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Original

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Infective endocarditis treated in a secondary hospital: epidemiological, clinical, microbiological characteristics and prognosis, with special reference to patients transferred to a third level hospital

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ABSTRACT

Introduction. To analyse the clinical and epidemiological characteristics and mortality-related factors of patients admitted to a secondary hospital with Infective Endocarditis (IE).

Methods. Observational study of a cohort of patients who have been diagnosed with IE in a secondary hospital and evaluated in accordance with a pre-established protocol.

Results. A total of 101 cases were evaluated (years 2000-2017), with an average age of 64 years and a male-to-female ratio of 2:1. 76% of the cases had an age-adjusted Charlson comorbidity index of >6, with 21% having had a dental procedure and 36% with a history of heart valve disease. The most common microorganism was methicillin-susceptible *S. aureus* (36%), with bacterial focus of unknown origin in 54%. The diagnostic delay time was 12 days in patients who were transferred, compared to 8 days in patients who were not transferred (p=0.07); the median surgery indication delay time was 5 days (IQR 13.5). The in-hospital mortality rate was 34.6% and the prognostic factors independently associated with mortality were: cerebrovascular events (OR 98.7%, 95% CI, 70.9–164.4); heart failure (OR 27.3, 95% CI, 10.2–149.1); and unsuitable antibiotic treatment (OR 7.2, 95% CI, 1.5–10.5). The mortality rate of the patients who were transferred and who therefore underwent surgery was 20% (5/25).

Conclusions. The onset of cerebrovascular events, heart failure and unsuitable antibiotic treatment are independently and significantly associated with in-hospital mortality. The mortality rate was higher than the published average (35%); the diagnostic delay was greater in patients for whom surgery was indicated.

Keywords: infective endocarditis, drug therapy, surgery

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La endocarditis infecciosa en un hospital de 2º nivel: epidemiologia, clínica y análisis de factores pronósticos, con especial referencia a los pacientes trasladados a un hospital de tercer nivel

RESUMEN

Introducción. Analizar las características clínico-epidemiológicas y los factores asociados a mortalidad de los pacientes ingresados por endocarditis infecciosa (EI) en un Hospital de 2º nivel.

Métodos. Estudio observacional de una cohorte de pacientes diagnosticados de EI en un hospital de 2º nivel y evaluados de acuerdo a un protocolo preestablecido.

Resultados. Se evaluaron 101 casos (2000-2017), edad media de 64 años, relación hombre/mujer 2:1, presentando un índice de Charlson corregido por edad >6 en el 76% de los casos, antecedentes de manipulaciones dentarias en el 21% y valvulopatía previa en el 36%. El microorganismo más frecuente fue *Staphylococcus aureus* sensible a meticilina (36%), con foco bacteriémico de origen desconocido en el 54%. El tiempo de demora diagnóstica fue de 12 días en pacientes transferidos frente a 8 en los no transferidos (p= 0.07); el de demora de indicación de cirugía tuvo una mediana de 5 días (RIQ 13.5). La mortalidad intrahospitalaria fue del 34.6% y los factores pronósticos asociados de forma independiente fueron la presencia de eventos vasculares cerebrales (OR 98.7, IC 95% 70.9-164.4), el fallo cardiaco (OR 27.3, IC 95% 10.2 – 149.1) y el tratamiento antibiótico inadecuado (OR 7.2, IC 95% 1.5–10.5). La mortalidad intrahospitalaria de los pacientes transferidos y por tanto intervenidos fue del 20% (5/25).

Conclusiones. El desarrollo de eventos vasculares cerebrales, el fallo cardiaco y el tratamiento antibiótico inadecuado se asocian de forma independiente y significativa con mortalidad intrahospitalaria. La mortalidad fue superior a la media publicada (35%); la demora diagnóstica fue mayor en los pacientes con indicación quirúrgica.

Palabras clave: endocarditis infecciosa, tratamiento, cirugía

A. I. Peláez Ballesta, et al.

Infective endocarditis treated in a secondary hospital: epidemiological, clinical, microbiological characteristics and prognosis, with special reference to patients transferred to a third level hospital

INTRODUCTION

Despite the improvement in diagnostic techniques and medical and surgical treatment protocols, infective endocarditis (IE) is associated with high morbidity and mortality related to the development of serious complications [1-5]. In general, the published series of IE patients refer to hospitals with more than 600 beds and referral surgical departments, including cardiovascular surgery. The characteristics of IE patients who are assessed in secondary hospitals with fewer than 300 beds and no cardiovascular surgery departments or interventional radiology units are probably different to patients who are assessed in general hospitals equipped with referral services in their area of geographical influence. It also has yet to be established whether assessments in regional hospitals without multidisciplinary IE teams and with less experience in a less prevalent disease than other infections may affect the diagnosis of IE, patient outcomes and the time to referral to specialist hospitals.

