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Current Epidemiology and Outcome of Infective Endocarditis

A Multicenter, Prospective, Cohort Study

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Abstract: The aim of the study was to describe the epidemiologic and clinical characteristics and identify the risk factors of short-term and 1-year mortality in a recent cohort of patients with infective endocarditis (IE).

From January 2008, multidisciplinary teams have prospectively collected all consecutive cases of IE, diagnosed according to the Duke criteria, in 25 Spanish hospitals.

Overall, 1804 patients were diagnosed. The median age was 69 years (interquartile range, 55–77), 68.0% were men, and 37.1% of the cases were nosocomial or health care-related IE. Gram-positive microorganisms accounted for 79.3% of the episodes, followed by Gram-negative (5.2%), fungi (2.4%), anaerobes (0.9%), polymicrobial infections (1.9%), and unknown etiology (9.1%). Heart surgery was performed in 44.2%, and in-hospital mortality was 28.8%. Risk factors for in-hospital mortality were age, previous heart surgery, cerebrovascular disease, atrial fibrillation, *Staphylococcus* or *Candida* etiology, intracardiac complications, heart failure, and septic shock. The 1-year independent risk factors for mortality were age (odds ratio [OR], 1.02), neoplasia (OR, 2.46), renal insufficiency (OR, 1.59), and heart failure (OR, 4.42). Surgery was an independent protective factor for 1-year mortality (OR, 0.44).

IE remains a severe disease with a high rate of in-hospital (28.9%) and 1-year mortality (11.2%). Surgery was the only intervention that significantly reduced 1-year mortality.

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Abbreviations: 16S rRNA PCR = 16S ribosomal RNA (rRNA) gene polymerase chain reaction (PCR), CNS = central nervous system, GAMES = The Spanish Collaboration on Endocarditis-Grupo de Apoyo al Manejo de la Endocarditis Infecciosa en España, ICE = International Collaboration on Endocarditis, IE = infective endocarditis, IQR = interquartile range, IVDU = intravenous drug users, OR = odds ratio.

INTRODUCTION

Infective endocarditis (IE) is a severe disease with high morbidity, and prolonged hospital stay. Mortality during the IE admission ranges from 13% to 25%, and a further 9% to 20% of the patients will die during the first year after discharge.[1–5]

Owing to the low incidence of IE (1.7–7.9 cases/100,000 inhabitants[3,4,6–9]), data on clinical presentation, complications, and outcomes are mainly obtained from series collected over prolonged periods, in single centers, or over shorter periods in multicenter, multinational studies from selected centers.[3,9–11] Consequently, they do not necessarily represent the current situation of a whole country.

In 2008, in association with the International Collaboration on Endocarditis (ICE),[1,12] we created a national cooperative endocarditis study group, The Spanish Collaboration on Endocarditis-Grupo de Apoyo al Manejo de la Endocarditis Infecciosa en España (GAMES), with the objectives of improving the care of IE patients and conducting research in Spain.

The objective of the present study was to define the characteristics of IE in a prospective multicenter, nationwide study, performed in 25 centers of Spain and to identify risk factors of early and late mortality.

MATERIALS AND METHODS

Patients

The study sample comprised all consecutive patients with IE in the 25 centers from January 1, 2008 to December 31, 2012.

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GAMES is a prospective registry performed by multidisciplinary group dedicated to improve the management of IE. Hospital-based endocarditis groups include microbiologists, infectious disease physicians, heart surgeons, echocardiographers, imaging specialists, and cardiologists. These groups prospectively recorded all consecutive episodes of IE at their institutions and collected the data according to a preestablished clinical form with common standard definitions.[13–15] At discharge, the clinical forms were sent to the coordinating center or data were entered directly by the investigators through a secure data entry system. In the coordinating center, specialized clinicians and data managers reviewed the data for accuracy and contacted the referring centers, if necessary, for queries and clarifications. Patients were followed for 1 year.

Episodes were classified into 4 distinct categories representing different populations: native valve IE in intravenous drug users (IVDU), native valve IE in non-IVDU, prosthetic valve IE, and IE involving implantable cardiac devices.

