable (76%). The most frequent indications for active phase surgery were heart failure (37%) and persistent sepsis (13%). The percentage of patients operated for heart failure increased (22%, 32%, and 46%; $P < .002$) but the percentage operated for persistent sepsis remained stable (13%, 12%, and 14%; $P = .93$). Only 5 patients underwent surgery indicated for repeated embolisms. The increased rate of surgery affected elective interventions only; the urgent surgery rate did not change significantly (Table 4). Early mortality (19%) remained unchanged in patients undergoing interventions (20%) and in those receiving medical treatment only (18%). Mortality in patients undergoing active phase interventions fell (27% in the first subperiod, 21% in the second, and 16% in the last), although differences were nonsignificant ($P = .23$).

DISCUSSION

The present study, conducted in a tertiary center, analyzed changes in IE epidemiology over a considerable period. By comparing 3 subperiods, we were able to analyze trends in these changes. Although other multicenter studies with larger numbers of patients have been published, both in Spain[5] and elsewhere,[11–13] the advantage of our series is that data collection was prospective and the data source was a single hospital department with a stable medical and surgical team throughout the study period.

Although IE incidence in the general population was not analyzed, results indicate that despite advances in healthcare in recent decades IE is an illness that, far from disappearing, remains a challenge for the cardiologist, especially as the current pattern of presentation differs substantially from that of some years ago. The greater number of patients diagnosed in recent years may be due to a positive detection bias as a consequence of improved techniques for isolating organisms and better resolution, especially in transesophageal echocardiograms, rather than a genuine increase in the number of cases. However, transesophageal echocardiography has

Table 2
Risk Factors and Lesion Predisposing Infective Endocarditis

	1987-1994 (n = 67)	1995-2002 (n = 74)	2003-2009 (n = 87)	*P*
Portal of entry				.008
Dental	7 (10)	7 (9)	9 (10)	
Respiratory	0	0	2 (2)	
Digestive	0	4 (5)	7 (8)	
Genitourinary	4 (6)	0	2 (2)	
Other	8 (12)	20 (27)	12 (14)	
No	48 (72)	43 (58)	55 (63)	
Predisposing heart disease				
Mitral valve prolapse	8 (12)	13 (18)	9 (11)	.69
Aortic valve disease[a]	20 (30)	12 (16)	10 (11)	.05
Other	22 (33)	15 (20)	10 (11)	.05
No	17 (25)	34 (46)	58 (67)	.001
Awareness of lesion	30 (45)	20 (27)	18 (21)	.001

Data are expressed as n (%).
[a] Includes aortic stenosis, aortic regurgitation and bicuspid valve.

Table 3
Infective Endocarditis Causative Organism

	1987-1994 (n = 67)	1995-2002 (n = 74)	2003-2009 (n = 87)	*P*
Organism type				
Streptococcus viridans	15 (22)	15 (20)	21 (24)	.76
Enterococcus	7 (10)	17 (23)	14 (16)	.42
Staphylococcus aureus	19 (28)	22 (30)	18 (21)	.25
Staphylococcus epidermidis	3 (4)	5 (7)	15 (17)	.01
Fungi	2 (4)	0	1 (1)	.37
Coxiella burnetii	2 (3)	3 (4)	3 (3)	.89
Others	10 (15)	4 (5)	5 (6)	.001
Unknown	9 (13)	8 (11)	10 (11)	.73

Data are expressed as n (%).

Table 4
Surgery and Early Mortality due to Infective Endocarditis

	1987-1994 (n = 67)	1995-2002 (n = 74)	2003-2009 (n = 87)	*P*
Severe complications	53 (79)	51 (69)	70 (80)	.74
Cardiac	24 (36)	35 (47)	52 (60)	.012
Embolisms	25 (37)	15 (20)	14 (16)	.007
Neurological	15 (22)	12 (16)	18 (21)	.62
Persistent sepsis	14 (21)	14 (19)	27 (31)	.14
Renal	5 (7)	6 (8)	6 (7)	.96
Perivalvular abscesses	10 (15)	8 (11)	11 (13)	.74
Early surgery	30 (45)	42 (57)	57 (65)	.01
Urgent surgery	14 (21)	11 (15)	15 (17)	.59
Elective surgery	16 (24)	31 (42)	42 (48)	.003
Early mortality	15 (22)	12 (16)	17 (20)	.73

Data are expressed as n (%).

been available in our center since its early years and is therefore unlikely to have influenced results.