The objectives of this study were: to analyse the epidemiological, clinical and microbiological characteristics of a cohort of patients diagnosed with IE in a secondary hospital over a 17-year period (2000-2017); to analyse the prognostic factors associated with in-hospital mortality; to analyse the delay until diagnosis and referral to another hospital, if required; and to assess the degree of suitability of antibiotic therapy, so as to identify how the management of these patients in non-specialist hospitals can be improved.

MATERIAL AND METHODS

A retrospective, descriptive and observational study was conducted on adult patients who were diagnosed with IE between January 2000 and May 2014, and prospectively between May 2014 and December 2017.

Characteristics of the hospital. Hospital General Universitario Rafael Méndez de Lorca is a secondary hospital with 287 beds, with a catchment area of 175,154 inhabitants.

Patient study. During the study periods, all medical records of patients with the Diagnosis-related Group (DRG) of "Infective Endocarditis" at discharge were reviewed. All cases which did not comply with the diagnostic criteria of definite or possible IE were excluded [6-9].

For each patient, both the digital hospital discharge report corresponding to the clinical process and the digital and physical medical record (of previous admissions and admission due to the episode of IE) were reviewed. The microbiological information was supplemented with the hospital's laboratory records. The protocol of the Task Force for the Management of Infective Endocarditis of the Spanish Society of Cardiovascular Infections (GAME-SEICAV) study was used for data collection. Patients were classified according to comorbidity and prognosis of their underlying disease using the simple and age-adjusted Charlson comorbidity index [10].

The antibiotic therapy administered for IE was considered correct or incorrect according to current guidelines [7,11-12]. Empirical treatment was defined as treatment administered at the onset of symptoms, before blood culture results were available, and targeted treatment was defined as when empirical antibiotic therapy was modified according to the antibiogram results. Empirical and targeted treatment were considered adequate when an antibiotic was used (at the correct doses and intervals) to which the microorganism was sensitive *in vitro*, and whose indication was correct in terms of pharmacokinetics and pharmacodynamics for IE and in relation to the focus of infection that gave rise to the bacteraemia causing the development of IE. Those treatments that adhered to the therapeutic guidelines corresponding to cases of IE with negative blood cultures and serology were also considered appropriate. If this was not the case, the treatment was defined as unsuitable or incorrect.
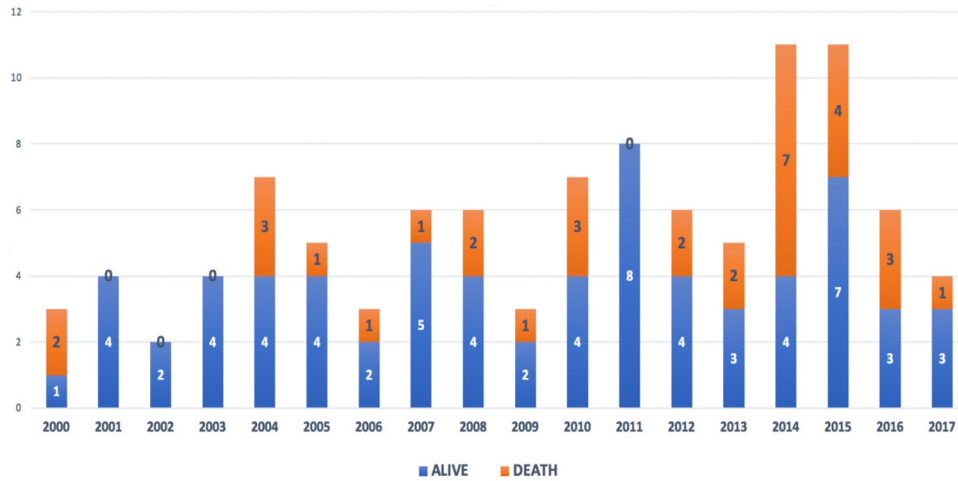
Surgery indication delay time is defined as the time (in days) between the diagnosis of IE and the need for surgery being indicated. Surgery delay time is defined as the time (in days) between surgery being indicated by the heart surgeon and that surgery being performed.

