UNIVERSITAT DE BARCELONA

Epidemiological and clinical changes, role of [18F] FDG-PET/CT in the diagnosis and management and new antibiotic treatments of cardiac implantable electronic device infections

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Epidemiological and clinical changes, role of [18F] FDG-PET/CT in the diagnosis and management and new antibiotic treatments of cardiac implantable electronic device infections

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Be not afraid of going slowly.

Be afraid of standing still.

Chinese Proverb

Les coses importants són les que no ho semblen

Mercè Rodoreda

Todo crecimiento está fuera de la zona de confort.

Tener éxito no consiste sino en ser un fracasado que nunca se da por vencido.

Charlas con mi padre antes de dormir

En honor al Dr. Enrique Hernández Ortega, Cardiólogo y humanista.

Mi padre, mi guía, mi ejemplo.

Y a la Dra. Alicia Conde Martel, Internista, investigadora, profesora y mi maestra:

A quien debo el aprendizaje de la esencia de ser médico.

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Glossary

[18F] FDG PET/CT	18F-fluorodeoxyglucose positron emission tomography / computed tomography
AHA	American heart association.
CVIs	Cardiovascular infections
CAS	Chronic oral suppression
CIED	Cardiac implantable electronic device
CI	Confidence interval
CRT	Cardiac resynchronization therapy
CoNS	Coagulase-negative Staphylococci
CT	Computerized tomography
CTL	Ceftaroline
DAP	Daptomycin
EHR	Electronic health records
EHRA	European Hearth Rhythm Association
ESBL	Extended-spectrum beta-lactamase
GI	Gastrointestinal
GNB	Gram-negative bacilli
GPC	Gram-positive cocci
GU	Genito-urinary
ICD	Implantable cardioverter defibrillator
ICE	Intracardiac echocardiography
ICU	Intensive care unit
IE	Infective endocarditis
IQR	Interquartile range
IVDU	Intravenous drug user
LI	Local infections
MDR	Multidrug-resistant

MIC	Minimum inhibitory concentrations
MSSA	Methicillin sensitive *Staphylococcus aureus*
MSSE	Methicillin sensitive *Staphylococcus epidermidis*
MRSA	Methicillin resistant *Staphylococcus aureus*
MRSE	Methicillin resistant *Staphylococcus epidermidis*
PPM	Pacemaker
PVE	Prosthetic valve endocarditis
SD	Standard deviation
SI	Systemic infection
TEE	Transesophageal echocardiography
TTE	Transthoracic echocardiography
WBC	White blood cell

LIST OF ARTICLES IN THE THESIS

This doctoral thesis is based on the compendium of four hypotheses and objectives developed in the following five original articles published or submitted to indexed journals. This thesis also comprises two published and indexed reviews, two international-collaboration originals, and one published case report and systematic literature review.

ORIGINAL ARTICLES

1. **Epidemiological Changes and Improvement in Outcomes of Infective Endocarditis in Europe in the 21st Century**. Ambrosioni J*, Hernández-Meneses M*, Durante-Mangoni E, Tattevin P, Olaison L, Freiberger T, Hurley J, Hannan M.M, Chu V, Hoen B, Moreno A, Llopis J, Cuervo G, Miró JM., and International Collaboration for Endocarditis (ICE) investigators. Infect Dis Ther. 2023 Mar 15. doi: 10.1007/s40121-023-00763-8. Online ahead of print. PMID: 36922460.
   Infectious diseases and therapy, 2023. Impact factor 6.119 (2nd quartile). *These authors contributed equally.

2. **Forty-Year Trends in Cardiac Implantable Electronic Device Infective Endocarditis.** Hernández-Meneses M, Llopis J, Sandoval E, Ninot S, Almela M, Falces C, Pericàs JM, Vidal B, Perissinotti A, Marco F, Mestres CA, Paré C, García de la María C, Cuervo G, Quintana E, Tolosana JM, Moreno A, Miró JM; Hospital Clinic Infective Endocarditis Team Investigators. Open Forum Infect Dis. 2022 Oct 14;9(11): ofac547. doi: 10.1093/ofid/ofac547. PMID: 36381626; PMCID: PMC9648563.
   Open forum infectious diseases, 2022. Impact factor 4.423 (2nd quartile).

3. **Reappraisal of [18F] FDG-PET/CT for diagnosis and management of cardiac implantable electronic device infections.** Hernández-Meneses M*, Perissinotti A*, Páez-Martínez S, Llopis J, Dahl A, Sandoval E, Falces C, Ambrosioni J, Vidal B, Marco F, Cuervo G, Moreno A, Bosch J, Tolosana JM, Fuster D, Miró JM.
   Revista Española de Cardiologia, accepted 2023. Impact factor 7.05 (1st quartile). *These authors contributed equally.

4. **Prevalence, risk factors and impact of chronic antibiotic suppression in patients with cardiac implantable electronic device infective endocarditis without device removal.** Hernández-Meneses M, Llopis J, Sandoval E, Cuervo G, Ninot S, Fernández M, Falces C, Vidal B, Perissinotti A, Marco F, Garcia-de-la-Maria C, Quintana E, Tolosana JM, Moreno A, Miro JM. Submitted.

5. **Effectiveness of Daptomycin plus Ceftaroline in the treatment of methicillin-resistant and vancomycin resistant *Staphylococcus epidermidis* Experimental Endocarditis** C. García-de-la-Mària*, Marta Hernández-Meneses*, A. Cañas-Pacheco*, Guillermo Cuervo, J. García-González, J.M. Miró. Manuscript in preparation.

SPANISH THESIS SUMMARY

Título: Cambios epidemiológicos, clínicos, papel del [18F] FDG-PET/TC en el diagnóstico y manejo y nuevos tratamientos antibióticos de las infecciones de dispositivos de electroestimulación cardíaca

1. Introducción

En las últimas décadas se han producido avances en los dispositivos de electroestimulación cardiaca (DEC) con un incremento en el número de implantes y de DEC más sofisticados sobre una población diana más envejecida y con más comorbilidades lo que conlleva más tasas de infección y mayor morbimortalidad.

En esta tesis doctoral se pretenden analizar las nuevas características epidemiológicas, clínicas, diagnóstico por imagen (Tomografía por emisión de positrones con 18F Fluorodesoxiglucosa [18F FDG-PET/TC] y ecocardiografía transesofágica [ETE]), manejo de los DEC infectados que no se pueden retirar y nuevas estrategias de tratamiento antimicrobiano en el modelo de endocarditis experimental. Se ha estudiado en las últimas cuatro décadas en una sola institución (Hospital Clínic de Barcelona [HCB]) y se ha analizado también en el marco europeo, a través de la cohorte internacional de endocarditis (*International Collaboration on Endocarditis* [ICE]), prestando especial atención a su forma más grave, la endocarditis infecciosa (EI) sobre DEC.

2. Hipótesis

Hipótesis 1

Ha aumentado la prevalencia y cambiado el perfil en las EI en general y la EI sobre DEC, con un aumento de complejidad y disminución de la supervivencia.

Hipótesis 2

El [18]FDG-PET/TC tiene una sensibilidad y especificidad elevadas en las infecciones del bolsillo, que irá descendiendo en el resto segmentos del DEC. Combinado con la ETE, podrían diagnosticarse mejor las infecciones sistémicas, y la negativización del [18]FDG-PET/TC podría guiar la duración del tratamiento antibiótico supresivo (TAS) en los casos de no retirada de DEC.

Hipótesis 3

Ha aumentado la proporción de pacientes con infecciones del DEC sin retirada completa del mismo debido a factores dependientes del huésped más que de la complejidad del dispositivo. El TAS podría prevenir recidivas.

Hipótesis 4

La combinación de daptomicina más ceftarolina será sinérgica y bactericida *in vitro* e *in vivo* en las infecciones por *Staphylococcus epidermdis* resistente a la meticilina (MRSE) y vancomicina (VRSE).

3. Objetivos

Objetivo 1

Conocer los cambios de la EI en Europa durante el siglo XXI y analizar las posibles diferencias interregionales. Estudiar la evolución de la EI sobre DEC a lo largo de 40 años e identificar factores pronósticos de supervivencia al año.

Objetivo 2

Estudiar la rentabilidad diagnóstica del [18F]FDG-PET/TC en las cuatro regiones topográficas del DEC. Determinar su rendimiento en las infecciones sistémicas en combinación con TEE y si el hipermetabolismo del bazo/médula ósea distingue entre las infecciones locales y sistémicas. Determinar su utilidad para interrumpir de forma segura el TAS.