We coincide with other authors[6,11,13] in finding that IE remains an illness that primarily affects men and, increasingly, older men. The increased age of patients with IE coincides with other studies conducted in the last decade.[5] This phenomenon may be explained by the greater life expectancy of the population at large and the increased number of cases related to invasive techniques and hospitalization. One of the most significant findings of our study is the progressive fall in rheumatic heart disease (both in mitral and aortic infection) as the predisposing lesion and, above all, the absence of predisposing heart disease. In fact, in the last 7 years, IE mainly occurred in patients without predisposing heart disease (64%). This has been reported elsewhere.[3,12–14] Prevalence of mitral valve prolapse has remained stable. The increasing number of patients with no predisposing heart disease, or unaware of having predisposing heart disease which is potentially subsidiary to prophylaxis, could justify the substantial modification to IE prophylaxis found in recent European clinical practice guidelines.[15]

Published studies differ over which causative organism is most frequent.[3,11–14,16–18] Results vary greatly as a function of the study population. Some series include IVDU patients, leading to a greater number of cases caused by *S. aureus,*[4,13] and others include patients with prosthetic valve IE, which makes the series not really comparable. We have systematically excluded IVDU patients because they have a highly specific clinical, epidemiologic, and prognostic profile that differs notably from the rest. In our study, incidence of IE due to *S. viridans* and *S. aureus* did not vary substantially, and the frequency of both types of IE are practically equal. *S. aureus* was the more common cause of infection in patients without and *S. viridans* in patients with predisposing heart disease. Although we do not know the prevalence of IVDU patients in our region, the incidence of IE due to staphylococcus surely would have been greater had our series not excluded IVDU patients.

The percentage of patients undergoing active phase interventions has increased significantly in recent years but we have been unable to reduce mortality due to IE. Although the rate of severe complications in the active phase has not changed, the rate of cardiac complications–often requiring active phase surgery–has increased significantly. In fact, the main cause of surgery was heart failure. This increase in cardiac complications may be related to later diagnosis of IE and, therefore, the greater chance of valve destruction or the appearance of perivalvular complications, given that a greater percentage of those diagnosed are patients with no predisposing heart disease in whom IE is less commonly suspected and consequently diagnosis is delayed. However, although seemingly paradoxical, the rate of embolisms fell despite the fact that prevalence of IE with mitral infection was similar and vegetation size has increased in recent years. One possible explanation is that, thanks to the widespread use of transesophageal echocardiography, patients are operated earlier once the diagnosis has been made. As other authors indicate, the larger vegetations may have contributed to a greater need for active phase surgery.[19]

In-hospital mortality has remained high and has not varied substantially. We suppose that in recent years the patient risk profile has increased–despite greater use of surgery–and contributed to a continuing high mortality rate. In addition to heart failure on admission, authors have identified patient referral from another center or infection due to *S. aureus* as variables affecting

poor prognosis.[20] In our series, although the percentage of patients with infection due to *S. aureus* did not change, the rate of cardiac complications increased significantly in recent years (36% in the first sub-period vs 60% in the third), as did patient age, which undoubtedly contributed to keeping in-hospital mortality high.

The principle limitation of our study is the obvious bias of being conducted in a tertiary hospital that is the cardiovascular surgery referral center, so that the study included patients diagnosed in our center and those transferred from other hospitals for intervention; therefore, we are unaware of patients not referred either because of their good clinical course or because their condition may have been compromised and surgery discounted due to high surgical risk. Although the opening of new hospitals has brought substantial changes to the healthcare map of Spain over the last decade, our center's area of influence has remained the same over these years because new cardiovascular surgery centers have not been added. We remain the referral center for cardiovascular surgery and assume that the referral policy in patients with IE has not changed. Another possible limitation might be differences in managing these patients over the 23 years of the study, although there was no change in staff attending patients and indication for surgery criteria have not differed substantially. On the other hand, our team has always been especially sensitive to this disease, so the level of suspicion when faced with a patient presenting a persistently high temperature has always been great. Bearing in mind that our study aims to analyze the epidemiologic changes in native valve IE, it would have been interesting to know how much the presence of other comorbidities might have influenced prognosis and how patients evolved over the study period. However, these variables were not included in our initial database so we had insufficient information to conduct this analysis.

CONCLUSIONS

Our study shows that IE epidemiology has undergone significant changes in recent years. In our area at least, the incidence of IE without predisposing heart disease is increasing significantly and in this increase staphylococci are the most frequent causative organism. The fact that this form of IE increased in recent years while the proportion of *S. viridans* remained stable brings into question the value of IE prophylaxis in patients undergoing dental, digestive, or genitourinary procedures.

CONFLICTS OF INTEREST

None declared.

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