Statistical analysis. The data were analysed using the statistical program SPSS18. For the descriptive analysis, the quantitative variables were expressed as mean/median (standard deviation, range), while qualitative variables were expressed as percentages. The link or relationship between pairs of qualitative variables was ascertained by conducting an analysis of the contingency tables using Pearson's chi-squared (x^2) test, completed with a residual analysis to determine the direction of dependence with Fisher's exact test. The means of the quantitative variables were compared with the Student's t-test. The difference was considered to be significant when $p<0.05$ and the confidence intervals (CI) were set at 95%. A bivariate analysis of the prognostic factors associated with in-hospital mortality was also conducted. A multivariate analysis of the significant factors and the non-significant factors that were considered clinically relevant for in-hospital mortality was conducted using the logistic regression method to determine the factors independently associated with mortality.
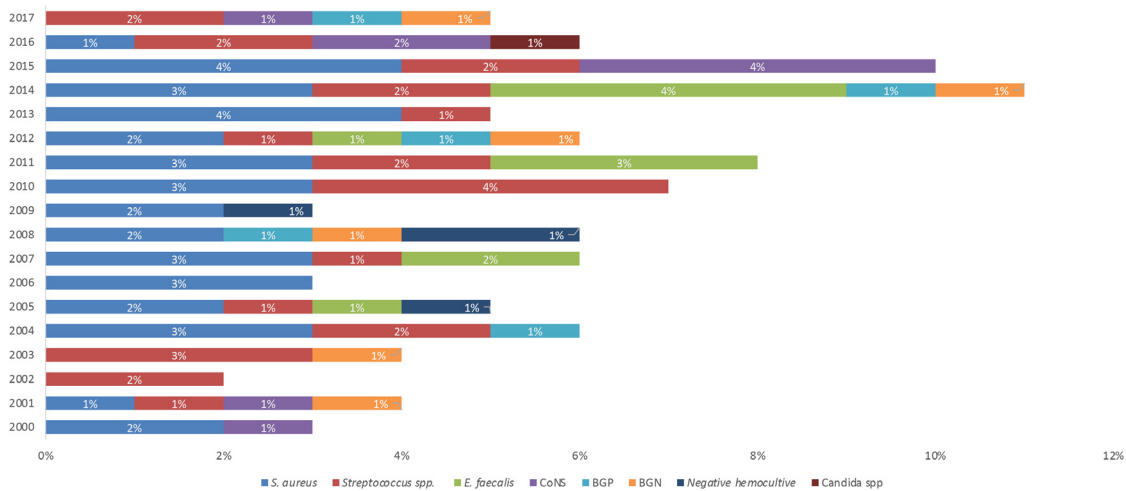
RESULTS

In total, 101 patients were assessed to ascertain whether they meet definite or possible IE criteria in accordance with the Modified Duke Infective Endocarditis Criteria, of which 68.3% (n = 69) correspond to the retrospective period (2000-2013) and 31.7% (n = 32) to the prospective period (2014-2017) with an increase in the number of cases in the prospective collection (Figure 1); with an average age of 64 years (range 16–88) and a male-to-female ratio of 2:1. The prevalence of IE amongst admitted patients was 0.057%, with an incidence of 3 per 1000 patients per year.

There was a predominant involvement of native valves (82%), with the mitral valve being the most commonly affect-

A. I. Peláez Ballesta, et al.

Infective endocarditis treated in a secondary hospital: epidemiological, clinical, microbiological characteristics and prognosis, with special reference to patients transferred to a third level hospital

Figure 1 | New cases by year and associated in-hospital mortality of IE.

Figure 2 | Evolution of microbiological data by years. Regarding *S. aureus*, there were 3 cases of methicillin-resistant *S. aureus* (one case in 2007, one case in 2012, and one case in 2013).

BGN: Gram-negative bacillus; BGP: Gram positive bacillus; CoNS: Coagulase-negative *staphylococci*.

ed (46.5%). 76% of patients had an age-adjusted Charlson co-morbidity index of >6, with 31.6% having a Charlson comorbidity index of >3. Predisposing factors included previous valve disease (35.6%, with degenerative valve disease in 20.8% of the cases). It should also be noted that 20% of cases had undergone a previous procedure that may explain the origin of the bacteraemia (insertion of catheters (9), dental procedures (5) and urinary procedures (3). No pre-procedure antibiotic prophylaxis was recorded in the medical records.