Definitions

IE was defined according to the modified Duke criteria.[14,16] Site of IE acquisition was defined following ICE recommendations.[13] In brief, community-acquired IE was defined as IE diagnosed within the first 48 hours of admission in a patient who did not fulfill the criteria for nosocomial or health care-associated infection. Nosocomial IE was defined as IE in a patient who had been hospitalized for >48 hours before the onset of signs or symptoms consistent with IE. Health care-associated IE was an IE diagnosed within 48 hours of admission of an outpatient with any of the following criteria[17]: intravenous therapy, wound care, or specialized nursing care at home within the 30 days before the onset of IE; attendance at a hospital or hemodialysis clinic or receipt of intravenous chemotherapy within the 30 days before the onset of IE; hospitalization in an acute care hospital for 2 or more days during the 90 days before the onset of IE; or residence in a nursing home or long-term care facility. An implantable cardiac device was defined as a permanent pacemaker and/or cardioverter-defibrillator. Perivalvular extension was considered to be substantial when abscesses were present or other echocardiography findings suggested that the infection was invasive (communication between chambers, wall dissection, or large valvular dehiscence). Prosthetic valve IE was defined as an endovascular infection occurring on parts of a valve prosthesis or on reconstructed native heart valves whether a mechanical prosthesis, and/or a bioprosthetic xenograft, stented or unstented, and/or a repaired native valve with implantation of an annular ring. The EuroSCORE[20] was used to assess operative risk.[18,19] We used the Charlson comorbidity index as a method of categorizing comorbidities of the patients.[20]

Chronic immunosuppressive therapy was defined as the administration of recognized immunosuppressive agents for >30 days at the time of IE diagnosis.

Central nervous system (CNS) event was defined as an acute neurological deficit of vascular etiology lasting >24 hours.[21] Systemic embolization was defined as an embolic event outside of the CNS. Congestive heart failure was defined according to the New York Heart Association classification system.[22]

Statistical Analysis

The 4 classic types of IE were compared: native valve IE in IVDU and in non-IVDU, prosthetic valve IE, and IE affecting intracardiac devices. Quantitative variables were expressed as mean ± standard deviation or as medians with interquartile range (IQR), as appropriate; qualitative variables were expressed as frequency and percentage. Continuous variables were compared using the *t* test, and categorical variables were compared using the χ^2 test or Fisher exact test when the χ^2 test was not appropriate. Adjusted odds ratios (ORs)[23] were computed using logistic regression analysis. Stepwise logistic regression analysis was performed including variables with a *P* value ≤0.1 in the univariate analysis. All statistical analyses were performed using SPSS software version 18 (IBM PASW Statistics 18.0, Armonk, New York, NY).

Ethics

The project and the common case report form were approved by the national and local institutional review boards and ethics committees (E.C. 18/07).

RESULTS

Incidence of IE

The study sample comprises total of 1804 IE cases from 25 centers, located throughout Spain. Those institutions attend an estimated population of 10,218,634 habitants, that is, 21.7% of the Spanish population.[24] Therefore, we estimated an annual incidence of at least 3.5 cases of IE per 100,000 inhabitants.

General Characteristics of the Cohort

The median age of the cohort was 69 years (IQR, 55–77; mean, 65.1), and 1228 (68.0%) patients were male. The most common ''extracardiac underlying conditions'' are shown in Table 1. The main comorbidities were diabetes mellitus (471, 26.1%), pulmonary disease (312, 17.3%), and neoplasm (290, 16.1%). Other comorbidities that were not as frequent, but nevertheless had a high impact on clinical course were, hemodialysis (79, 4.4%), HIV infection (39, 2.2%), and transplantation (27, 1.5%). The mean Charlson-age corrected comorbidity index was 4.49 ± 2.6. The most common ''predisposing heart conditions'' were native valve disease (41.8%) (degenerative [27%]; rheumatic valve disease [8.0%]; and congenital heart disease [3.2%]), followed by previous valve surgery (34.4%) and previous IE episode (6.9%).