Objetivo 3

Conocer la prevalencia e identificar los factores de riesgo asociados a la no retirada completa del DEC. Evaluar la seguridad y eficacia del TAS.

Objetivo 4

Estudiar la actividad *in-vitro* e *in-vivo* de la combinación de daptomicina y ceftarolina frente a MRSE y VRSE.

4. Métodos por objetivos

El **objetivo 1** se abordó mediante dos estudios. El primero, del ICE, analizó 4.195 episodios consecutivos de EI con diagnóstico definitivo comparando su evolución en dos periodos de tiempo (2000-06 vs. 2008-12) y dos zonas geográficas (norte/centro vs. sur). En el segundo estudio comparó la evolución de 138 episodios consecutivos de EI sobre DEC con diagnóstico definitivo en el HCB en dos períodos de tiempo (1981-2000 vs. 2001-2020) e investigó los factores predictores de supervivencia al año.

El **objetivo 2** evaluó, mediante un estudio de casos (N=54) y controles (N=54), el rendimiento del [18F]FDG-PET/CT en los segmentos del DEC, su rendimiento diagnóstico combinado con el ETE para las infecciones sistémicas, el papel del hipermetabolismo del bazo/médula ósea y su utilidad para suspender el TAS en pacientes sin retirada del DEC.

El **objetivo 3** estudió la prevalencia y los factores predictores de no retirada del DEC.

El **objetivo 4** estudio la eficacia *in-vitro* de la combinación de daptomicina y ceftarolina mediante curvas de letalidad a inóculo estándar y elevado en cinco cepas MRSE y una VRSE e *in-vivo* mediante el modelo de endocarditis-experimental por MRSE y VRSE.

5. Resultados por objetivos

En el **primer artículo,** el segundo periodo se asoció con mayor edad, hemodiálisis, cáncer, diabetes-mellitus, cirugía cardiaca, EI protésica y de DEC. Las tasas de mortalidad entre regiones fueron comparables, mientras que en el periodo más reciente aumentó la cirugía cardíaca y mejoró la supervivencia.

El **segundo estudio** demostró que en el segundo periodo la EI sobre DEC fue 4,5 veces más frecuente y aumentaron: edad, comorbilidades, infecciones nosocomiales, traslados desde otros centros, MRSE y *Enterococcus faecalis*. Las tasas de cirugía y mortalidad fueron más bajas. El índice de Charlson y el shock séptico se asociaron con un peor pronóstico, mientras que la extracción del DEC, traslados y el segundo período mejoraron la supervivencia.

En el **tercer artículo**, el [18F]FDG-PET/CT mostró una especificidad del 100%, y sensibilidad del 79% bolsillo, 57% cable-subcutáneo, 22% cable-endovascular y 10% cable-intracardiaco. En las infecciones sistémicas, en combinación con ETE, aumentó el diagnóstico. Los casos con bacteriemia e infección sistémica tuvieron mayor hipermetabolismo en el bazo/médula ósea. En seis pacientes sin extracción completa de DEC un [18F]FDG-PET/TC de seguimiento negativo permitió suspender el TAS sin recaídas.

En el **cuarto artículo** la prevalencia de no retirada completa del DEC fue del 12 %, los factores de riesgo, la edad avanzada y *Staphylococcus aureus*. El TAS fue eficaz y seguro para la prevención de recidivas.

El **quinto trabajo** demostró que la combinación de daptomicina más ceftarolina tuvo una actividad bactericida potente, rápida y sinérgica *in-vitro* e *in-vivo*.

6. Conclusiones

El perfil epidemiológico, clínico y evolución de la EI en Europa ha cambiado en las dos primeras décadas del siglo XXI con un aumento de la edad y complejidad. La proporción de EI sobre DEC ha aumentado, así como el número de pacientes sin retirada completa del DEC. Sin embargo, la supervivencia al año ha mejorado. El [18F]-FDG-PET/CT presenta un rendimiento alto en infecciones locales de DEC, combinado con el TEE aumentó el diagnostico de infecciones sistémicas, y su negativización ayudó a guiar en la retirada del TAS. Finalmente, la combinación de daptomicina más ceftarolina fue muy activa *in vitro e in vivo* frente a MRSE y VRSE y estos resultados son la base para realizar estudios clínicos.

1. Introduction

Cardiovascular infections (CVIs) comprehend a broad spectrum of clinical syndromes sharing potential intracardiac and/or endovascular involvement, metastatic multi-organ dissemination, many complications, and life-threatening diseases with high morbid mortality rates [1].

Changes in infective endocarditis (IE) has been deeply studied and characterized over the years [2,3]. However, recent studies have suggested an increasing incidence of other CVSIs: cardiac implantable electronic device (CIED) infections, including the most severe clinical syndrome: cardiac electronic device infective endocarditis [4]; vascular graft infections (aortic or non-aortic graft infections); pericarditis, and myopericarditis (**figure 1**).

Abbreviations: PVE: prosthetic valve endocarditis; IVDU-IE: intravenous drug use related infective endocarditis; CIED IE: cardiac implantable electronic device infective endocarditis.

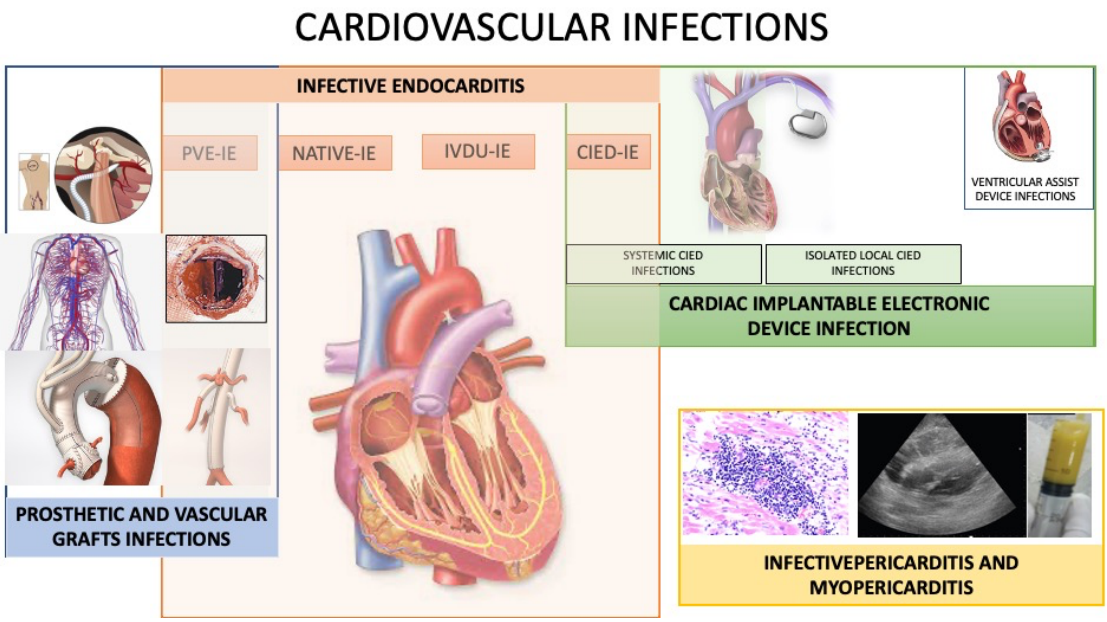


Figure 1. Types of cardiovascular infections: Infective endocarditis, prosthetic and vascular grafts infections, cardiac implantable electronic device infections, ventricular assist device infections, infective pericarditis and myopericarditis.

CVSIs are characterized by the extent of local tissue or valve or vascular destruction with or without hemodynamic sequelae, a perivalvular extension of infection, septic embolization to any organ in the systemic arterial circulation or to the lungs, as in the case of right-sided involvement, and the consequences of circulating immune complexes and systemic immunopathologic factors. Diagnosis is often challenging and is based on the conjunction of clinical, microbiological, and imaging information, with notable progress in recent years in the accuracy of echocardiographic data, coupled with the recent emergence of other useful imaging techniques such as cardiac computed tomography and nuclear medicine tools, particularly 18F-Fluorodeoxyglucose-Positron Emission Tomography/Computed Tomography ([18F] FDG-PET/CT) [5]. Antimicrobial treatment, mostly combined therapy, is mandatory due to multi-metastatic, rapidly devastating, and high inoculum infections. The surgical approach is the other key to cure the infection in more than half of cases. Moreover, there is a high risk of relapse, requiring long-term treatment in some cases, and extensive follow-up. Prevention development strategies have been described as the best approach to avoid these incoming CVSIs.