Blood cultures were taken from all patients, with positive results in 95 cases (94%). Negative results were only recorded

in five of the 12 patients who had received antibiotic therapy prior to the blood culture extraction (4.9%). The source of the bacteraemia was not clarified in 54% of the cases. Serology tests were only conducted on 10 patients (9.9%), all yielding negative results. In no case were nucleic acid amplification molecular biology studies performed in blood or in dried valves for aetiological documentation.

The most commonly documented microorganisms in blood cultures were *S. aureus* (34.6%; methicillin-susceptible *S. aureus* (MSSA) in 31.6%); *Streptococcus* spp. (34%); Coagulase-negative *staphylococcus* (CoNS, 12%); and *Enterococcus*

A. I. Peláez Ballesta, et al.

Infective endocarditis treated in a secondary hospital: epidemiological, clinical, microbiological characteristics and prognosis, with special reference to patients transferred to a third level hospital

Table 1   **Analysis of the characteristics of patients transferred to the reference hospital versus not transferred.**

Characteristic	Transferred N=25 N (%)	Not transferred N=76 N (%)	Total N=101 N (%)	p	OR (IC 95%)
EPIDEMIOLOGY					
Age (median + / IQR; range)	66 +/- 16 (20-74)	71 +/- 14 (16-88)	64.5+/- 16 (16-88)	0.016	
Man	18 (72)	51 (67.1)	69 (68.3)		
Woman	5 (28)	25 (32.9)	32 (31.7)	0.648	0.7 (0.2-2.1)
Death	5 (20)	30 (39.5)	35 (34.7)	0.076	0.3 (0.1-1.1)
Sequelaes	11 (44)	35 (46.1)	46 (45.5)	0.857	0.9 (0.3-2.3)
Valve affected					
Native	18 (72)	66 (86.8)	83 (82)	0.217	
Prosthetics	6 (24)	9 (11.8)	15 (14)		
Pacemaker / ICD	1 (4)	1 (1.3)	2 (2)		
Location					
Mitral	9 (36)	32 (42.1)	47 (46.5)		
Aortic	15 (60)	32 (42.1)	41 (40.5)		
Tricuspid	0	8 (10.5)	8 (7.9)	0.217	
Pulmonary	0	3 (3.9)	3 (3)		
Pacemaker / ICD Cable	1 (4)	1 (1.3)	2 (2)		
COMORBIDITIES					
Coronary heart disease	5 (20)	20 (26.7)	25 (24.8)	0.526	0.7 (0.2-2.1)
Atrial fibrillation	3 (12)	17 (22.4)	20 (19.8)	0.259	0.5 (0.1-1.8)
Heart failure	11 (44)	19 (25)	30 (29.7)	0.710	2.3 (0.9-6.1)
Diabetes Mellitus	4 (16)	26 (34.2)	30 (29.7)	0.084	0.4 (0.1-1.1)
Peripheral vascular disease	2 (8)	21 (27.6)	23 (22.8)	0.042	0.8 (0.6-0.9)
Cerebrovascular disease	1 (4)	8 (10.5)	9 (8.9)	0.320	0.3 (0.1-2.9)
Neoplasia	1 (4)	14 (18.4)	15 (14.8)	0.079	0.2 (0.1-1.5)
Renal insufficiency	2 (8)	13 (17.1)	15 (14.8)	0.416	
Charlson comorbidity index ≥3	6 (24)	26 (34.2)	32 (31.6)	0.740	3.2 (0.1-2.3)
Charlson comorbidity index adjusted for age ≥6	19 (76)	58 (76.3)	77 (76.2)	0.064	2.1 (0.1-2.5)
SYMPTOMS					
Fever	25 (100)	76 (100)	101 (100)	0.991	1.1 (0.1-10.2)
Vascular phenomena	5 (20)	4 (5.3)	9 (8.9)	0.025	4.5 (1.1-18.3)
Embolisms	6 (24)	23 (30.3)	29 (28.9)	0.548	0.7 (0.2-2.1)
Diagnostic delay time (median +/- IQR)	11.92 +/- 11.5	8.32 +/-8.52	8 +/13.5	0.075	
MICROBIOLOGY					
Streptococcus spp.	5 (20)	22 (28.9)	27 (26.7)		
Staphylococcus aureus	14 (56)	21 (27.6)	35 (34.6)		
MRSA	2 (8)	1 (1.3)	3 (2.9)		
Coagulase-negative staphylococci (CoNS)	5 (20)	17 (22.3)	12 (11.8)	0.088[a]	
Enterococcus spp.	0 (0)	11 (14.4)	11 (10.8)		
Gram-negative bacilli	3 (12)	2 (2.6)	5 (4.9)		
Gram-positive bacilli	0 (0)	5 (6.5)	5 (4.9)		
Candida spp.	0 (0)	1 (1.3)	1 (0.9)		
TREATMENT					
Inappropriate treatment	5 (20)	14 (18.4)	19 (19)	0.861	0.9 (0-2-2.8)