Affected Valve

Most of the patients (62.7%) had native valve IE, and most episodes were left-sided (mitral 808 [44.8%], aortic 852 [47.2%]). The tricuspid valve was involved in 99 cases (5.5%) and the pulmonary valve in 29 cases (1.6%). Prosthetic valve endocarditis occurred in 504 cases (27.9%) and device-related endocarditis in 169 patients (9.3%).

The ''site of acquisition'' was determined in 95.9% of patients (Table 1); 28.1% episodes were classified as nosocomial. In the case of community-acquired episodes, most patients (86%) were admitted within 1 month of the initial signs of illness (12.6% at 1–3 months and 6.3% >3 months). The ''source of the infection'' was suspected in 842 (46.6%) patients (vascular 305; gastrointestinal 127; skin and soft tissue 124; odontogenic 115; urinary 88; respiratory 21; others 62).

''Clinical manifestations'' are shown in Table 1. It is noteworthy that the classic signs of IE were uncommon. These included splenomegaly (11.6%), splinter hemorrhages (2.3%), Janeway spots (2.4%), and Osler nodes (1.9%). However, patients with IE had other common manifestations (respiratory [41%], renal [39%], neurological [19.7%], osteoarticular [11.5%], and ocular [6.3%]).

TABLE 1. Epidemiological and Clinical Characteristics of 1804 Episodes of Infective Endocarditis Prospectively Collected in Spain

	Total N = 1804	Native Non-IVDU N = 1079	Native IVDU N = 52	Prosthetic N = 504	Device N = 169	*P*
Median age (IQR)	69 (57–77)	68.7 (55–77)	39.9 (33–45)	71.1 (61–77)	71.4 (60–78)	<0.01
Male (%)	1228 (68.1)	728 (67.5)	42 (82.4)	337 (67.0)	121 (71.6)	0.10
Underlying conditions						
Charlson-age index	4.49 (2.6)	4.46	2.92	4.57	4.92	<0.01
Diabetes mellitus	471 (26.1)	289 (26.8)	1 (1.9)	131 (26.0)	50 (29.8)	<0.01
Mild renal insufficiency	188 (10.4)	88 (8.2)	1 (2.0)	70 (14.0)	29 (17.3)	<0.01
Severe renal insufficiency	280 (15.5)	168 (15.7)	5 (9.8)	73 (14.5)	34 (20.1)	0.22
Pulmonary disease	312 (17.3)	189 (18.0)	2 (3.9)	90 (18.2)	31 (18.9)	0.07
Neoplasm	290 (16.1)	203 (18.9)	0	69 (13.7)	18 (10.7)	<0.01
HIV infection	39 (2.2)	13 (1.2)	23 (44.2)	3 (0.6)	0	<0.01
Risk factors						
Previous cardiac surgery	620 (34.4)	95 (8.9)	1 (2.0)	504 (100)*	36 (21.4)	<0.01
Previous IE	126 (7.0)	43 (4.0)	6 (11.5)	64 (12.8)	13 (7.8)	<0.01
Heart failure	531 (29.4)	252 (23.6)	0	203 (40.7)	76 (46.3)	<0.01
Atrial fibrillation	457 (25.3)	190 (17.9)	0	219 (44.4)	48 (29.1)	<0.01
Site of acquisition						
Nosocomial	507 (28.1)	241 (23.1)	1 (1.9)	190 (39.7)	75 (46.9)	<0.01
Community-acquired	1061 (58.8)	701 (67.3)	49 (94.2)	251 (52.6)	60 (37.7)	<0.01
Health care-related	162 (9.0)	100 (9.6)	2 (3.8)	36 (7.5)	24 (15.1)	0.01
Transferred from other hospital	479 (26.6)	281 (26.0)	13 (25.0)	139 (27.6	46 (27.2)	0.91
Symptoms before admission (median days; IQR)	21 (7–60)	14 (5–55)	7 (4–21)	7 (3–21)	8 (5–60)	0.58
Affected valve						
Aortic	852 (47.2)	499 (46.2)	13 (25.0)	327 (64.8)	13 (7.7)	<0.01
Mitral	808 (44.8)	579 (53.7)	14 (26.9)	211 (41.9)	4 (2.4)	<0.01
Tricuspid	99 (5.5)	58 (5.4)	24 (46.2)	4 (0.8)	13 (7.7	<0.01
Pulmonary	29 (1.6)	16 (1.5)	3 (5.8)	8 (1.6)	2 (1.2)	0.11
Presentation						
Fever >38°C	1506 (83.4)	899 (84.0)	43 (84.3)	427 (85.9)	137 (82.0)	0.01
Splinter hemorrhages	41 (2.3)	34 (11.0)	4 (16.0)	3 (2.7)	–	0.01
Osler nodes	35 (1.9)	27 (8.4)	2 (7.7)	6 (5.0)	–	0.38
Janeway lesions	43 (2.4)	29 (9.5)	4 (16.0)	9 (8.0)	1 (6.3)	0.63
Roth spots	18 (1.0)	13 (4.5)	1 (4.0)	4 (3.8)	–	0.84
Splenomegaly	209 (11.6)	140 (13.7)	16 (31.4)	46 (9.5)	7 (4.3)	<0.01
New murmur	577 (32.0)	430 (44.8)	23 (50.0)	115 (26.4)	9 (5.7)	<0.01
Worsening of old murmur	221 (12.3)	138 (16.3)	2 (4.7)	74 (18.4)	7 (4.5)	<0.01
Mean CRP (SD)	61.5 (87.2)	65.8 (90.2)	37.2 (68.0)	55.2 (84.9)	60.9 (79.1)	0.015
Elevated RF	160 (8.9)	104 (25.8)	5 (26.3)	33 (17.8)	18 (26.1)	0.18