This Ph.D. is focused on **Cardiac implantable electronic device infections,** insofar as it represents one of the CVSIs with the highest increase in incidence, and at the same time, for which there is a glaring lack available of data published in the literature.

1.1 Cardiac implantable electronic device infections

The burden of rising life expectancy 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, with an increased use of last generation pacemakers (PPM), implantable cardioverter-defibrillator (ICD), and cardiac resynchronization therapy (CRT) [6, 10]. Infection is one of the most serious complications of CIED therapy and is associated with significant mortality, morbidity, and financial healthcare burdens. It is difficult to give a precise

rate of CIED infections owing to divergent definitions, varied populations, and the range of rates in retrospective and prospective studies, however, in all cases a recent increase in the incidence of CIED infections has been amply described in the literature.

In the CIED-Danish registry, including 46,299 consecutive patients who underwent PPM implantation between 1982 and 2007, the incidence of infection was 4.82/1000 device-years after primary implantation and 12.12/1000 device-years after replacement [11]. Greenspon et al. found that the incidence of CIED infection in the USA increased from 1.53% in 2004 to 2.41% in 2008. This National Inpatient Sample database study showed an increase from 1.45% to 3.41% (P <0.001) from 2000 through 2012, particularly for CRT devices. Dai M et al. described another large cohort from 1988 to 2015 with an increased incidence of CIED infection. They found incidence rosed every seven years from 1988 to 2015 to 1.3; 5.7; 4.1, and 4.7 per 1,000-person years, respectively. CIED infections were found to be most likely in elderly patients, complex devices, such as CRT and ICD, and repeated manipulation of device pockets, (**figure 2**) [7].

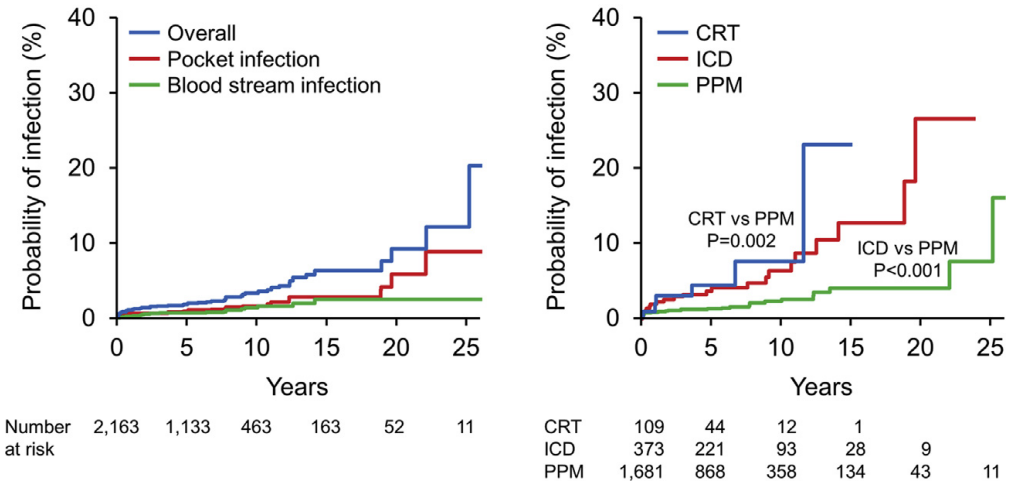


Figure 2. Cumulative probability of infection in patients with all CIEDs depending on type of infection (left) and type of device (right) [7]

On the other hand, infection rates in the prospective observational studies, registries, and more recent cross-over cluster PADIT [8] and randomized WRAP-IT trials [9], were only 0.6–1.3%, as compared to retrospective studies mentioned above, that reported significantly higher rates (2.3–3.4%) in the first year after implantation [10].

1.1.1 CIED infective endocarditis

Infective endocarditis (IE) has also undergone important changes in its epidemiology worldwide. In high-income countries, the proportion of IE related to prior rheumatic disease has decreased significantly and has been replaced proportionally by cases related to degenerative valvopathies, prosthetic valves, and cardiovascular implantable electronic devices [3].

Indeed, community-acquired, nosocomial, and healthcare-related IE cases, the proportion caused by staphylococci, and the median age of patients have all risen in recent years, which may be partially accounted for by a better reporting of cases and higher global life expectancy.

In this issue, the EURO-ENDO registry collected, between 2016 and 2018, 3116 IE episodes in Europe and elsewhere, providing an updated overview of IE and a comparison of national and international IE registries in the 21st century. They reported a higher prevalence than previously reported of CIED-IE: 208 episodes of 3116 total IE (10%), with greater prevalence in PPM-IE (52%), followed by ICD-IE (29%) [12]. This data could be compared with the ICE registry, which in 2009 reported 2781 cases of definite IE with a 7% prevalence of CIED-IE (195/2781) (**table 1**) [13].

Table 1. Comparison of IE types between ICE and EURO-ENDO cohorts [14] .

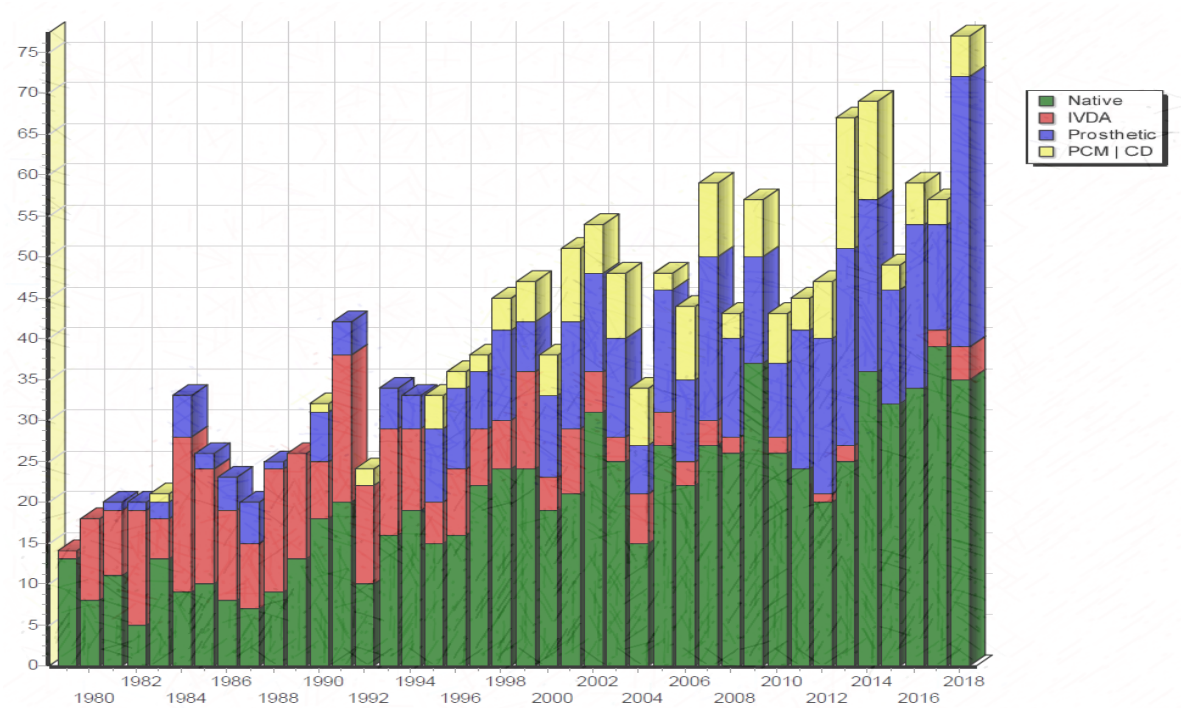
	ICE (2000-2006) N=2781/3284 (85%)	EURO-ENDO (2016-2018) N=3116
IE Type		
Native-IE	72%	59%
Prosthetic-IE	21%	31%
CIED-IE	**7%**	**10%**

Abbreviations: IE: infective endocarditis; CIED: cardiac implantable electronic devices.

These changes in the profile of IE, with an increase in PVE and CIED-IE, has also been described on a national level for several European countries [15–17]. In Spain, Muñoz P. et al. conducted a 2008 to 2012 multicenter study from twenty-five Spanish centers, which cover an estimated population of 10,218,634 inhabitants. They reported 1804 episodes of IE, with a prevalence of 9% for CIED-IE (169 episodes), 60% for native-IE, 28% for PVE-IE, and3% for intravenous drug users-IE (IDVU) [18].