ICD: implanted cardioverter defibrillator; IQR: interquartile range; MRSA: Methicillin resistant *Staphylococcus aureus.*
[a]All microorganisms were included in the analysis.

A. I. Peláez Ballesta, et al.

Infective endocarditis treated in a secondary hospital: epidemiological, clinical, microbiological characteristics and prognosis, with special reference to patients transferred to a third level hospital

Table 2	Bivariate analysis according to treatment regimen.		
Characteristic	Inadequate treatment N= 19 n (%)	Appropriate treatment N= 82 n (%)	p
"NEW" heart failure	19 (100)	57 (69,5)	0,006
Persistent bacteremia	17 (36.8)	8 (9.8)	0.003
Mechanic ventilation	10 (52.6)	13 (15.9)	0.001
Vasoactive drugs	13 (68.4)	24 (29.3)	0.001
Septic shock	13 (68.4)	34 (41.5)	0.034
Spread of infection	4 (21.1)	4 (4.9)	0.019
CCV indication	10 (52.6)	25 (30.5)	0.048
Death	12 (63.2)	21 (25.6)	0.002

CCV: Cardiovascular surgery.

Table 3	Multivariate analysis of factors independently associated with mortality.	
Characteristic	p	ORa (CI 95%)
CNS vascular event	0.033	98.7 (70.9 - 164.4)
New onset heart failure	0.003	27.3 (10.2 - 149.1)
Inadequate antibiotic treatment	0.003	7.2 (1.5– 10.5)

CNS: Central nervous system.

spp. (11%, all ampicillin-susceptible *Enterococcus)*. The distribution by year is shown in Figure 2.

The most commonly observed clinical manifestations were fever (100%), heart failure (75%) and recent murmur (64%). Vascular phenomena suggestive of endocarditis were observed in just nine (8.9%) of the patients during the examination. These included petechiae (n=7; 6.9%), Janeway lesions (n=6; 5.9%), splinter haemorrhages (n=3; 2.9%) and conjunctival haemorrhages (n=2; 1.9%), with no findings of Osler's nodes or Roth's spots recorded in any of the patients.

A transthoracic echocardiogram (TTE) was performed in 100 (99%) of the patients (a transoesophageal echocardiogram [TOE] was performed first in just one of the patients), which was positive for IE in 62 patients (62.6%). In the 38 patients with negative TTE, the diagnosis was made following TOE.

A 66% of the patients developed a complication, primarily embolic processes of the central nervous system (16.7%) and the spleen (7%).

Surgery was indicated for 34.6% of the patients (n=35). However, only 28 were assessed by the Heart Surgery Department (the rest were not assessed due to poor prognosis, advanced age and/or refusal of the patient or the family to undergo surgery). Ultimately, 25 patients underwent surgery