CRP = C-reactive protein, HCR = health care-related, IE = infective endocarditis, IQR = interquartile range, IVDU = intravenous drug users, RF = rheumatoid factor, SD = standard deviation.

* 2.8% of patients with prosthetic valve developed the infectious endocarditis during the same hospital admission of the first valve surgery.

Etiology

Most episodes (79.3%) were caused by Gram-positive microorganisms, followed by Gram-negative microorganisms (5.2%), fungi (2.4%), anaerobes (0.9%), and polymicrobial infections (1.9%). The distribution of the most common microorganisms is shown in Table 2. Twenty-two episodes were caused by microorganisms of the HACEK group. Other fastidious microorganisms included *Coxiella burnetii* (15), *Listeria monocytogenes* (6), *Tropheryma whipplei* (5), *Bartonella* spp. (4), and *Brucella melitensis* (1). Accordingly, the rate of unknown etiology of endocarditis was 9.1%.

Diagnosis

Blood cultures were obtained in 1787 patients (99.1%) and provided the etiology in 1523 (85.3%). Of the 264 patients (14.7%) with negative blood cultures, 34% had received antimicrobial agents in the previous week. An etiologic diagnosis was achieved in 106 cases with a combination of the following techniques: sequence analysis of the 16S ribosomal RNA (rRNA) gene polymerase chain reaction (PCR) 66, 25% (heart valve 56, 21.2%; blood 8, 3.0%; and cardiac device 5, 1.9%); serology 99, 37.5%; and extracardiac cultures 59, 22.3%. Transesophageal echocardiography was done in most patients (76.3%), and 1148 (83.4%) presented vegetations. Abscess was

TABLE 2. Etiology, Diagnosis, and Outcome of 1804 Episodes of Infective Endocarditis Prospectively Collected in Spain