In 2015 Hospital Clinic of Barcelona also published the experience of the Working Group on Infective Endocarditis and the annual distribution of IE cases from 1979 to 2014, showing a new IE paradigm with less IVDU-IE and significantly more PVE-IE and CIED-IE [19]. The present has extended of this data up to 2018 (**figure 3**).

Therefore, all reports conclude CIED-IE can represent 10% of overall IE, a figure which is rising. Nevertheless, little has been reported regarding the impact of this historical evolution of CIED-IE and the aforementioned fluctuations in epidemiology, clinical presentation, and outcomes on daily clinical practice.



Abbreviations: PVE: prosthetic valve endocarditis; IVDA: intravenous drug abuse; PCM: pacemaker, ICD: Implantable cardioverter defibrillator.

Figure 3. Changes in Hospital Clinic´s Infective Endocarditis cohort from 1980 to 2018.

1.2 Epidemiological changes in CIED infections

1.2.1 Historical evolution of CIED types

Cardiac pacing, electrical stimulation to modify or create cardiac mechanical activity, began in the 1930s with Hyman's "artificial pacemaker", in which a hand crank created an electric current that drove a generator whose electrical impulses were directed to the patient's right atrium through a needle electrode placed at the intercostal area [20].

Following World War II, public perception changed, and daring pioneers advanced. Large, external, alternating current–powered pacemakers tethered to an extension cord gave way to battery-powered, transistorized, "wearable" pacemakers. Since that time (**figure 4**), worldwide CIEDs have developed greatly, and technological achievement in reducing size and weight has been impressive. Consequently, and with the concomitant increase in their clinical applications

and indications, CIEDs implants have become more and more common, particularly in the elderly [21].

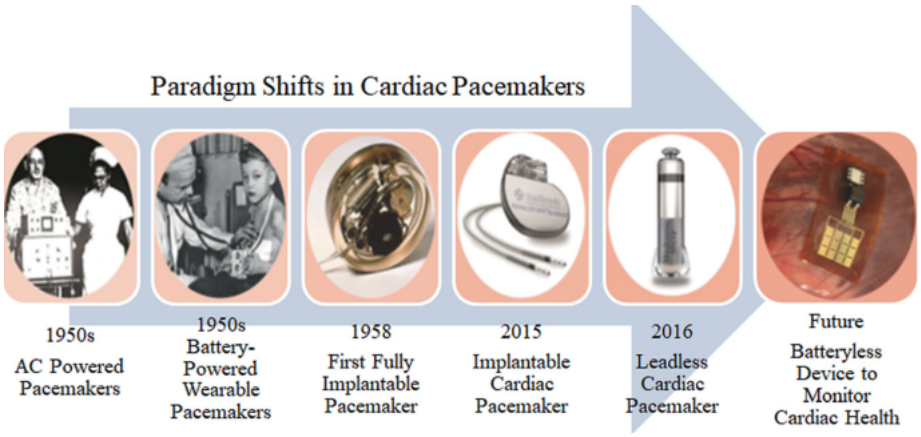


Figure 4. An overview of the history of cardiac pacing [21].

The first decades of the 21st century introduced leadless technology designed to reduce complications related to transvenous pacing leads and subcutaneous pockets—the most common sources of transvenous pacemaker-related complications. It represents a new paradigm for treating CIED infections.

Potential future advances are likely to focus on providing an alternative to transvenous electronic devices, such as through the introduction of biological pacemakers generated by somatic gene transfer, cell fusion, or cell transplantation. Somatic reprogramming strategies, which involve the transfer of genes encoding transcription factors to transform the working myocardium into a surrogate sinoatrial node. Both strategies are currently the furthest along in the translational pipeline. Even as electronic pacemakers become smaller and less invasive, biological pacemakers might expand the therapeutic armamentarium for conduction system disorders [22].

Alternatively, improving diagnosis and management in preventing sudden cardiac death and heart failure has brought on a higher use of implantable cardioverter defibrillator (ICD) and cardiac resynchronization therapy (CRT) use. This has resulted in an increasing number of patients with indication of ICD/CRT implantation among all age groups and in a profile of patients with multiple comorbidities [23,24].

The abovementioned implies a significantly raised prevalence of procedures, generator exchanges, and abandoned leads, representing greater complexity and a higher risk of infection. Deeper analyses on how this growth in CIED infective implants affects its epidemiological changes and prognosis over long periods need to be performed.

1.2.2. Demographical changes in population with an indication of CIED

Recent studies showed increased rates over time of CIED implantation in older patients with augmented comorbidity and remarkably higher risk for infection. The higher number of implants has affected all age groups but significantly more in elderly patients. Noticeably it has been reported ICD and CRT are younger but have considerably more comorbidities [25] Leading comorbidities associated with CIED infection were chronic renal failure and diabetes [26].

Rennert-May et al. designed an extensive administrative data study to provide an update of the current rates of CIED infection and its epidemiology in the United States. Of the 191,610 overall types of CIED implantations performed in 2016, 4.2% resulted in patient hospitalization for CIED infection. Median age was 66.6 years, and more than half of patients (68.9%) presented more than three comorbidities. More comorbidities were also associated with more prolonged in-hospital admission, increased costs, and a greater risk of mortality [27].

This newly observed variation in the demographic population is also likely to have impacted the etiology of CIED infection and the empirical approach to antimicrobial treatment. A higher prevalence of advance-age patients is associated with more chronic diseases, such as neoplastic processes, and emerging microorganisms, such as enterococcal species [28].

Finally, surgical management is influenced by this changing demographic profile, as well. The greater number of long-term leads, comorbid, and fragile patients, combined with a concomitant high risk of complications during extraction surgery, has developed CIED removal could not be achieved in several cases. In such cases, patients may require life-long oral suppressive antibiotic treatment, decreasing their quality of life and raising morbidity and mortality in the short and medium terms [11,29].

More studies are required of demographic characteristics in CIED infections, particularly the CIED-IE clinical profile, to study whether higher life expectancy, growth comorbidities, and age have settled more complex infections and predictors factors for elevated surgical risk.

1.3 Pathogenesis

CIED infections can occur through two major mechanisms. The first and most common is the contamination of pulse generator and/or leads during implantation or subsequent manipulation. Contamination, and subsequent bacterial colonization result in pocket infection, which can spread along the intravascular parts of the leads and progress to systemic infection. Furthermore, the patient's skin flora can be introduced into the wound at the time of skin incision and contaminate the device. Contamination may also occur before implantation via the air in the operating room (both host and staff) or via the hands of anyone handling the device [30].

The second mechanism is a bloodstream infection (**figure 5**). Direct lead seeding can occur during bacteremia caused by a distant infectious focus, such as a local septic thrombophlebitis, osteomyelitis, pneumonia, surgical site infection, contaminated vascular catheters or bacterial entry via the skin, mouth, gastrointestinal, or urinary tract [31].

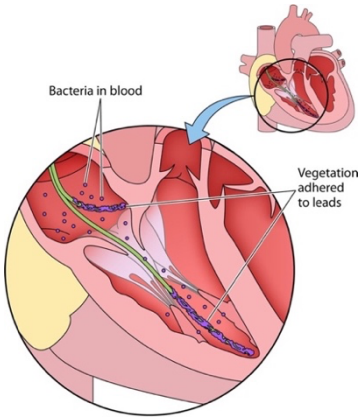


Figure 5. CIED lead infection: spread from a distant source of infection (2nd pathogenesis mechanism).

1.3.1 Pathogenic factors

Device-related infection is the product of the multifactorial interaction of bacterial, device, and host factors (**figure 6**). Of these three factors, the *bacterial factors* are probably the most important in the pathogenesis of device-associated infection, whereas the *device factors* are the most amenable to infection prevention strategies [30].

