

Forty-Year Trends in Cardiac Implantable Electronic Device Infective Endocarditis

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Background. Studies investigating cardiac implantable electronic device infective endocarditis (CIED-IE) epidemiological changes and prognosis over long periods of time are lacking.

Methods. Retrospective single cardiovascular surgery center cohort study of definite CIED-IE episodes between 1981–2020. A comparative analysis of two periods (1981–2000 vs 2001–2020) was conducted to analyze changes in epidemiology and outcome over time.

Results. One-hundred and thirty-eight CIED-IE episodes were diagnosed: 25 (18%) first period and 113 (82%) second. CIED-IE was 4.5 times more frequent in the second period, especially in implantable cardiac defibrillators. Age (63 [53–70] vs 71 [63–76] years, $P < .01$), comorbidities (CCI 3.0 [2–4] vs 4.5 [3–6], $P > .01$), nosocomial infections (4% vs 15.9%, $P = .02$) and transfers from other centers (8% vs 41.6%, $P < .01$) were significantly more frequent in the second period, as were methicillin-resistant coagulase-negative staphylococcal (MR-CoNS) (0% vs 13.3%, $P < .01$) and Enterococcus spp. (0% vs 5.3%, $P = .01$) infections, pulmonary embolism (0% vs 10.6%, $P < .01$) and heart failure (12% vs 28.3%, $p < .01$). Second period surgery rates were lower (96% vs 87.6%, $P = .09$), and there were no differences in in-hospital (20% vs 11.5%, $P = .11$) and one-year mortalities (24% vs 15%, $P = .33$), or relapses (8% vs 5.3%, $P = 0.65$). Multivariate analysis showed Charlson index (hazard ratios [95% confidence intervals]; 1.5 [1.16–1.94]) and septic shock (23.09 [4.57–116.67]) were associated with a worse prognosis, whereas device removal (0.11 [.02–.57]), transfers (0.13 [.02–0.95]), and second-period diagnosis (0.13 [.02–.71]) were associated with better one-year outcomes.

Conclusions. CIED-IE episodes increased more than four-fold during last 40 years. Despite CIED-IE involved an older population with more comorbidities, antibiotic-resistant MR-CoNS, and complex devices, one-year survival improved.

Keywords. 40 years; CIED infective endocarditis; device removal; epidemiology; prognosis.

Longevity in developing countries has increased remarkably in recent decades. In Spain, the average life expectancy in 1981 was 72 years and is 83.6 years in 2019, among the highest in

the world [1]. The toll of rising life expectations is the growth in comorbidities, primarily cardiovascular diseases; therefore, the number of people requiring cardiac implantable electronic devices (CIEDs) has increased. The technological development of cardiac medical devices has been noteworthy in recent years, increasing the use of last-generation pacemakers (PPMs), implantable cardioverter-defibrillators (ICDs), and cardiac resynchronization therapy (CRT) [2].

Although the reported incidence of CIED infections varies notably among different studies, the increase in implantations has augmented the overall device infection rate [3, 4]. Contemporary authors have published a prevalence ranging from 0.68% to 5.7% [3–6], and the risk seems to be higher in CRT than in ICDs and PPMs [5]. Infective endocarditis (IE) related to CIEDs (CIED-IE) is the most severe complication, representing 10% of overall IE [5]. CIED-IE's global characteristics and evolution over the years are poorly studied. Stratification of

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risk depending on the type of the device (PPM, ICD, CRT), the clinical profile according to the time of presenting symptoms (early or late), or the etiology could guide the diagnosis and management of CIED-IE. It is recognized that removing the entire device is the key to managing these infections [7, 8]. However, the main problem is that CIEDs might have been implanted a long time ago in older, comorbid, and fragile patients; thus, combined with a high risk of complications during extraction surgery, CIEDs can sometimes not be removed. In those cases, patients may require lifelong oral antibiotic suppression treatment, decreasing their quality of life and increasing morbidity and mortality in the short and medium terms [9, 10].

Changes in the CIED-IE paradigm due to the growth in comorbidities, age, and implantation rate of overall devices have resulted in more complex infections, elevated surgical risk, and more patients without complete device removal. Chronic oral suppression therapy indication has been poorly reviewed, and whether these variations might have overcome increasing mortality for CIED-IE has not been reported. This study investigates the historical evolution of consecutive CIED-IE episodes and defines changes in epidemiology, clinical presentation, outcomes, and 1-year mortality during the last 4 decades.

METHODS

Design

This was an observational retrospective study of prospectively followed CIED-IE at Hospital Clinic de Barcelona (HCB), a referral cardiovascular surgery center for IE and cardiovascular infections. Cases were followed since 1979, when the HCB IE database was created. The first pacemaker was implanted at our center in April 1980, and the first CIED-IE was diagnosed in January 1981. In addition, the first ICD was implanted in 1991 and the first CRT in 1999. Thus, data were collected during the index hospitalization between January 1981 to December 2020. All patients had 1-year follow-up. The study ended on 31 December 2021.

Patient Selection and Data Collection

We included 138 consecutive patients with definite CIED-IE. The management of all patients was discussed at weekly endocarditis team meetings since 1986 [11]. The final diagnosis was accomplished by consensus of the IE team.

Inclusion and Exclusion Criteria

Only patients with definite CIED-IE using the modified Duke criteria for IE and presented in the IE team meetings were included [4, 12]. All patients, with or without local signs of pocket infection, had valve vegetations in either valve or lead of the CIED and positive blood cultures and/or positive lead culture and/or 16S ribosomal RNA (rRNA) gene sequencing positive. Due to the aim of this study, we used only the first episode of

CIED-IE for each patient. Patients with no definite criteria for IE were excluded.

Definitions and Variables

CIED-related pocket infection was defined by local signs of inflammation at the generator of the device, including erythema, warmth, fluctuance, wound dehiscence, tenderness, purulent drainage, or erosion of the generator or lead through the skin and/or positive pocket swab or positive device or subcutaneous lead cultures or 16S rRNA gene sequencing positive.

CIED-IE was considered in patients who met the Duke criteria for IE. All patients presented positive blood cultures and/or lead, and/or valve cultures and/or 16S rRNA gene sequencing positive, and lead or valve vegetations in echocardiography.

Echocardiographic diagnosis was achieved by transthoracic echocardiography between 1981 and 1990, whereas, since January 1991, most cases have undergone transesophageal echocardiography (TEE). Any mass seen on a lead and/or valve in echocardiography in the context of bacteremia was assumed to be vegetation. A second investigator validated all echocardiography studies and discrepancies were sorted out by adopting the most prevalent opinion when consulting a third member of the endocarditis team.