	Total N = 1804	Native Non-IVDU N = 1079	Native IVDU N = 52	Prosthetic N = 504	Device N = 169	*P*
Definite IE	1498 (83.0)	919 (85.6)	48 (92.3)	409 (81.3)	122 (72.2)	<0.01
Possible IE	300 (16.6)	155 (14.4)	4 (7.7)	94 (18.7)	47 (27.8)	<0.01
Etiology						
Staphylococcus spp.	728 (40.3)	382 (35.3)	30 (55.8)	218 (43.2)	98 (58.0)	<0.01
S. aureus	426 (23.6)	278 (25.8)	26 (50.0)	77 (15.3)	45 (26.6)	<0.01
MSSA	360 (84.5)	235 (84.5)	24 (92.3)	64 (83.2)	37 (82.3)	0.46
MRSA	66 (15.5)	43 (15.5)	2 (7.7)	13 (16.8)	8 (17.7)	
CoNS	302 (16.7)	104 (9.7)	4 (7.7)	141 (28.0)	53 (31.5)	<0.01
Streptococcus spp.	440 (24.4)	329 (30.5)	8 (15.4)	86 (17.1)	17 (10.1)	<0.01
S. bovis	117 (6.4)	80 (7.4)	0	32 (6.5)	5 (3.0)	0.036
S. viridans group	223 (12.3)	171 (16.0)	7 (13.5)	38 (7.5)	7 (4.1)	<0.01
Others	100 (5.5)	79 (7.3)	1 (1.9)	15 (3.0)	5 (5.3)	0.001
Enterococcus spp.	230 (12.7)	142 (13.2)	5 (9.6)	77 (15.3)	6 (3.6)	0.001
Other Gram-positives*	26 (1.4)	14 (1.3)	2 (3.8)	8 (1.5)	2 (1.1)	0.48
Gram-negatives**	93 (5.2)	53 (4.9)	–	25 (5.0)	15 (8.9)	0.05
Fungi***	44 (2.4)	21 (1.9)	2 (3.8)	15 (3.0)	6 (3.6)	0.38
Negative BC	264 (14.7)	152 (14.0)	5 (9.6)	75 (14.8)	32 (18.9)	0.67
Echocardiogram						
TEE	1377 (76.3)	776 (72.0)	23 (44.2)	450 (89.3)	128 (76.2)	<0.01
Vegetations	1284 (71.2)	836 (77.6)	41 (78.8)	296 (58.8)	111 (65.7)	<0.01
Intracardiac complication	501 (27.8)	309 (28.9)	9 (17.6)	171 (33.9)	12 (7.1)	<0.01
Clinical course						
Embolisms	525 (29.1)	322 (30.5)	30 (60.0)	143 (28.9)	30 (18.2)	<0.01
New heart failure	698 (38.7)	488 (45.9)	15 (29.4)	214 (43.2)	32 (19.2)	<0.01
Persistent bacteremia	151 (8.4)	90 (8.6)	1 (2.0)	45 (9.2)	15 (9.0)	0.37
Surgery						
Indicated (%)	1152 (63.9)	661 (61.4)	25 (48.1)	341 (67.7)	125 (74.0)	<0.01
Performed (%)	797 (44.2)	452 (41.9)	15 (28.8)	220 (43.8)	110 (65.1)	<0.01
Criteria for surgery						
Cardiac insufficiency	373 (20.7)	257 (25.9)	6 (13.0)	104 (22.3)	6 (3.7)	<0.01
Early prosthetic IE	67 (14.4)	–	–	67 (14.4)	–	<0.01
Late prosthetic IE	74 (15.9)	–	–	74 (15.9)	–	<0.01
Valvular insufficiency	315 (17.5)	225 (22.7)	11 (23.9)	78 (16.8)	1 (0.6)	<0.01
Embolisms	50 (2.7)	35 (3.2)	3 (5.7)	10 (1.9)	2 (1.2)	0.11
Persistent bacteremia	53 (2.9)	30 (2.8)	–	13 (2.6)	10 (5.9)	0.09
Outcome						
Median hospital stay (IQR)	36 (21–53)	36 (21–51)	36 (22–48)	39 (18–54)	34 (23–53)	0.92
In-hospital mortality (%)	521 (28.9)	301 (27.9)	8 (15.4)	184 (36.5)	28 (16.6)	<0.01
1-y mortality (%)	116 (9.1)	81 (10.4)	1 (2.27)	29 (9.0)	5 (3.5)	0.05

BC = blood cultures, CoNS = coagulase-negative staphylococci, TEE = transesophageal echocardiogram, IE = infective endocarditis, IQR = interquartile range, IVDU = intravenous drug users, MRSA = methicillin-resistant *S. aureus*, MSSA = methicillin-sensitive *S. aureus*.

* Other Gram-positives: Abiotrophia 9, Corynebacterium 6, Gemella 8, Listeria 3.