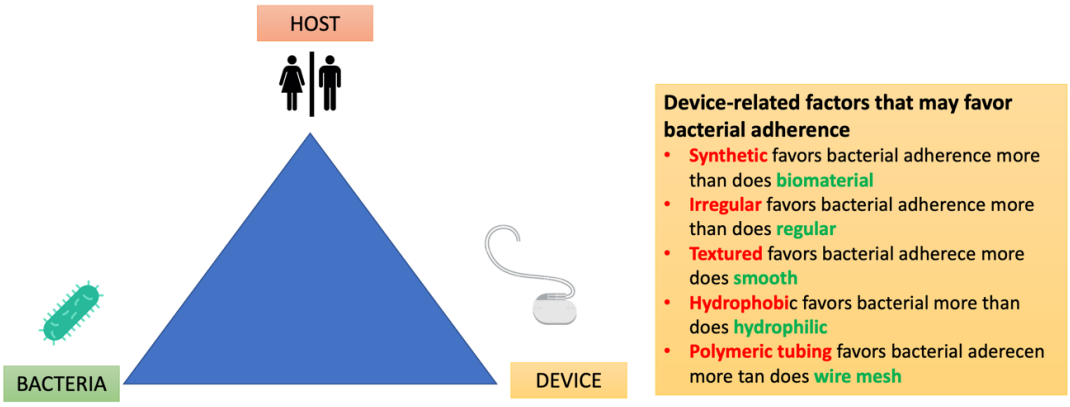


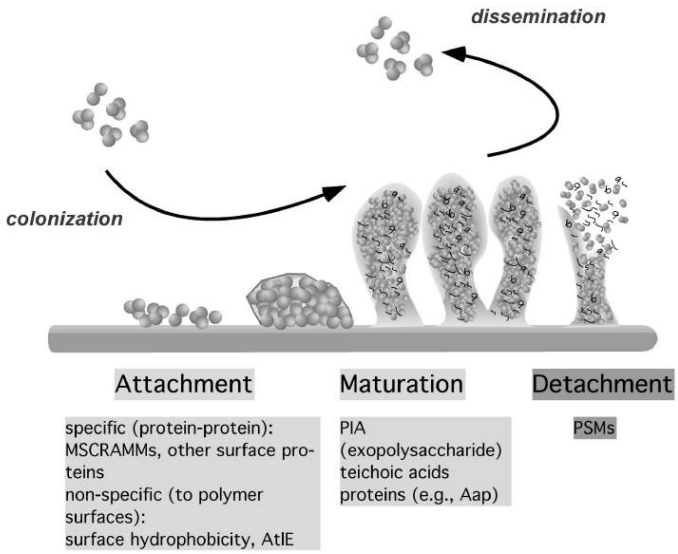
Figure 6. Device-related contributing factors for CIED infection.

The presence of the device can, in and of itself, enhance bacterial virulence. The *device-related factors* are those affecting bacterial adherence to the generator or lead and the biofilm formation on these surfaces (device-related factor **figure 6**). Bacterial adherence is facilitated by irregular and hydrophobic surfaces. Of the commonly used polymers, polyvinylchloride and silicone allow better adherence than polytetrafluoroethylene, while polyurethane allows less adherence than polyethylene. Metals also differ in their propensity for bacterial adherence: for instance, -that of titanium is lower that steel. Normally non-pathogenic microorganisms such as *Coagulase-negative Staphylococci* (CoNS) may adhere to the CIED and establish a focus of infection [32].

1.3.2 Main biofilm characteristics

Biofilms are complex communities of bacteria residing within an exopolysaccharide matrix that adheres to the surface of the device. They exist in two forms, i.e., planktonic state (i.e., free-floating microorganisms) and sessile state (i.e., microorganisms adhered to a surface).

The development of a biofilm is a two-step process involving an initial attachment, a subsequent maturation phase, and a final detachment (or dispersal) phase, which is crucial for the dissemination of the bacteria to new infection sites in the human body (**figure 7)**.



Abbreviations: MSCRAMMs: microbial surface components recognizing adhesive matrix molecules – a group of adhesins; PIA; polysaccharide intercellular adhesin; PSMs: Surfactant-like PSM peptides

Figure 7. Basis of biofilm formation [33].

Bacteria attach to surfaces, aggregate in a hydrated polymeric matrix of their synthesis, and express cationic glucosamine-based exopolysaccharides that help aggregate the bacterial cells.

The maturation and formation of these sessile communities and their inherent resistance to antimicrobial agents are at the root of many persistent and chronic bacterial infections.

Detachment of biofilms and dissemination of planktonic cells or aggregates of cells is essential in the context of infection insofar as planktonic release events can disseminate the infection to other parts of the body or spawn episodes of acute infection. Furthermore, single biofilms have been observed to include structural areas that are strong enough to resist detachment (e.g., during

high-shear stress events) and others which are weak enough to permit the release of planktonic cells [33,34].

Additionally, biofilms possess biological properties which intrinsically conferred resistance to host defenses and antibiotics. Antimicrobial resistance is provided due to the limited diffusion of antibiotics in the context of the extracellular matrix; while, surface polymers induced electrostatic repulsion, and sequestration. Moreover, resting-state bacteria present reduced susceptibility to systemic antibiotics, topical antiseptics, and antimicrobial components of the host defense (i.e., antimicrobial peptide production and resistance to neutrophil phagocytosis) [35].

Therefore, biofilm formation represents a facile microbial survival strategy where microorganisms, including pathogens, exist in a dynamic equilibrium where cell clusters form, mature, and detach to disseminate to new surfaces. Hence, considering the essential mechanism in CIED infections, device removal is mandatory to cure the infection.

Both gram-positive and gram-negative bacteria can form biofilms on medical devices, but the most common forms are *Enterococcus faecalis*, *Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus viridans, Escherichia. coli, Klebsiella pneumoniae, Proteus mirabilis and Pseudomonas aeruginosa* [36]. Amongst them, *S. aureus* and *S. epidermidis* are estimated to be responsible for approximately 40–50% of prosthetic heart valve infections, 50–70% of catheter biofilm infections and 87% of bloodstream infections. As such, the constitute the leading causes of hospital-acquired, surgical site, and bloodstream infections [33,34,37,38].

1.3.2.1 Staphylococcal Biofilm

In contrast to many other medical biofilms, such as multi-species dental plaque formation, biofilm-associated infections with staphylococci are usually not mixed with other species [39]. In addition, it is rare to find more than one strain in an infection. A possible explanation for this phenomenon is interspecies communication by quorum-sensing signals, which in staphylococci leads to interspecies inhibition of virulence factor expression [35].

As mentioned below, attachment to human matrix proteins represents the first step of biofilm formation. In this regard, adherence of *Staphylococcus sp.* to the surface of the device is not a one-time phenomenon but rather an evolving process. Initially, there is a rapid attachment of bacteria to the surface of the device that is mediated by factors that are either nonspecific (e.g., surface tension, hydrophobicity, and electrostatic forces) or specific. Among this latter group are adhesins, known as microbial surface components recognizing adhesive matrix molecules (MSCRAMMs), which are different between inter-species such as *S. aureus* and CoNS); the proteinaceous autolysin encoded by the atlE gene; and the capsular polysaccharide intercellular adhesin (PSA) probably encoded by the ica operon. This initial phase of *Staphylococcus sp.* adherence is followed by an accumulative phase during which bacteria adhere to each other and form a biofilm, a process that is mediated by the polysaccharide intercellular adhesin (PIA) encoded by the ica operon [33].

Staphylococcal biofilms have a physiological status that is characterized by a general down-regulation of active cell processes, such as protein, DNA, and cell-wall biosynthesis, which is typical of slow-growing cells. On other hand, the up-regulation of urease and the arginine-deiminase pathway, which ultimately produce ammonia compounds, has been explained as a switch which limits the deleterious effects of the reduced pH associated with anaerobic growth conditions. In addition, specific resistance mechanisms have been found to be upregulated in staphylococcal biofilms. Thus, gene-regulatory effects add to biofilms´ intrinsic structure-based resistance to antibiotics and other antibacterial agents [33–35,38,40].

Finally, novel animal models of staphylococcal biofilm-associated infection have provided us important information concerning which factors define biofilm formation *in vivo*. These recent advances constitute an important basis for the development of anti-staphylococcal drugs and vaccines [33]. The evidence for treating Staphylococcal biofilm infections based on animal endocarditis-biofilm experimental models is crucial. More experimental studies are needed to define better strategies for combined treatment and monotherapies against device-related infections.

1.4 Risk factors for CIED infection and risk stratification

Risk factors for CIED infection may be divided into patient-related, procedure-related, and device-related factors. These risk factors can be modifiable or non-modifiable.

Of the *patient-related factors,* multiple comorbid conditions, such as renal failure, respiratory failure, heart failure, and diabetes mellitus, corticosteroid use, previous CIED infection, malignancy, pre-procedural fever, anticoagulant drug use, and skin disorders were related with increased odds of CIED infection [10]. Furthermore, in a study based on the National Danish Pacemaker Registry, the association between patient age and sex and the risk of CIED infection was evaluated having divided risk factors into systemic and local (pocket) factors for CIED infection (**figure 8)**. The study found the male sex, a younger age at device implantation, and a lack of antibiotic prophylaxis to be associated with a higher rate of PPM infection (P<0.001). The authors also attributed increased rates of infection in younger patients to the presence of non-transvenous systems. Finally, besides the implantation technique employed, the experience of the operator was also determined to have an impact on the risk of CIED infection [41].