18F-fluorodeoxyglucose positron emission tomography/computed tomography (¹⁸FDG-PET/CT) was included in our center in 2014 and was not considered as a diagnostic CIED-IE criterion for this study; we recorded all ¹⁸FDG-PET/CT data of CIED-IE patients on whom it was performed.

Microbiological diagnosis included microorganisms detected by blood cultures or cultures of cardiac device lead and/or 16S rRNA gene sequencing positive. 16S rRNA polymerase chain reaction (PCR) was implemented since 2015.

Type of Device

Devices included in this study were PPMs, ICDs, and CRT.

Place of Infection

Healthcare-associated IE was defined in outpatients with extensive healthcare contact as reflected by any of the following: (1) received intravenous therapy, wound care, or specialized nursing care at home within 30 days before admission; (2) attended a hospital or hemodialysis clinic or received intravenous chemotherapy within 30 days before diagnosis; (3) was hospitalized in an acute care hospital for 2 or more days within 90 days before admission; or (4) resided in a nursing home or long-term care facility. Nosocomial IE was defined as an infection diagnosed after 72 hours of admission in an outpatient [13].

Early and Late Infections

Early CIED-IE was defined as signs and symptoms within 6 months of the most recent CIED procedure. Signs and

symptoms occurring >6 months after surgery were described as late CIED-IE [13, 14].

The Charlson Comorbidity Index (CCI) was used to assess patient morbidities. The CCI consists of 19 different disease categories with varying numerical weights (1, 2, 3, or 6 points based on adjusted 1-year mortality relative risk) allotted to specific diseases [15]. It has been previously validated as a predictor of mortality in many clinical contexts, including patients with permanent CIED implantation.

Complications

The following systemic complications were recorded: heart failure (HF), central nervous system complications, pulmonary embolisms, acute renal failure, persistent bacteremia, and septic shock. Persistent bacteremia was defined as positive blood cultures yielding the causative microorganism after 7 days of effective antibiotic therapy [13].

Management and Follow-up

We analyzed indication of device removal, type of device removal procedure, cause of surgery rejection, and length of antimicrobial treatment. Patients without a complete device removal underwent oral antibiotic suppression therapy. The duration of oral suppression treatment was recorded, and antimicrobial susceptibilities were used to guide the definitive oral antimicrobial therapy.

Relapse was defined as the isolation of the same microorganism in blood cultures within 180 days after the end of antibiotic treatment. Reinfection was described as a new episode of IE caused by a different microorganism or by the same microorganism ≥ 180 days after the end of the antibiotic treatment.

Cardiac surgery and mortality were classified into in-hospital and 1-year surgery/mortality.

Statistical Analysis

Primary endpoints were in-hospital and 1-year mortality, and secondary endpoints were device removal and relapses. We compared the prevalence, epidemiology, clinical characteristics, and outcomes between 1981–2000 and 2001–2020. We also compared the clinical characteristics and outcomes of CIED-IE according to etiology (coagulase-negative staphylococci [CoNS] vs no CoNS), timing of diagnosis (early-presenting [≤ 6 months from device implantation] vs late-presenting symptoms [>6 months]), and device type (PPM versus ICD/CRT).

Data are presented as median (interquartile range [IQR]) for continuous variables and as frequencies (percentages) for categorical variables. As appropriate, continuous variables were compared using Student *t* test or the Mann-Whitney *U* test. Categorical variables were compared using the χ^2 or Fisher tests, as appropriate.

Predicted factors of 1-year mortality were also studied. Risk factors for in-hospital and 1-year mortality were analyzed using

a logistic regression model with comparisons reporting odds ratios (ORs) or hazard ratios (HRs) with 95% confidence intervals (CIs), as appropriate. Variables found to have a simple association with mortality ($P < .10$) were considered for the final models. The 1-year mortality multivariate analysis was calculated considering just the related survival clinical variables. Age, diabetes, and chronic renal failure were excluded from the model, as they are included in the CCI. For all tests, statistical significance was determined at the $P = .05$ level. Survival analysis was performed using the Kaplan-Meier method. All statistical analyses were performed using Stata statistical package version 14 (StataCorp LLC).

Ethical Considerations

The Institutional Review Board of the Hospital Clinic of Barcelona approved the implementation of this study (ERB number HCB/2018/0538). The study's retrospective nature waived the requirement for informed written consent. Patient identification was encoded, complying with the needs of the Organic Law on Data Protection 15/1999.

RESULTS

Epidemiological, Clinical, and Prognosis Changes Between 1981–2000 and 2001–2020

One hundred thirty-eight CIED-IE episodes were included in the study. We compared them according to 2 periods (1981–2000 versus 2001–2020) and between the last 2 decades (2001–2010 versus 2011–2020). The characteristics of the 4 groups are depicted in Table 1.

The first (1981–2000) and the second (2001–2020) periods included 25 (18%) and 113 (82%) CIED-IEs, respectively. In the recent period, age (median, 63 years [IQR, 53–70] vs 71 [IQR, 63–76]; $P < .01$), comorbidities (median CCI score, 3.0 [IQR, 2–4] vs 4.5 [IQR, 3–6]; $P < .01$), nosocomial acquisition (4% vs 16%; $P = .02$), and referral from other centers (8% vs 41.6%; $P < .01$) were significantly more frequent. The performance of ^{18}F FDG-PET/CT was described only for the second period, as it was only introduced in 2014; 29 patients underwent ^{18}F FDG-PET/CT to complement the diagnostic approach, with 24 receiving positive results (82.8%). Specifically, 16 of 24 (66.7%) had a positive ^{18}F FDG-PET/CT at the pocket \pm subcutaneous, 11 of 16 (68.75%) had a pocket and subcutaneous pathological uptake, and only (33.3%) showed endovascular involvement. Although in the second period there was a trend toward more patients on oral antibiotic suppression therapy (4% vs 10.6%; $P = .18$), there were fewer, but not significantly so, complete removals of device systems (96% vs 87.6%; $P = .09$) and no differences in the rates of in-hospital mortality (20% vs 11.5%; $P = .11$) or relapse (8% vs 5.3%; $P = .65$) between the 2 periods. In the recent period, complex infections due to methicillin-resistant CoNS (0 vs 13.3%; $P < .01$) and

Table 1. Comparison of Demographics, Baseline Comorbidities, Type of Infection, Echocardiographic Findings, Microbiology, and Outcome of Cardiac Implantable Electronic Device Infective Endocarditis Cases According to Both Periods (1981–2000 vs 2001–2020) and the Last 2 Decades (2001–2010 vs 2011–2020)