(the other three patients were rejected for surgery). Table 1 summarises the characteristics of the cohort of patients who were transferred to a specialist surgical centre and those who were not. Only patients indicated for surgery were transferred. Insofar as the surgery indication delay time is concerned, the median time was five days (interquartile range [IQR] 13.5). The median surgery delay time was three days (IQR 10).
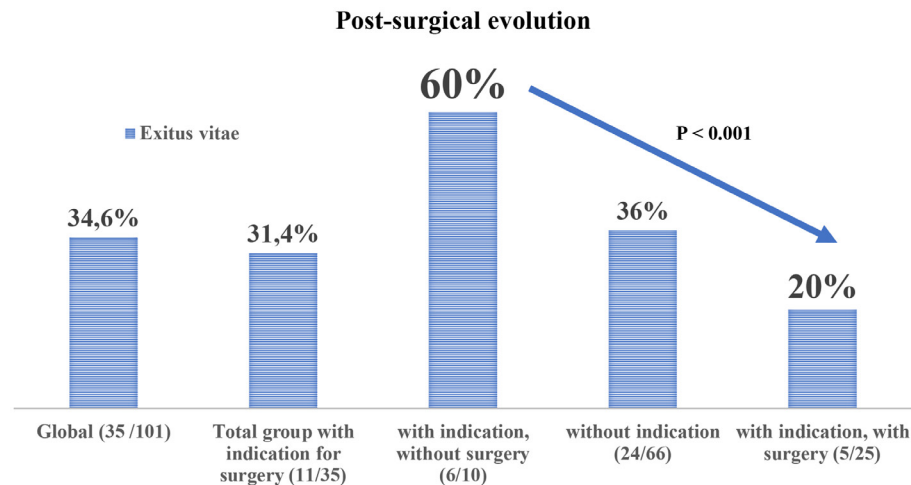
Regarding the treatment regimen, it was observed that the onset of complications such as heart failure, septic shock and the spread of infection, maintained bacteraemia, the need for mechanical ventilation and vasoactive drugs, the indication for heart surgery and mortality were more common and statistically significant in the group of patients receiving unsuitable treatment (Table 2).

The in-hospital mortality rate was 34.7%, with the onset of acute vascular processes of the central nervous system (OR 98.7, 95% CI, 70.9–164.4), heart failure (OR 27.3, 95% CI, 10.2–149.1) and receiving unsuitable treatment (OR 7.2, 95% CI, 1.5–10.5) being prognostic factors independently associated with mortality (Table 3). It is striking that the mortality rate of the group of patients for whom surgery was indicated, but who did not end up undergoing surgery, was 60% (6/10), while the mortality rate for those who did end up receiving surgery, and who were therefore transferred, was 20% (5/25) (p<0.001). The in-hospital mortality rate of the group of patients for whom surgery was not indicated was 36%, similar to that of the overall cohort (Figure 3).

DISCUSSION

The most relevant epidemiological characteristics of this group of patients were: the incidence of 2-4 cases per year; an average age of 64 years; the male-to-female ratio of 2:1; the age-adjusted Charlson comorbidity index of >6 in 76%; the history of dental procedures (21%); previous valve disease (36%); the isolation in blood of MSSA (36%) as the most common microorganism; and the absence of a focus of origin in 54% of the patients. In total, 88% of the patients met the criteria for definite infective endocarditis. These results are similar to those found in other studies [1,4,13-16], with the high mortality rate (35%)—which was lower in patients who had been transferred for surgery (20%)—being particularly noteworthy.

Our study may suffer from several limitations: it is a partially retrospective cohort, meaning information could be missing in the medical records; it covers a broad period of time (2000 to 2017), during which structural and organisational changes may have taken place in our hospital, introducing variables that we weren't able to detect owing to the size of the sample; and not having conducted a peer review of the cases, which could have led to biases when assessing the suitability of antibiotic therapy. Finally, although we used the guidelines and protocols that are accepted in the medical literature, some of the recommendations have a low level of evidence, or the opinions of experts regarding said recommendations may vary.

A. I. Peláez Ballesta, et al.

Infective endocarditis treated in a secondary hospital: epidemiological, clinical, microbiological characteristics and prognosis, with special reference to patients transferred to a third level hospital

Post-surgical evolution

| Figure 3 | Mortality according to patient group. |

In relation to aetiology, several series in the literature show that there has been an evolutionary change [4,7,13-14,16-17]. Our findings show that MSSA is the most common (34%), followed by CoNS (11.8%), while the prevalence of methicillin-resistant *S. aureus* (MRSA) is extremely low (3/35; 2.9%). In the cases of IE owing to *Streptococcus* spp. (24%) and *E. faecalis* (11%), unlike other studies, no correlation was found with neoplastic gastrointestinal diseases, probably owing to the lack of suitable gastrointestinal studies [4,18-21]. The aetiology by Gram-negative bacilli was found to be 4.7%, similar to that reported by other investigators [4,13-14,16-17,22-23].