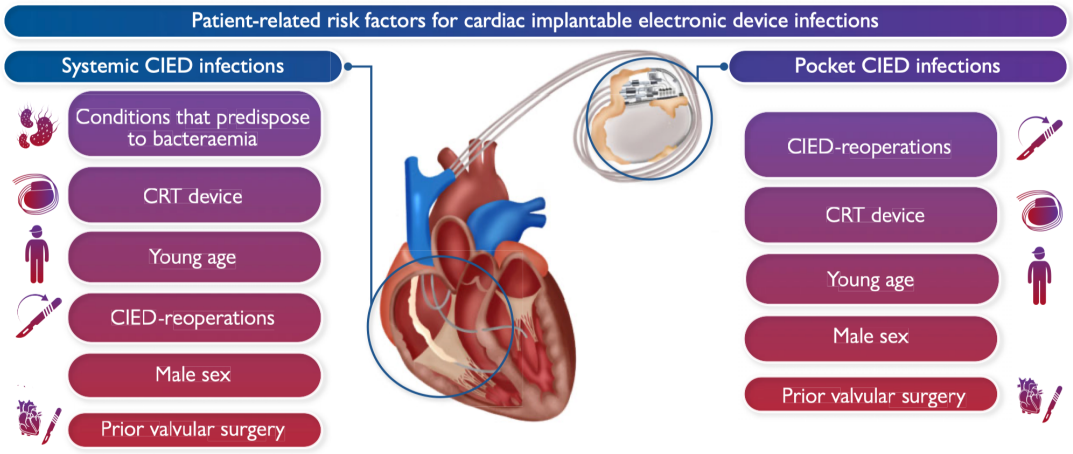


Figure 8. Summary of risk factors for isolated local CIED infection and systemic CIED infection [41].

Regarding *procedure-related factors*, studies have shown antibiotic prophylaxis to be associated with a 70% relative risk reduction in infection and is now the standard of care. Moreover, presence of hematoma has been found to account for an approximately nine-fold increased risk of infection. Lastly, procedure duration, replacement, revision, upgrade, early reintervention, temporary pacing, operator experience, and lead dislodgement have also been linked to a multifold increased risk of infection [42,43].

Concerning *device-related factors*, greater infection risk has also been identified with the use of ICD or CRT, more than two leads, and epicardial leads, as well as the implantation of abdominal pockets [41].

1.4.1 Risk scores for CIED infection

Many CIED patients are likely to develop a CIED infection during their lifetime, the proper elaboration of a precise risk scoring system is crucial, insofar as it could help guide individualized additional prophylactic strategies for high-risk patients. In this regard, different risk scores have been proposed (**table 2**) [44].

Table 2. Summary of risk scores for CIED infection.

Infective risk score	Risk factors	Points	Score	Infection risk
PADIT Prospective, multicenter, cluster-randomized 19,603 patients One-year follow-up Infection rate 0.9% External validation	Age <60 years	2	0-4	Low (<1%)
	Age 60-69 years	1		
	Renal insufficiency (eGFI <30mL/min)	1		
	Immunocompromised	3	5-6	Intermediate (1-3%)
	Procedure type ICD	2		
	Procedure type CRT	4		
	Procedure type Revision/upgrade	5	>/= 7	High (>3%)
	Number of previous procedures 1	1		
	Number of previous procedures >/=2	4		
	Diabetes	1	<3	Low (<1%)
	Heart failure	1		
	Oral anticoagulation	1		
	Chronic corticosteroid use	1		

SHARIF Retrospective, single center 1476 patients Six-months follow-up Infection rate 1.29% External validation	Renal insufficiency (Cr. >1.5 mg/dL)	1		
	Prior CIED infection	1	>3	High (2.4%)
	>2 leads	1		
	Epicardial lead(s)	1		
	Temporary pacing	1		
	Generator replacement or upgrade	1		
KOLEK Prospective, single center 899 patients Two-years follow-up Infection rate 2.2% External validation	Diabetes	1	<2	Low
	Renal insufficiency (Cr. >1.5 mg/dL)	1		
	Systemic anticoagulation	1		
	Chronic corticosteroid use	1		
	Preimplant fever +/or leukocytosis	1		
	Prior CIED infection	1	>/=2	High (1.9 – 2%)
	>/= 3 transvenous leads	1		
	Pacemaker dependence	1		
	Early pocket reentry (within 2 weeks of implantation	1		
MITTAL Retrospective, single center 2891 patients Six-months follow-up Infection rate 1.14% No external validation	Early pocket reintervention	11	0-7	Low (1%)
	Male sex	6		
	Diabetes	3	8-14	Intermediate (3.4%)
	Upgrade	2		
	Heart failure	1		
	Hypertension	1	>/=15	High (11.1%)
	Renal dysfunction (eGFI < 60 mL/min)	1		
PACE DRAP Prospective single center 1000 patients One-year follow-up Infection rate 1.8% No external validation	Valvular prosthesis	2	<6	Low (0.7%)
	Hypertension (>160/100 mmHg)	2		
	Cancer (within last 5 years)	2		
	Aye >/= 75 years	2		
	CRT / ICT surgery	2		
	Upgrade	2	>/= 6	High (4.6%)
	Antiplatelets. Clopidogrel	2		
	Ticagrelor	3		
	Renal dysfunction (eGFI < 60 mL/min)	1		
RI-AIAC Prospective single center 2675 patients One-year follow-up Infection rate 1.1% External validation	Revision / upgrading / reimplantation	2	0	Low
	CIED replacement	1		
	Diabetes	1	>/= 1	High
	Hospital-acquired infection	1		

While some of the abovementioned risk factors are common to different scores, they vary in terms of definitions and weight. In 2022, with the previously cited study validating the RI-AIAC score, Boriani et al. also provided a comparison between the former and the pre-existing PADIT, KOLEK, and SHARIFF scores [45]. Interestingly, in this study, only the PADIT and RI-AIAC infection scores could significantly predict higher risk of CIED infection (C-index 0.64 for both, p=0.01), while KOLEK and SHARIFF could not (C-index 0.56 and 0.58, p=0.26 and p=0.15, respectively). After adjusted regression analysis, the RI-AIAC infection score showed the strongest association with outcome (OR 2.38, 95% CI 1.6–3.55 for each point), whereas PADIT was shown to be less powerful (OR 1.28, 95% CI 1.1–1.5). However, in the external validation cohort of 1017 patients, none of the four scores was able to predict infections (PADIT C-index 0.53, p=0.74, KOLEK C-index 0.64, p=0.06, SHARIFF C-index 0.62, p=0.13, RI-AIAC infection C-index 0.58, p=0.29). Among the different scores, PADIT has been validated in many more patients; however, when compared to others, it has proven less powerful than PACE DRAP, KOLEK, SHARIFF, and RI-AIAC. Above all, the predictive power of each score is low. Further epidemiological and descriptive studies are needed to better understand CIED infection risk.

1.5 Clinical manifestations of overall CIED infections

1.5.1 CIED local infections

Pocket infection is defined as an infection limited to the generator pocket. It is clinically associated with local signs of inflammation characterized by erythema, warmth, and fluctuation. Deformation of the pocket, adherence or threatened erosion are often signs of low grade, indolent infection (**figure 9A**) [10]. Symptoms and signs of an infected surgical wound may fluctuate. Once a wound dehiscence occurs, a purulent drainage or a sinus is established, and a pocket infection is clearly present. If the pocket or proximal leads are exposed, the device should be considered infected regardless of the microbiological results (**figure 9B**). Of all clinical presentations of CIED infections, isolated local CIED infections, representing more than 60% of

the whole, is the most frequent form [7] and may be associated with pocket needle aspirate cultures or exudate smears, and/or positive 16S rRNA gene sequencing (16SrRNA-PCR).