Variable	Total (N = 138)	1981–2000 (n = 25)	2001–2020 (n = 113)	P Value	2001–2010 (n = 56)	2011–2020 (n = 57)	P Value
Age, y, median (IQR)	70 (60–76)	63 (53–71)	71 (63–76)	<.01	69.5 (61–76)	73.0 (64–78)	.15
Male sex	116 (84.1)	20 (80)	96 (85)	.57	45 (80.4)	51 (89.5)	.18
Fever	94 (68.1)	19 (76)	75 (66.4)	.32	44 (78.6)	31 (54.4)	<.01
Concomitant pocket infection	55 (39.9)	9 (36)	46 (40.7)	.66	46 (46.4)	20 (35.1)	.22
Place of acquisition							
Community	80 (58)	18 (72)	62 (54.9)	.09	32 (57.1)	30 (52.6)	.63
Nosocomial	19 (13.8)	1 (4)	18 (15.9)	.02	9 (16.1)	9 (15.8)	.96
Healthcare-associated infection	39 (28.2)	6 (24)	33 (29.2)	.59	15 (26.8)	18 (31.6)	.58
Transferred from other hospital	49 (35.5)	2 (8)	47 (41.6)	<.01	21 (37.5)	26 (45.6)	.38
Type of cardiac device							
PPM	114 (82.6)	23 (92)	91 (80.5)	.08	47 (83.9)	44 (77.2)	.36
ICD	23 (16.7)	2 (8)	21 (18.6)	.11	9 (16.1)	12 (21)	.49
CRT	1 (0.7)	0	1 (0.9)	.32	0	1 (1.8)	.32
Type of CIED-IE							
Early (<1 y)	39 (28.3)	11 (44)	28 (24.8)	.07	13 (23.2)	15 (26.3)	.71
Late (>1 y)	99 (71.7)	14 (56)	85 (75.2)	.07	43 (76.8)	42 (73.7)	.71
CIED-IE only	89 (64.5%)	18 (72)	71 (62.8)	.36	40 (71.4)	31 (54.4)	.06
CIED-IE + valve infection	49 (35.5)	7 (28)	42 (37.2)	.36	16 (28.6)	26 (45.6)	.06
Comorbidities							
CCI score, median (IQR)	4.0 (3.0–6.0)	3.0 (2.0–4.0)	4.5 (3.0–6.0)	<.01	4 (3.0–5.0)	5 (4.0–6.5)	<.01
Diabetes mellitus	46 (33.3)	5 (20)	41 (36.3)	.08	16 (28.6)	25 (43.9)	.08
Chronic kidney disease	19 (13.8)	1 (4)	18 (15.9)	.02	5 (8.9)	13 (22.8)	.04
Coronary heart disease	43 (31.2)	8 (32)	35 (31)	.92	15 (26.8)	20 (35.1)	.34
Previous heart failure	29 (21)	4 (16)	25 (22.1)	.46	11 (19.6)	14 (24.6)	.53
Echocardiography							
Vegetation on device	138 (100)	25 (100)	113 (100)	NA	56 (100)	57 (100)	NA
Tricuspid valve vegetation	31 (22.5)	7 (28)	24 (21.2)	.49	8 (14.3)	16 (28.1)	.07
Other	16 (11.6)	0	16 (14.2)	.32	8 (14.3)	8 (14.1)	.25
Valve vegetation size, mm, median (IQR)	10 (7–20)	16.5 (9–28)	10 (7–19)	.15	10.0 (7.0–20.0)	10 (7–18.0)	.78
¹⁸ F-DG-PET/CT	29 (21)	0	29 (25.7)	<.01	2 (3.6)	27 (47.4)	<.01
Positive ¹⁸ F-DG-PET/CT result	24/29 (82.8)	0	24/29 (82.8)	NA	1 (50)	23 (85.2)	.34
Microbiology							
Positive pocket/lead cultures	55 (39.9)	9 (36)	46 (40.7)	.66	46 (46.4)	20 (35.1)	.22
Positive blood cultures	138 (100)	25 (100)	113 (100)	1	56 (100)	57 (100)	NA
Lead 16S rRNA PCR	30 (21.7)	0	30 (26.5)	<.01	4 (7.1)	26 (45.6)	<.01
Lead-positive 16S rRNA PCR result	17/30 (56.7)	0	17/30 (56.7)	NA	2 (50)	15 (57.7)	.77
<i>Staphylococcus aureus</i>	46 (33.3)	7 (28)	39 (34.5)	.52	17 (30.4)	22 (38.6)	.36
Methicillin resistant	13 (9.4)	1 (4)	12 (10.6)	.18	7 (12.5)	5 (8.8)	.52
Coagulase-negative staphylococci	62 (44.9)	12 (48)	50 (44.2)	.32	28 (50)	22 (38.6)	.22
Methicillin resistant	15 (10.9)	0	15 (13.3)	<.01	8 (14.3)	7 (12.3)	.75
<i>Enterococcus</i> spp	6 (4.3)	0	6 (5.3)	.01	2 (3.6)	4 (7)	.41
Viridans group streptococci	1 (0.7)	0	1 (0.9)	.15	1 (1.8)	0	.32
Gram-negative bacilli	10 (7.2)	3 (12)	7 (6.2)	.41	3 (5.3)	4 (7)	.71
Polymicrobial	7 (5.2)	3 (12)	4 (3.5)	.21	2 (3.6)	2 (3.5)	.98
Others	6 (4.4)	0	6 (5.4)	.08	3 (5.3)	3 (5.3)	.55
Complications	75 (54.3)	7 (28)	68 (60.2)	<.01	26 (46.4)	42 (73.7)	<.01
Pulmonary embolism	12 (8.7)	0	12 (10.6)	<.01	1 (1.8)	11 (19.3)	<.01
Sepsis/shock	15 (10.9)	1 (4)	14 (12.4)	.09	3 (5.4)	11 (19.3)	.02
Treatment							
Removal of cardiac device system	123 (89.1)	24 (96)	99 (87.6)	.35	54 (96.4)	45 (78.9)	<.01
Interval from diagnosis to removal, d, median (IQR)	29.0 (20.0–42.0)	21.5 (18–46)	29.5 (23.0–42.0)		18.5 (12.5–25)	14.0 (10.0–19.5)	.18
Type of removal							
Traction	95 (77.2)	19 (79.2)	76 (76.8)	.79	40 (74.1)	36 (80)	.45
Open surgery	28 (22.8)	5 (20.8)	23 (23.2)	.88	13 (24.1)	9 (20)	.31