** Gram-negatives: Acinetobacter 2, Actinobacillus 4, Alcaligenes 1, Bartonella 4, Brucella 1, Campylobacter 3, Cardiobacterium 2, Coxiella 15, Enterobacter 3, Escherichia 13, Haemophilus 7, Klebsiella 3, Moraxella 1, Neisseria 2, Pseudomonas 11, Salmonella 3, Serratia 2, Stenotrophomonas 1, Tropheryma 5, Yersinia 1.

*** Fungi: Aspergillus 5, Scedosporium 1, Candida 37, Rhodotorula 1.

the most common paravalvular complication (27.8%), whereas 26.6% of patients with prosthetic valve IE had evidence of a prosthetic valve complication such as dehiscence or new paravalvular regurgitation.

COMPARISON OF THE 4 TYPES OF IE

Non-IVDU Patients With Native Valve IE

Most of the patients in our series (59.8%) were non-IVDU, which is therefore the most heterogeneous group. Although it is difficult to identify one characteristic that stands out, these patients presented less frequently history of heart failure (23.6%) or renal failure (23.9%). Most cases were community-acquired, and *Streptococcus* spp. was the most common pathogen involved.

''Native valve IE in IVDU'' accounted for the smallest group of our series. Native valve IE affected significantly younger patients with fewer comorbid conditions, except in the case of HIV infection (44.2%). Acquisition was nosocomial in only 1.9% of the cases and, interestingly, half of these patients had left-sided IE. A typical clinical presentation was

more evident in this population including splinter hemorrhages (16%) and splenomegaly (31.4%). *Staphylococcus aureus* predominated as the etiological microorganism (53.8%), and embolisms were frequent (60.0%). Outcome was clearly better in this group.

Prosthetic Valve IE

The highest in-hospital mortality was recorded in patients with prosthetic valve IE (36.5%, $P < 0.01$); however, it is of even greater concern that infection was nosocomial in 39.7% of these patients. Coagulase-negative staphylococci accounted for 28.0% of the cases. Accordingly, intracardiac complications were significantly more frequent (33.9%).

Cardiac Device IE

Patients with heart devices were older, with the highest comorbidity index and a great part were nosocomial or health care-related IE (62%). The device involved was surgically removed in 65.1% of the cases.

Short-Term and Long-Term Risk Factors for Mortality

Table 3 shows a comparison of the patients who survived (71.1%) and those who died (28.9%) during admission; Table 4 shows the independent risk factors associated with a higher risk of in-hospital death. Independent mortality risk factors could be grouped as epidemiological characteristics of the patient, endocarditis etiology (*Staphylococcus* spp. [OR, 2.34], fungi [OR, 3.12]) and complications (intracardiac complication [OR, 1.67], heart failure [OR, 2.97], and septic shock [OR, 5.18]).

Independent risk factors for 1-year mortality are shown in Table 5, and include increasing age (OR, 1.02), neoplasm (OR, 2.46), renal insufficiency (OR, 1.59), and heart failure (OR, 4.42). Surgery was independently associated with a decreased risk of 1-year mortality (OR, 0.44) and was the only factor amenable of intervention.

DISCUSSION

Our very large series, collected from different institutions in a single country over a short period of time, shows that IE is mainly a disease of the elderly, with multiple predisposing conditions, frequently nosocomial, and has still a very high mortality, both during admission and during the 1-year follow-up.

Incidence rates of IE have been collected over long periods of time, and data based on population studies are scarce. In our series, including population-based studies of endocarditis recruited from 1960 to 2008, incidence rates range from 3 to 10 cases/100,000 habitants,[4,6–9] and our figure of 3.5 IE cases/100,000 habitants is concordant with that. The advantage of our series is its large dimension collected over a short period.