In-hospital mortality in our series was 34.6%, with independently associated prognostic factors including cerebrovascular events, refractory heart failure and unsuitable antibiotic therapy. The mortality rate described in the literature [2,5,13-16] is generally below 30%. It should be noted that, in our cohort, the in-hospital mortality rate of patients who were transferred to the regional referral hospital for heart surgery was lower at 20%, which is more in line with the rate published by other authors. In this regard, in a study of a cohort of IE patients in a secondary hospital, López Dupla et al. [15] found that after the introduction of protocols and the launching of a multi-disciplinary team, the intra-hospital mortality rate decreased from 21% to 14%.

A multi-centre study conducted by the ICE (International Collaboration on Endocarditis) [24] compared its cohort of transferred patients with the non-transferred patients and identified the presence of complications as factors associated with transfer. Despite this, the mortality rates were similar (17% vs 18%), and they concluded that the most severe patients would be transferred, thus introducing a bias in the comparisons. The study did not analyse the variable of suitable or unsuitable antibiotic therapy or the variable of surgery. In

another 2011 cohort [1], a sub-group of patients in Barcelona who were transferred to a referral centre were analysed, and it was again observed that they exhibited more complications than the rest of the cohort. Logically, this is also a sub-group that undergoes heart surgery with greater frequency (69% vs 22%), as this is probably the reason why they were transferred. However, they had a lower mortality rate (23% vs 31%, although this was not deemed to be statistically significant). The authors highlighted that only 45% of the transferred patients received suitable antibiotic therapy, compared to 100% of patients who were treated in the referral hospital from the very beginning. Receiving unsuitable treatment during transfer was a risk factor (OR 3.3; 95% CI, 1.1–10) for death, although the multivariate analysis of risk factors for mortality was not provided.

Other authors have analysed cohorts of patients treated in hospitals without heart surgery facilities, highlighting cohorts with a lower mortality rate than that which is usually published (19%). They also found that the creation of a multi-disciplinary working group and the implementation of protocols reduces this figure even further (8-14%) [11,25-29]. A more recent cohort suggests that patients treated in secondary centres may be older and have more comorbidities [30]. In 2014, a national study [31] compared two tertiary hospitals, with and without heart surgery facilities, and detected mortality rates of 18% vs 32%. However, in the multivariate analysis, only the variables of age and onset of complications, as well as the need for emergency surgery, were associated with death—not whether the patient was treated at one hospital or another (despite statistically significant differences in the surgery delay time). It is worth noting, however, that the variable of unsuitable antibiotic therapy was not analysed. In our experience, the development of complications, unsuitable antibiotic therapy and the severity of the diagnosis are risk factors of mortality.

A. I. Peláez Ballesta, et al.

Infective endocarditis treated in a secondary hospital: epidemiological, clinical, microbiological characteristics and prognosis, with special reference to patients transferred to a third level hospital

However, being treated in a secondary hospital is not necessarily a risk factor.

There is currently a lack of data to establish definitive recommendations regarding the question of whether or not IE patients should be transferred to a referral hospital, but it is very likely that a lack of a protocol, a lack of multidisciplinary teams and a higher prevalence of unsuitable antibiotic therapy are variables associated with a poorer prognosis for IE patients. Some studies indicate that these characteristics may be more prevalent in secondary hospitals, where a delay in referral to specialist hospitals may further increase the mortality rate. In view of this, it is essential to implement agreed protocols adapted to the characteristics of each hospital and to draw up user-friendly guidelines, benefitting from the services of at least one clinical consultant specialising in infectious diseases in secondary hospitals. The active participation of the infectious disease consultant has been associated with better outcomes in patients with bacteraemia and endocarditis, specified in various guidelines as being an alternative—almost mandatory—in the diagnostic and therapeutic assessment and during the monitoring of these patients [11,25-29,32]. Unsuitable antibiotic therapy is a particularly relevant factor, as it can be modified. In our analysis, and consistent with Fayad et al. [33], it was independently associated with a mortality rate that was seven times higher (OR 7.2). This section probably emerges as one of the areas of improvement with the greatest clinical impact, due to its potential positive influence on the outcomes of these patients.

Infective endocarditis is a complex infectious disease that is difficult to manage, which is why the existence of a multidisciplinary medical and surgical team that specialises in these processes would optimise its treatment and could lead to reduced morbidity and mortality.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest

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