Table 1. Continued

Variable	Total (N = 138)	1981–2000 (n = 25)	2001–2020 (n = 113)	P Value	2001–2010 (n = 56)	2011–2020 (n = 57)	P Value
Reimplantation	84 (68.3)	16 (66.7)	68 (68.7)	.85	40 (74.1)	28 (62.2)	.17
Oral antibiotic suppression therapy in patient w/o complete removal	13 (9.4)	1 (4)	12 (10.6)	.18	2 (3.6)	10 (17.5)	.01
In-hospital mortality	18 (13)	5 (20)	13 (11.5)	.32	5 (8.9)	8 (14)	.39
1-y follow-up							
Surgery	8 (5.8)	3 (12)	5 (4.4)	.26	0	5 (8.8)	.02
Mortality	23 (16.7)	6 (24)	17 (15)	.33	7 (12.5)	10 (17.5)	.45
Relapse	8 (5.8)	2 (8)	6 (5.3)	.65	0	6 (10.5)	.01

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ¹⁸F-DG-PET/CT, 18F-fluorodeoxyglucose positron emission tomography/computed tomography; CCI, Charlson Comorbidity Index; CIED-ID, cardiac implantable electronic device infective endocarditis; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; NA, not applicable; PCR, polymerase chain reaction; PPM, pacemaker; rRNA, ribosomal RNA.

Enterococcus spp (0 vs 5.3%; $P = .01$) were more frequent, as were complications, for example, pulmonary embolism (0 vs 10.6%; $P < .01$) and HF (12% vs 28.3%; $P < .01$). Figure 1A summarizes the proportion of CIED-IE compared with overall IE episodes over the 4 decades. Figure 1B compares changes in the proportion of CIED-IE episodes according to the type of device (PPM and ICD/CRT). Between the 2 defined periods, the cumulative number of CIED-IE episodes was 4.5-fold higher in the second period (25 vs 113 cases), especially in ICD (2 vs 21 cases).

Focusing on the comparison of the last 2 decades (2001–2010 vs 2011–2020), in the most recent period, there was a tendency for greater age (median, 73 years [IQR, 64–78] vs 69 years [IQR, 61–76]; $P = .15$) and significantly more comorbidities (median CCI score, 5 [IQR, 4–6.5] vs 4 [IQR, 3–5]; $P < .01$) and CRT (22.8% vs 8.9%; $P = .04$). Diagnostic tests—for example,

¹⁸F-DG-PET/CT (47.4% vs 3.6%; $P < .01$) and molecular biology (45.6% vs 7.1%; $P < .01$)—were statistically more frequent in the most recent decade. In the 2011–2020 period, patients were less likely to undergo device removal (78.9% vs 96.4%; $P < .01$), so there were more patients on oral chronic suppression therapy (17.5% vs 3.6%; $P = .01$). Complicated CIED-IE cases were more frequent in the 2011–2020 period (73.7% vs 46.4%; $P < .01$). However, in terms of in-hospital and 1-year mortality, there were no differences between periods (14% vs 8.9%, $P = .39$ and 17.5% vs 12.5%, $P = .45$, respectively) although significantly more patients had relapses (10.5% vs 0%; $P = .01$) and underwent late surgery (8.8% vs 0%; $P = .02$) in the latter period.

Comparison Between CoNS and Non-CoNS CIED-IE

Of the overall cohort, 62 episodes were due to CoNS and 76 due to other microorganisms (Table 2). CIED-IE due to CoNS had

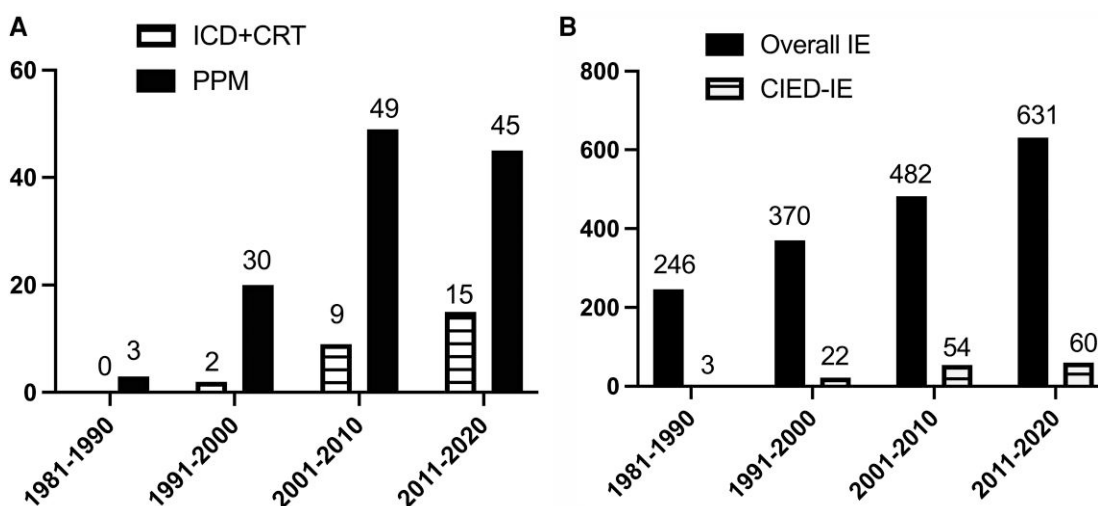


Figure 1. A, Evolution of cardiac implantable electronic device infective endocarditis (CIED-IE) incidence according to device type: pacemaker (PPM), implantable cardioverter-defibrillator (ICD), and cardiac resynchronization therapy (CRT) over 4 decades. B, Evolution of CIED-IE incidence compared to overall types of infective endocarditis (IE) over 4 decades.

significantly more concomitant pocket infections (50% vs 31.6%; $P=.03$) and fewer comorbidities (median CCI score, 4.0 [IQR, 2.0–5.0] vs 5.0 [IQR, 4.0–7.0]; $P<.01$). Patients with CoNS CIED-IE had a larger valve vegetation size (18.0 mm vs 9.0 mm; $P<.01$) and were significantly more likely to undergo removal of the cardiac device system (96.8% vs 82.9%; $P<.01$); consequently, there were significantly more reimplants (76.76% vs 60.3%; $P=.04$). Oral antibiotic suppression therapy in patients without removal of the cardiac device system was significantly higher in CoNS CIED-IE than in the other etiologies (14.5% vs 3.2%; $P=.01$).

Comparison of CIED-IE According to the Timing Diagnosis, Type of Device, and Vegetation Involvement

Considering the timing of diagnosis, early CIED-IE had tended toward local signs of infection predominancy (51.3% vs 35.4%; $P=.09$); meanwhile, fever was significantly the typical clinical manifestation of late-presenting CIED-IE (73.7% vs 53.8%; $P=.03$). Community-acquired (64.6% vs 41%; $P=.01$) and polymicrobial infections (7.1% vs 0%; $P<.01$) were significantly more frequent in late CIED-IE, as was the presence of vegetations in any valve (see summarized data in [Supplementary Table 1](#)). Thus, peripheral embolisms were more prevalent in late CIED-IE (11.1 vs 2.6%; $P=.04$).