The underlying conditions of patients with IE have also drastically changed,[3,4,7] and most of our cases presented with severe comorbid conditions. This population of fragile patients is frequently exposed to health care-related and nosocomial complications. In our series, 28% of the episodes were classified as nosocomial; this percentage is similar to that reported by Fernandez-Hidalgo et al.[25]

Clinical presentation of the disease has also changed, and the signs that were once typical of IE (splinter hemorrhages, Janeway lesions, and Osler nodes) are now only seen in 2% of the patients. One possible explanation is that IE patients are now diagnosed earlier (86% were admitted $\leq$1 month of the initial signs of illness), thus reducing the incidence of immunological manifestations.[1] On the contrary, we commonly observed complications such as respiratory manifestations (41%), kidney failure (39%), neurological events (19.7%), osteoarticular symptoms (11.5%), and ocular manifestations (6.3%). The rate of embolic events in our series was 29%, and although our results are similar to the ones reported by others,[1,26] we believe that this figure could be underestimated, as the extension study depends on the institutional protocol and the technology available in each center. The introduction of newer diagnostic imaging tools such as positron emission tomography–computed tomography as part of the diagnostic algorithm in patients with IE, as suggested by Saby et al,[27] should prove to be of great interest in this field.

A shift in the type of patient with IE has been observed: one major change in our series was the very low proportion of IE now occurring in IVDU. In Spain, this is probably related with the programs to control IVDUs and particularly the methadone maintenance program.[28] Although historically native valve IE in IVDU represented an important number of affected patients,[29] in our series this population accounted for the smallest group while the number of patients with prosthetic valve and device IE (37%), on the other hand, seems to be increasing.[4,9]

Microbiological diagnostic tools have changed and improved over recent decades, and although etiology was confirmed by blood culture in most cases (85%), there are still cases in which the etiology is unknown (9%). Molecular techniques such as 16S rRNA PCR of the heart valves enabled us to establish the etiology in 21% of the negative blood culture episodes that would otherwise have been considered IE of unknown etiology. However, even though molecular methods have been used to diagnose IE, are long time, well-known methods,[30] this diagnostic approach is still not routinely available in all diagnostic laboratories.

The most common microorganisms in our series were staphylococci, streptococci, and enterococci. Thus, a major change in the microbiology of IE is that *Enterococcus* spp. has emerged as the third most important group of pathogens and is now causative of 13% of IE cases. Because enterococci have shown the ability to develop antibiotic resistance,[31] further studies are needed to evaluate novel approaches to this increasingly frequent problem[32] and specially to identify factors that enable the early selection of patients who are at risk for Enterococcal IE.[33]

As for mortality, IE is a severe disease with a poor outcome. In our series, in-hospital mortality was 29%, and it seems that IE mortality has remained close to 25% since the 1970s[3] despite the introduction of broad-spectrum antibiotics and new diagnostic tools. This is probably related with the increase in age and comorbidity. Although it is a complex procedure and it is not free of complications, surgery, when indicated, seems to have a major impact on mortality. In our experience, surgery was independently associated with a decreased risk of 1-year mortality (OR, 0.44); our results agree with those of a recent analysis of published studies[34,35] that shows a significant correlation between the rate of early surgery and mortality.

Study Limitations

Our series may not represent the situation of IE in other countries where levels of health care differ from those of Spain (public run universal health care), but in our opinion represents well the situation in many western countries.