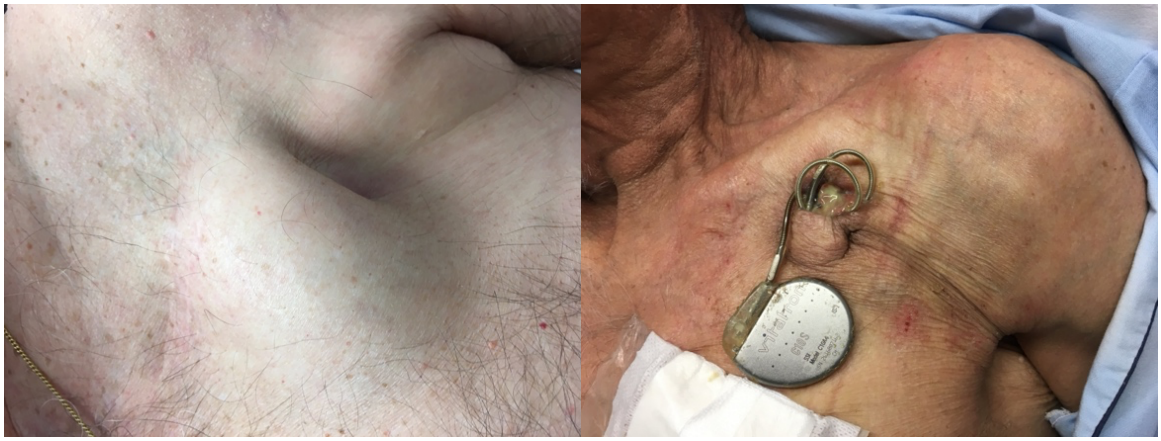


Figure 9. A. CIED deformation, adherence and threatened erosion. **B.** CIED external exposure with purulence and edema.

The 2017 HRS expert consensus statement on CIED lead management and extraction categorized isolated local CIED infections as follows [46]:

- Isolated generator pocket infection: localized erythema, swelling, pain, tenderness, warmth, or drainage with negative blood cultures.
- Isolated pocket erosion: device and/or lead(s) through skin, with exposure of generator or leads, with or without local signs of infection.
- Superficial incisional infection involving only skin and subcutaneous tissue of incision, not deep soft tissues (e.g., fascia and/or muscle) of incision.

These definitions have been maintained in the 2019 European Heart Rhythm Association (EHRA) international consensus document [10].

1.5.2 CIED systemic infections

Symptoms may be non-specific (fever, chills, night sweats, or even signs of sepsis: tachycardia, hypotension, shock), and a long period may elapse between CIED implantation and symptom

onset as well as diagnosis. In 70-80% of cases, patients have concomitant signs of localized infection. Furthermore, the involvement of endovascular and/or intracardiac lead, or even the heart valves themselves, has been observed in approximately 10-25% of cases. C-reactive protein (CRP) and procalcitonin, although non-specific, may be helpful for differentiation, especially if positive (>0.05), due to the high specificity for pocket infection compared to non-infection and in case of embolic phenomena [10,25]. There is no standardized diagnostic tool for CIED-IE. To date, patients with CIED-IE are diagnosed by applying the modified Duke criteria [47]. The presence of vegetation at the TEE is more frequent in the tricuspid valve (reported in up to 10-25% of all CIED-IE cases) than in pulmonary valve or CIED-IE with concomitant mitral or aortic valve involvement (**figure 10**).

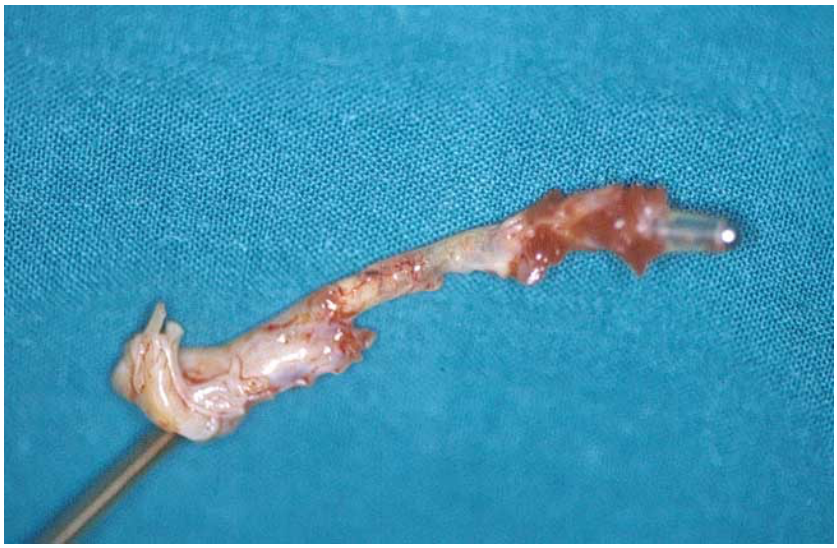


Figure 10. Presence of lead vegetation in systemic CIED infection case (courtesy dr. CA Mestres).

The 2017 HRS expert consensus statement on CIED lead management and extraction categorized systemic CIED infections, with or without local involvement, describing the following clinical scenarios [46]:

- Pocket site infection with bacteremia: local infection signs and positive blood cultures.

- Pocket site infection with lead/valvular endocarditis: local signs and positive blood cultures and lead or valvular vegetation(s).
- Lead infection: lead vegetation and positive blood cultures.
- CIED endocarditis without pocket infection: positive blood cultures and lead or valvular vegetation(s).
- Situations in which CIED infection not certain: impending exteriorization and isolated left heart valvular endocarditis in patient with CIED.
- Occult bacteremia with probable CIED infection: absence of alternative source, resolve after CIED extraction.

These definitions remain the same in the 2019 EHRA international consensus document [10].

In contrast to patients with native or prosthetic valve endocarditis, rarely in CIED-IE have been reported splenomegaly, vascular phenomena, or new-onset murmurs. Rather, CIED-IE is known to mainly affect the right heart valves, which occasionally cause pulmonary embolisms, pleural effusions, and abscesses, frequently misdiagnosed as pulmonary infections. Left heart involvement and extrapulmonary septic metastases, such as spondylitis, are possible but uncommon and usually associated with virulent organisms (*e.g., S. aureus*) [4,48].

1.6 Etiology

Staphylococcal species cause the majority of CIED infections, with around 60%-80% of cases represented by coagulase-negative *Staphylococcus* (CoNS) (37.6% of the isolates) and *Staphylococcus aureus* (30.8%) [49]. CoNS is well recognized as a common cause of microbiological specimen contamination, and thus, repeated isolation of the same species of CoNS with an identical antibiotic susceptibility pattern is desired to support its role as an etiologic agent in CIED infections. Furthermore, polymicrobial infection sometimes involves more than one species of CoNS. The prevalence of oxacillin resistance among staphylococcal strains has varied among studies, which can affect the empirical antimicrobial approach to treat CIED

infections [46,49]. *Corynebacterium* species, *Cutebacterium* (formerly *Propionibacterium) acnes, gram-negative bacilli* including *P. aeruginosa*, and *Candida species* have been reported to cause a minority of CIED infections. Fungi other than Candida and non-tuberculosis mycobacteria are rarely identified as pathogens in CIED infection (**figure 11)** [10].

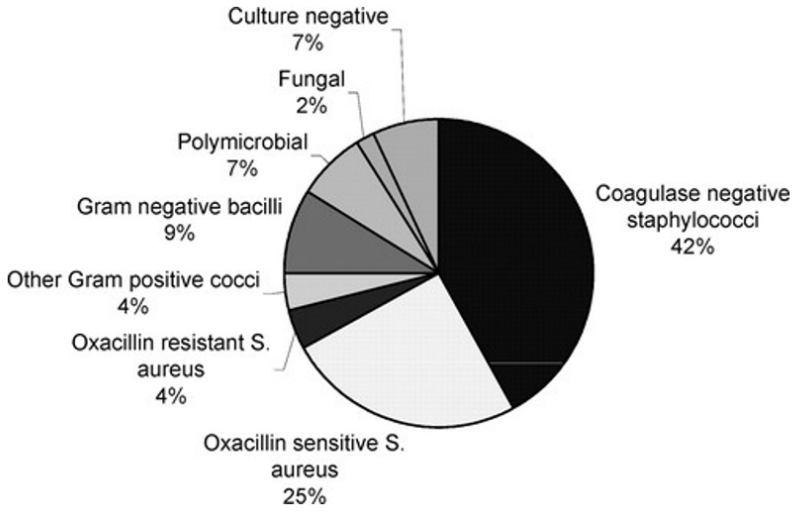


Figure 11. Microbiology distribution of PPM/ICD infections in United States [49].

1.6.1 Microbiology according to CIED implantation timing

The etiology of CIED infection can vary depending on time between CIED implantation and infection development. The Multicenter Electrophysiologic Device Infection Cohort (MEDIC) registry is an international registry consisting of 10 academic medical centers that study the overall characteristics of CIED infection. They have analyzed the impact of the timing of CIED implantation on the causative microorganism (see **figure 12**). **Early CIED infection** was defined as signs and symptoms that occurred within six months of the most recent CIED procedure, and **late CIED infection** was when signs and symptoms appeared more than six months following surgery. The proportion of *S. aureus* and CoNS did not change between early and late CIED infections, although *Enterococcus spp*. and methicillin-resistant were associated slightly more with late CIED infections [50].