Regarding the type of device, PPM-IE represented 114 episodes from 138 (82.6%), whereas 24 episodes were on ICD/CRT-IE. PPM-IE patients were older (median age, 72 [IQR, 63–77] vs 62.5 [IQR, 54–68] years; $P<.01$), had significantly higher proportion of females (19.3% vs 4.2%; $P<.01$), and had more late IE (70.2% vs 41.7%; $P=.01$), as presented in [Table 3](#). PPM-IE episodes more frequently had mitral valve vegetation (7% vs 0, $P<.01$). There were no differences between PCM-IE and ICD/CRT-IE regarding device removal, reimplantation rate, antibiotic suppression therapy, relapses, and hospital or 1-year mortality.

Vegetation involvement is analyzed in [Supplementary Table 2](#). A comparison between CIED-IE with isolated lead vegetations, CIED-IE with tricuspid valve vegetations (right-side), and CIED-IE with left-side valve vegetations (with or without lead vegetations) was performed. CIED-IE with lead and left-side involvement was significantly found in older patients than others (median age 74.5 vs 67 vs 71 years; $P=.04$), with a tendency for more comorbidities and earlier infection (50% vs 9.7% and 30.3%; $P=.03$), whereas CIED-IE with only lead involvement had more concomitant pocket infection (50.6% vs 22.6% and 16.7%; $P=.02$). CIED-IE with left-side and right-side valve involvement presented more complications (77.8% and 74.2% vs 42.7%; $P=.04$), for example, HF and central nervous system embolism, and was more likely to result in open surgery for device removal (66.7% vs 26% vs 12.8%; $P<.01$). There were no differences between in-hospital and 1-year mortality ([Figure 2C](#)), 1-year surgery, or relapses among the 3 groups.

Predictors of 1-Year Mortality

From the overall cohort, 112 CIED-IE patients were alive and 23 died (16.7%) at 1 year of follow-up. [Supplementary Table 3](#) compares the main differences between patients who were alive or had died at 1 year. Survivors had more concomitant pocket infections (43.8% vs 21.7%; $P=.03$), were more likely to have been transferred (39.3% vs 17.4%; $P=.01$), had fewer comorbidities (CCI score, 4.0 vs 5.0; $P<.019$), were more likely to have polymicrobial infections (6.3% vs 0; $P<.01$) and removal of cardiac device systems (93.8% vs 69.6%; $P=.01$). Conversely, complications (49.1% vs 82.6%; $P<.01$) such as HF (17.9% vs 65.2%; $P<.01$) and septic shock (4.5% vs 43.5%; $P<.01$) were more frequent in patients who had died at 1 year. [Figure 2](#) shows the Kaplan-Meier survival curve for 1-year mortality in the overall cohort of patients with CIED-IE ([Figure 2A](#)) and the comparison of survival curves between the 2 studied periods (1981–2000 vs 2001–2020) ([Figure 2B](#)), among the 3 groups of valve vegetations ([Figure 2C](#)), and in patients with and without device removal ([Figure 2D](#)).

Results of the 1-year survival multivariate analysis are shown in [Table 4](#). CCI (HR, 1.44 [95% CI, 1.11–1.88]) and septic shock (HR, 13.12 [95% CI, 2.16–79.47]) were associated with a worse prognosis, whereas device removal (HR, 0.14 [95% CI, .02–.76]), being transferred from another center (HR, 0.13 [95% CI, .02–.95]), and a 2001–2020 period diagnosis (HR, 0.13 [95% CI, .02–.71]) were associated with lower 1-year mortality.

DISCUSSION

This is the largest historical cohort focused on CIED-IE over 40 years of study and managed by a single IE team in a referral center. As our IE team was created in 1985, all cases have been evaluated with uniform diagnostic and medical and surgical management criteria [11]. Several works have tried to define the epidemiological profile of CIED infections in recent years. For example, Dai et al [5] described another large cohort of CIED infections from the last 3 decades; however, they included overall CIED infections and did not incorporate the assessment of an IE team. All recent studies did factor in rising device implantation rates, likely related to a significant increase in PPM indication and lifetime use, more elderly patients, and higher ICD implantation, for sudden death prevention [5, 12–16]. Our study has also demonstrated fundamental changes in the epidemiology: an increase in median age, more comorbidities, and new types of CIED. We also reported new diagnostic techniques and greater resistance to antimicrobials in isolated pathogens. Despite all of these changes, in-hospital mortality did not significantly increase (20% during 1981–2000 vs 11.5% during 2001–2020, and 8.9% during 2001–2010 vs 14% during 2011–2020), and neither did 1-year mortality (24% during 1981–2000 vs 15% during 2001–2020; and 12.5% during 2001–2010

Table 2. Comparison Between Coagulase-Negative Staphylococcal (CoNS) Cardiac Implantable Electronic Device Infective Endocarditis (CIED-IE) and Non-CoNS CIED-IE^a