TABLE 3. Risk Factors for In-Hospital Mortality

	Alive N = 1283	Dead N = 521	*P*
Median age (IQR)	67.6 (53.7–76)	73 (62.9–78.9)	<0.01
Male	907 (70.7)	321 (61.8)	<0.01
Underlying condition			
Heart failure	326 (25.6)	205 (40.0)	<0.01
Previous cardiac surgery	411 (32.4)	209 (40.4)	0.001
Diabetes mellitus	294 (22.9)	177 (34.1)	<0.01
Mild renal insufficiency	117 (9.2)	71 (13.8)	0.004
Severe renal insufficiency	163 (12.8)	117 (22.7)	<0.01
Atrial fibrillation	288 (22.8)	169 (33.2)	<0.01
Lung disease	209 (16.7)	103 (20.4)	0.067
Neoplasm	199 (15.5)	91 (17.5)	0.296
HIV infection	29 (2.3)	10 (2.0)	0.675
Previous IE	101 (7.9)	25 (4.8)	0.020
Charlson-age comorbidity (SD)	4.1 (2.5)	5.4 (2.5)	<0.01
Transferred from other hospital	340 (26.5)	139 (26.7)	0.938
Symptoms before admission (median days [IQR])	6 (1–18)	2 (0–8)	<0.01
Affected valve			
Aortic	594 (46.3)	258 (49.5)	0.214
Mitral	541 (42.2)	267 (51.2)	<0.01
Tricuspid	80 (6.2)	19 (3.6)	0.029
Pulmonary	22 (1.7)	7 (1.3)	0.570
Proven endocarditis	1054 (82.3)	444 (85.9)	0.064
Possible endocarditis	227 (17.7)	73 (14.1)	0.064
Etiology (%)			
S. aureus	237 (18.5)	189 (36.5)	<0.01
Methicillin-resistant *S. aureus*	34 (2.7)	32 (6.1)	<0.01
Coagulase-negative staphylococci	201 (15.7)	101 (19.4)	0.058
Streptococcus spp.	371 (28.9)	69 (13.2)	<0.01
Enterococcus spp.	177 (13.8)	53 (10.2)	0.037
Other Gram-positive microorganisms	19 (1.5)	7 (1.3)	0.824
Gram-negative microorganisms	76 (5.9)	17 (3.3)	0.021
Fungi	25 (2.0)	19 (3.6)	0.034
Negative blood cultures	110 (8.6)	54 (10.4)	0.230
Vegetation	887 (69.1)	397 (76.5)	0.002
Intracardiac complication	310 (24.3)	191 (37.0)	<0.01
Transesophageal echocardiogram	1004 (78.3)	375 (71.9)	<0.01
Persistent bacteremia	69 (5.5)	82 (16.7)	<0.01
Heart surgery			
Indicated	728 (56.8)	424 (81.4)	<0.01
Operated on	598 (46.7)	199 (38.2)	0.001
Reasons for surgery (%)			
Cardiac insufficiency	254 (21.5)	119 (24.5)	0.185
Early prosthetic IE	47 (4.0)	31 (6.4)	0.036
Late prosthetic IE	46 (3.9)	32 (6.6)	0.019
Valvular insufficiency	245 (20.8)	70 (14.4)	0.003
Median hospital stay (IQR)	41 (27–55)	23 (11–42)	<0.01

BC = blood cultures, IE = infective endocarditis, IQR = interquartile range, SD = standard deviation, TEE = transesophageal echocardiogram.

In conclusion, well inside the XXI century, IE, collected in a large number of institutions in a western country, remains an uncommon but devastating infectious disease. It commonly affects elderly patients with severe comorbidities, is frequently nosocomially acquired, and may be underdiagnosed if only suspected in the presence of classic clinical signs or typical microorganisms bacteremia. Surgery seems the only clear protective intervention and mortality within 1 year after discharge remains disappointedly high. Multidisciplinary teams are essential to optimize the management and outcome of this severe disease.

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TABLE 4. Independent Risk Factors for In-Hospital Mortality

Factor	OR	95% CI	*P*
Age	1.02	1.01–1.03	<0.01
Immunosuppressive therapy	2.61	1.68–4.04	<0.01
Previous heart surgery (previous to the episode of IE)	1.53	1.17–2.00	.002
CNS event	2.47	1.91–3.19	<0.01
Atrial fibrillation	1.45	1.09–1.93	.011
S. aureus	2.34	1.75–3.12	<0.01
Fungi	3.12	1.50–6.49	.002
Intracardiac complication	1.67	1.30–2.14	<0.01
Heart failure	2.97	2.30–3.83	<0.01
Septic shock	5.18	3.62–7.40	<0.01

CI = confidence interval, CNS = central nervous system, IE = infective endocarditis, OR = odds ratio.

TABLE 5. Independent Risk Factors for 1-Year Mortality

Factor	OR	95% CI	*P*
Age	1.02	1.00–1.03	0.005
Neoplasm	2.46	1.57–3.86	<0.01
Surgery	0.44	0.286–0.694	<0.01
Renal insufficiency	1.59	1.04–2.42	0.030
Heart failure	4.42	1.06–18.40	0.041

CI = confidence interval, OR = odds ratio.

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