Variable	CoNS CIED-IE (n = 62)	Non-CoNS CIED-IE ^b (n = 76)	P Value
Age, y, median (IQR)	69.0 (60.0–76.0)	71.0 (59.5–75.5)	.85
Male sex	53 (85.5)	63 (82.9)	.68
Fever	42 (67.7)	54 (68.4)	.93
Concomitant pocket infection	31 (50)	24 (31.6)	.03
Interval from implant to exchange, d, median (IQR), diagnosis <60 d	1815 (353–3947)	769 (208.5–2759)	.07
Study period			
1981–2000	12 (19.4)	13 (17.1)	.74
2001–2020	50 (80.6)	63 (82.9)	.74
Place of acquisition			
Community	39 (62.9)	41 (53.9)	.29
Nosocomial	6 (9.7)	13 (17.1)	.20
Healthcare-associated infection	17 (27.4)	22 (28.9)	.84
Transferred from other hospital	17 (27.4)	32 (42.1)	.07
Type of cardiac device			
PPM	55 (88.7)	59 (77.6)	.08
ICD	7 (11.3)	16 (21.1)	.12
CRT	0	1 (1.3)	.32
Type of CIED-IE			
Early (<1 y)	16 (25.8)	23 (30.3)	.56
Late (>1 y)	46 (74.2)	53 (69.7)	.56
CIED-IE only	41 (66.1)	48 (63.2)	.72
CIED-IE + valve infection	21 (33.9)	28 (36.8)	.72
Comorbidities			
CCI score, median (IQR)	4.0 (2.0–5.0)	5.0 (4.0–7.0)	<.01
Diabetes mellitus	15 (24.2)	31 (40.8)	.04
Chronic kidney disease	4 (6.5)	15 (19.7)	.02
Coronary heart disease	15 (24.2)	28 (36.8)	.11
Previous heart failure	7 (11.3)	22 (28.9)	<.01
Echocardiography			
Vegetation on device	62 (100)	76 (100)	NA
Tricuspid valve vegetation	15 (24.4)	16 (21.1)	.66
Other	5 (8.1)	10 (13.2)	.08
Valve vegetation size, mm, median (IQR)	18.0 (8.0–25.0)	9.0 (7.0–14.0)	<.01
¹⁸ FDG-PET/CT	14 (22.6)	15 (19.7)	.69
Positive ¹⁸ FDG-PET/CT result	12/14 (85.7)	12/15 (80)	.69
Positive blood cultures or lead/valve culture	62 (100)	76 (100)	NA
16S rRNA PCR	13 (21)	17 (22.4)	.12
Positive 16S rRNA PCR result	8/13 (61.5)	9/17 (52.9)	.64
Complications	34 (54.8)	41 (53.9)	.92
Pulmonary embolism	4 (6.5)	8 (10.5)	.38
Heart failure	11 (17.7)	24 (31.6)	.05
Sepsis/shock	4 (6.5)	11 (14.5)	.12
Persistent bacteremia	1 (1.6)	2 (2.6)	.68
Treatment			
Removal of cardiac device system	60 (96.8)	63 (82.9)	<.01
Type of removal			
Traction	43 (71.7)	52 (82.5)	.13

Table 2. Continued

Variable	CoNS CIED-IE (n = 62)	Non-CoNS CIED-IE ^b (n = 76)	P Value
Open surgery	17 (28.3)	2 (17.5)	.08
Reimplantation	46 (76.7)	38 (60.3)	.04
Interval from removal to reimplantation, d, median (IQR)	14.0 (11.0–20.0)	17.0 (11.0–23.0)	.55
Oral antibiotic suppression therapy	2/62 (3.2)	11/76 (14.5)	.01
Oral antibiotic suppression therapy in patients without complete removal	2/2 (100)	11/13 (84.6)	.87
In-hospital mortality	6 (9.7)	12 (15.8)	.28
1-y follow-up			
Surgery	3 (4.8)	5 (6.6)	.66
Mortality	7 (11.3)	16 (21.1)	.66
Relapse	3 (4.8)	5 (6.6)	.12

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ¹⁸FDG-PET/CT, ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography; CCI, Charlson Comorbidity Index; CIED-ID, cardiac implantable electronic device infective endocarditis; CoNS, coagulase-negative staphylococci; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; NA, not applicable; PCR, polymerase chain reaction; PPM, pacemaker; rRNA, ribosomal RNA.

^aThere were 108 staphylococcal CIED-IE: 62 episodes were due to CoNS, and 46 episodes were due to *Staphylococcus aureus*. Other microorganisms caused the remaining 30 CIED-IE with the following distribution: 6 *Enterococcus* spp, 1 viridans group streptococci, 10 gram-negative bacilli, and 7 polymicrobial CIED-IE.

^bPatients from the “non-CoNS group” received oral suppression at a rate of 14.5% of the overall subgroup, representing 84.6% of patients without complete device removal. The microbiological distribution of the 13 “non-CoNS group” CIED-IE cases without complete device removal were: 10 (76.9%) *S aureus*, 1 (7.7%) *Escherichia coli*, 1 (7.7%) *Propionibacterium acnes*, and 1 (7.7%) *Enterococcus faecalis*.

vs 17.4% during 2011–2020). However, the proportion of patients with unremovable CIEDs has notably increased over time (4% vs 12.4%; $P = .09$), mainly in the last decade (21.1%; $P < .01$) due to the population aging and the increase of comorbid conditions and complexity of devices. The cause of the higher number of infections, despite a decrease in overall device-related complications, is not clear [14, 17, 18]. One possibility is the accumulative numbers of ICDs and CRT, whose longevity is lower than PPMs, requiring more complex procedures and battery exchanges, which are strongly associated with risk of infection [13]. TEE plays an essential role in the diagnosis of CIED-IE when it is suspected in patients. However, it may prove challenging to differentiate vegetations from lead strands or small-adhered thrombi. George et al [8] described a case-control retrospective observational study showing how TEE could not distinguish the general characteristics of vegetations obtained from blinded TEE reports unless there was knowledge of clinical and microbiological parameters. In our cohort, incorporating ¹⁸FDG-PET/CT and molecular biology had a significant impact in the second period, having a sensitivity of 82.8% and 52.7%, respectively. However, this study was not designed to evaluate the diagnostic yield of these methods.

Table 3. Comparison of Cardiac Implantable Electronic Device Infective Endocarditis Cases According to the Type of Device System: Pacemaker or Implantable Defibrillator Device Plus Cardiac Resynchronization Therapy

Variable	PCM (n = 114)	ICD + CRT (n = 24)	P Value
Age, y, median (IQR)	72 (63–77)	62.5 (54–68)	<.01
Male sex	92 (80.7)	23 (95.8)	<.01
Fever	78 (68.4)	16 (66.7)	.87
Concomitant pocket infection	43 (37.7)	XX (50)	.27
Interval from implant to exchange, d, median (IQR), diagnosis <60 d	1007 (233–3138)	1888 (510–3188)	.34
Study period			
1981–2000	23 (20.2)	2 (8.3)	.17
2001–2020	91 (79.8)	22 (91.7)	
Place of acquisition			
Community	64 (56.1)	16 (66.7)	.33
Nosocomial	17 (14.9)	2 (8.3)	.32
Healthcare-associated infection	33 (29)	6 (25)	.69
Transferred from other hospital	38 (33.3)	11 (45.8)	.26
Type of cardiac device			
PPM	114 (100)	0	NA
ICD	0	23 (95.8)	NA
CRT	0	1 (4.2)	NA
Type of CIED-IE			
Early (<1 y)	34 (29.8)	5 (20.8)	.34
Late (>1 y)	80 (70.2)	10 (41.7)	.01
CIED-IE only	73 (63)	16 (66.7)	.81
CIED-IE + valve infection	41 (36)	8 (33.3)	.81
Comorbidities			
CCI score, median (IQR)	4.0 (3.0–6.0)	4.0 (2.0–5.5)	.49
Diabetes mellitus	33 (29)	13 (54.2)	.02
Chronic kidney disease	15 (13.2)	4 (16.7)	.67
Coronary heart disease	31 (27.2)	12 (50)	.04
Previous heart failure	18 (15.8)	11 (45.8)	
Echocardiography			
Vegetation on device	114 (100)	24 (100)	NA
Tricuspid valve vegetation	24 (21.1)	7 (29.2)	.42
Other	14 (12.3)	1 (4.2)	.81
Valve vegetation size, mm, median (IQR)	10.0 (8.0–20.0)	9.5 (7.0–19.0)	.21
¹⁸ F-DG-PET/CT	21 (84)	3 (75)	.69
Microbiology			
Positive blood cultures or lead/valve culture	114 (100)	24 (100)	NA
16S rRNA PCR	26 (22.8)	4 (16.7)	.48
Positive 16S rRNA PCR result	16 (61.5)	1 (25)	.13
<i>Staphylococcus aureus</i>	35 (30.7)	11 (45.8)	.17
Methicillin-resistant	10 (8.8)	3 (12.5)	.61
Coagulase-negative staphylococci	55 (48.2)	7 (29.3)	.07
Methicillin-resistant	13 (11.4)	2 (8.3)	.63
<i>Enterococcus</i> spp	4 (3.5)	2 (8.3)	.42
Viridans group streptococci	1 (0.9)	0	.32
Gram-negative bacillus	8 (7)	2 (8.3)	.83
Polymicrobial	5 (4.4)	2 (8.3)	.51

Table 3. Continued

Variable	PCM (n = 114)	ICD + CRT (n = 24)	P Value
Others	6 (5.3)	0	.08
Complications	58 (50.9)	17 (70.8)	.06
Pulmonary embolism	9 (7.9)	3 (12.5)	.52
Heart failure	25 (21.9)	10 (41.7)	.07
Sepsis/shock	13 (11.4)	2 (8.3)	.63
Persistent bacteremia	3 (2.6)	0	.08
Treatment			
Removal of cardiac device system	78 (77.2)	17 (77.3)	.99
Type of removal			
Traction	78 (77.2)	17 (77.3)	.99
Open surgery	23 (22.8)	4 (18.2)	.60
Reimplantation	67 (66.3)	17 (77.3)	.26
Interval from removal to reimplantation, d, median (IQR)	14 (10–21)	20 (15–28)	.34
Antibiotic suppression oral therapy in patients without complete removal	11 (9.6)	2 (8.3)	.83
In-hospital mortality	16 (14)	2 (8.3)	.38
1-y follow-up			
Surgery	6 (5.3)	2 (8.3)	.61
Mortality	19 (16.7)	4 (16.7)	1
Relapse	6 (5.3)	2 (8.3)	.61

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ¹⁸F-DG-PET/CT, ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography; CCI, Charlson Comorbidity Index; CIED-IE, cardiac implantable electronic device infective endocarditis; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; PCR, polymerase chain reaction; PPM, pacemaker; rRNA, ribosomal RNA.

Our analysis revealed a 4.5-fold increase in ICD/CRT-IE compared with PPM-IE when analyzing the cases from the 2 different periods. In the second period, the demographic and clinical characteristics of PPM-IE<.01 compared with those of ICD/CRT-IE were entirely different. Patients who received ICD/CRT were younger, predominantly male, and had more ischemic cardiomyopathy, diabetes, and HF. Greenspon et al [13] showed the nonvariation of the 4 significant comorbidities (renal failure, respiratory failure, HF, and diabetes) over almost the 2 last decades, but, similarly, there was a substantial increase in infection rate, mostly in ICDs (ICDs represented 35% of all devices, and CIED infection rates reported increased by 2.1% to 2.41% in 2008; $P < .001$).

The etiology of CIED-IE was characterized by a predominance of staphylococcal infections, as is reported in our cohort, and fairly described by other investigators [5, 6, 14, 17–20]. However, interestingly, we identified an increase of *Enterococcus* spp infections in the second period, probably due to aging and more frequent comorbidities. In their study of the MEDIC cohort, Oh et al [21] conducted a descriptive analysis and reported 4.8% of enterococcal CIED infections from the whole database of 433 patients. Although they found

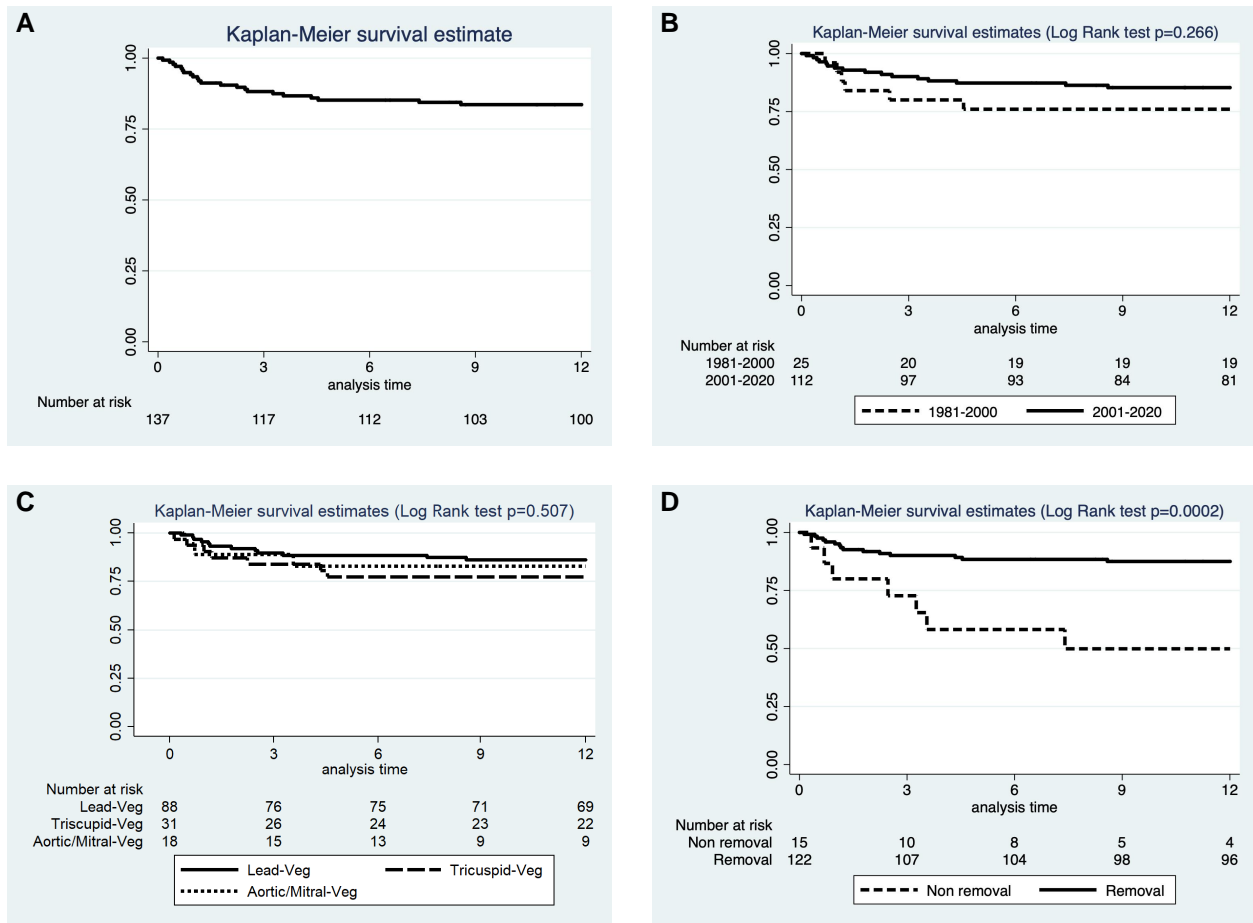


Figure 2. A, Kaplan-Meier survival curve for 1-year mortality in patients with cardiac implantable electronic device infective endocarditis (CIED-IE). B, Comparison of Kaplan-Meier survival curve for 1-year mortality according to the 2 periods (1981–2000 vs 2001–2020). C, Comparison of Kaplan-Meier survival curves for 1-year mortality according to the 3 groups: CIED-IE with isolated lead involvement, tricuspid valve involvement, and left-side valve involvement; D, Kaplan-Meier survival curve for 1-year mortality comparing device removal and non-device removal.

no significant increase in enterococcal CIED infections over time, we did find a significant increase (up to 5.3%) in the second period of our study ($P = .01$). However, both studies consistently reported the profile of an elderly (median age, 70 years) combined with multiple underlying comorbidities (median CCI score, 6) and late infections. In our cohort, CoNS were the primary cause of CIED-IE, and methicillin resistance was expanding, in line with numerous medical reports [22], as were the CoNS factors of virulence and their presence in infections related to medical devices [23].

The medical and surgical approach has not changed between the 2 periods, and removing the entire device is mandatory [24, 25]. In the second period, the population was overall older and presented more frequent comorbidities; the proportion of non-removal of the devices also increased, but mortality did not. The number of patients receiving antibiotic suppression therapy also increased. Other authors have also reported the

increasing use of suppression therapy to manage CIED-IE when device removal is not possible [26, 27].

Since CIED-IE has low in-hospital mortality rates when compared to left-sided IE, we have calculated variables associated with survival at 1 year, given the greater perspective on the global management of these patients obtained over that length of time [28]. We identified CCI as an independent prognostic factor for 1-year mortality, as has been observed by other authors over the years [14]. In our analysis, we excluded age, chronic renal failure, and diabetes mellitus, because they are contained in CCI, although they are well-known risk factors for IE-related death [28, 29]. Septic shock was also associated with a worse prognosis, as has been broadly reported in other studies [5, 14, 19]. Our study identifies patient transfer from community centers as an independent protective factor. It was also more frequent in the second period. This finding may be explained by the tendency to transfer patients with

Table 4. Univariate and Multivariate Analysis for Predictors of 1-Year Mortality

Variable	Univariate			Multivariate		
	OR	(95% CI)	P Value	OR	(95% CI)	P Value
Male sex	0.85	(.26–2.81)	.70
CCI score	1.30	(1.09–1.54)	<.01	1.50	(1.16–1.94)	<.01
2001–2020 vs 1981–2000	0.57	(.20–1.66)	.31	0.15	(.02–.77)	.01
Late vs early CIED-IE	0.68	(.26–1.77)	.43
Community-acquired CIED-IE	0.59	(.24–1.46)	.25
PPM vs ICD/CRT	1.03	(.32–3.36)	.95
Transferred from another hospital	0.32	(.10–1.02)	.05	0.13	(.01–.94)	.04
CoNS CIED-IE	0.47	(.18–1.23)	.12
Septic shock	16.0	(4.73–54.11)	<.01	23.09	(4.57–116.67)	<.01
Heart failure	8.53	(3.18–22.84)	<.01
Device removal	0.15	(.005–.49)	<.01	0.11	(.02–.57)	.01

Abbreviations: CCI, Charlson Comorbidity Index; CI, confidence interval; CIED-ID, cardiac implantable electronic device infective endocarditis; CoNS, coagulase-negative staphylococci; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; OR, odds ratio; PPM, pacemaker.

better prognoses and fewer comorbidities for device removal [28, 30]. Complete device removal is the most important protective factor as has been shown in many studies [14, 24]. Finally, despite aging and greater patient complexity, the latter period was associated as a protective factor. This may be explained by improvements in diagnosis and medical and surgical management. Indeed, more accurate microbiological diagnosis using molecular techniques (eg, 16S rRNA PCR) [31, 32], and imaging diagnosis (eg, ¹⁸FDG-PET/CT) [32], in addition to improved surgical removal techniques, may support these results.

Our study has several limitations. The first stems from the retrospective design. Nevertheless, the prospective homogenous diagnostic and therapeutic management provided by an IE team assessing the cases over 4 decades has allowed us to overcome this issue. Second, a selection bias might have partially influenced our temporal perspective of the profile of CIED-IE cases, because we are a referral center for cardiovascular surgery, and the characteristics of episodes managed at community noncardiac surgery centers are lacking. Third, although we included a large population-based cohort with long-term follow-up, this is a single-center study. A multicenter study may be more appropriate for obtaining a better population sample and render the study more broadly applicable. However, studies of this nature are unfeasible, because few sites maintain databases including patients over such long periods. Fourth, we were unable to accomplish the degrees of tricuspid valvular regurgitation in all CIED-IE episodes, and we did not record the notations of functional device failure-to-capture during CIED-IE episodes in our analysis. Finally, we randomly selected the 2 comparison periods considering the division by decades, and these small sample-sized subgroups might have hindered some statistical comparisons, so our findings should therefore be interpreted carefully.

In conclusion, CIED-IE episodes have increased >4-fold over the last 40 years and more frequently presented infections caused by methicillin-resistant CoNS and *Enterococcus* spp. One-year

survival significantly has improved over the last 2 decades compared to the last 20 years of the 20th century, despite increasing age and comorbidities among patients, who also now present more complex infections. Further studies are needed to clarify the upcoming challenges in diagnosing and managing CIED-IE when device removal is precluded in a growing high-risk population.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. All authors contributed to the conception and design, acquisition of data, drafting of the article, critical revision, and final approval of the manuscript.

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

APPENDIX

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