Other studies have reported CoNS were isolated more in late local CIED infections (53.6% vs. 40%), defined as signs and symptoms that occurred after the first year of the most recent CIED procedure. *S. aureus* was more likely in early infections (30.2% vs. 16.3%). The same proportion of methicillin-resistance was observed in early and late CIED infections. Regarding systemic CIED infections, the majority appear to have occurred more than one-year after implantation or pocket manipulation (late), with the most prevalent microorganism being *S. aureus* [51].

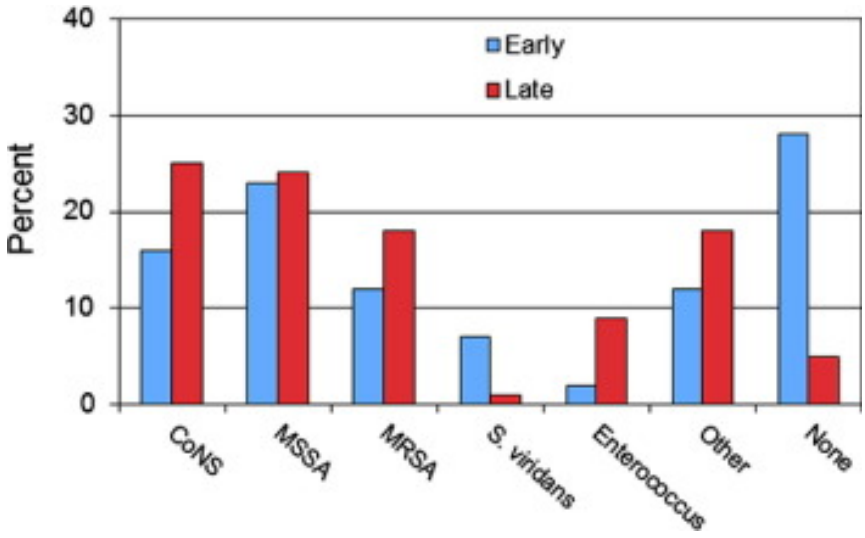


Figure 12. Etiological differences between early and late CIED infection [50].

1.6.2 Epidemiological changes in microbiology over geographical areas

Regarding the most common microbiological causes of CIED infections, both CoNs, one of the principal nosocomial pathogens, among which *S. epidermidis* is the most significant species, and methicillin-sensitive *S. aureus* (MSSA), and methicillin-resistant *S. aureus* (MRSA), are account for 60%–80% of all cases [10,12,46,52,53]. However, unusual organisms, such as gram-negative bacilli, are also present in CIED infections. Geographical differences can affect the types of microorganisms that cause CIED infections. Factors such as climate, local epidemiology of infections, and access to healthcare can influence bacteria prevalence. In some regions, infections caused by coagulase-negative staphylococci and enterococci are more common, while in others,

including tropical and subtropical regions like, Southeast Asia, and certain areas in South America, gram-negative bacteria such as *P. aeruginosa* are more prevalent [55]. However, it is important to note that the prevalence of different microorganisms causing CIED infections can vary widely even within the same region, depending on factors such as local healthcare practices and access to medical care. Additionally, as the specific microorganisms causing infections can change over time, ongoing surveillance is necessary for an accurate tracking of the epidemiology of these infections. **Table 3** is a summary of the latest evidence on microbiological changes over CIED infections.

Table 3. Pathogen isolates in patients with CIED infection from three large patients' cohorts [51,54,55].

	Percentage of isolates		
Pathogen	**North America** [51]	**Europe** [54]	**Asia** [55]
Study period	**2000-2011**	**2000-2011**	**2011-2014**
CoNS	37.6	69	45.2
Methicillin-resistant	18.8	-	-
Methicillin-sensitive	18.8	-	-
S. aureus	30.8	13.8	4.1
Methicillin-resistant	15.0	-	-
Methicillin-sensitive	15.8	-	-
Streptococcus spp.	2.5		
Enterococcus spp.	4.2		
Vancomycin-resistant	1.4		
Vancomycin-sensitive	2.8		
Corynebacterium spp.		5	
Cutebacterium spp.		2.5	
Gram-negative bacteria	8.9	6.1	9.1
Enterobacteriaceae		3	3.2
Non-fermentative bacilli		1.5	5.9
Anaerobes	1.6		
Fungi	0.9	1	0.9
Mycobacteria	0.2		

Polymicrobial			2,3
Other			4.6
Negative results	13.2	-	33.8

1.6.3 Epidemiological changes in microbiology over time

Over the past decade, the rates of staphylococcal methicillin resistance seem to be greater than those reported earlier [10]. Even though several studies have reported the increase of CIED implantation in the elderly and comorbid population and the higher prevalence of CIED infections, there is a lack of data regarding the impact on the etiology of these demographic variations over time.

Hussein et al., reported in their cohort one-third of CIED infections involved methicillin- resistant staphylococci. They stated that, over the course of 12 years, there did not seem to be a temporal trend in the epidemiology of culprit organisms. However, the rates of methicillin resistance seemed to be higher than those reported in the preceding decade, which raises concerns regarding the wide use of broad-spectrum antibiotics and likelihood of acquisition in health care environments [51].

Moreover, Oh et al. analyzed MEDIC registry data focusing on enterococcal CIED infection showing an association between age and higher Charlson index and enterococcal infections. In their study, most patients were of an advanced age combined with multiple underlying comorbidities (median CCI = 6) and with late CIED infection (i.e., median time to infection from the last device-related procedure = 570 days) [28]. Longer time to infection suggests secondary infection resulting from blood-borne seeding of the device in the context of transient bacteremia originating from another source (second pathogenesis mechanism explained in this thesis) rather than the introduction of the organism via inoculation of the pocket at the time of the device procedure. Bloodstream invasion with enterococci is typically thought to originate from a GI or GU source; however, this blood-borne seeding event may be asymptomatic and unprovoked,

consistent with the absence of any documented GI or GU procedure in the 90 days preceding confirmed diagnosis of enterococcal CIED infection in this subgroup patient population.

Whereas a trend of higher enterococcal and methicillin-resistance in the etiology of CIED infections over the last decades has been hypothesized, whether the epidemiological changes in CIED infection have impacted the etiology, emergent pathogens, and fluctuations in antibiotic sensitivity patterns in the last 40 years has not been characterized sufficiently in the literature.

1.7 Diagnostic criteria

1.7.1 Microbiological diagnosis

Identification of the causative microorganisms for a CIED infection is pivotal for effective antibiotic therapy. Therefore, every effort should be made to obtain cultures prior to the institution of antibiotic therapy. Blood cultures should be repeated in patients with CIED and fever without clear signs of local infections and infective endocarditis [10,49]. Every positive blood culture, including a single bottle with CoNS or other gram-positive organisms, should be carefully evaluated and prompt active exclusion of CIED infection with other diagnostic techniques should employed [10].

1.7.1.1 Cultures

Swabs collected from the chronic draining sinus or fistula for culture are discouraged. Instead, tissue or fluid collected from the pocket via an adjacent intact portion of the skin (via a sterile needle or syringe) is encouraged in order to avoid passing through the sinus. The culture-based approach should only be used to make a bacterial diagnosis, not to determine the presence of a pocket infection. Furthermore, entering an intact pocket should be avoided to prevent bacterial inoculation. Finally, cultures of extracted CIED should be performed [46].

During an extraction procedure, if present, distal and proximal lead fragments, lead vegetation, and generator pocket tissue should be sent for culture. Gram stain is still encouraged. Culture media suggested are chocolate agar incubated in 5% CO 2 for 48–72 h, MacConkey agar incubated for 48h, blood agar in anaerobic condition for 48–72h, and Sabouraud agar incubated

for five days or more, in case of suspicion of slow-growing microorganisms. In addition to swabs and tissue samples of bacteria from CIED leads and tissue, it may be helpful in patients with clinical signs of infection, for which the method clearly merits further investigational study [56-58].

1.7.1.2 Sonication

Gram stain has been shown to have limited utility in the diagnosis of device-related infections, and cultures may be negative for a variety of reasons, including on the one hand, concentration of organisms in biofilms on the device surface and consequently not in the surrounding tissue, and, on the other hand, the presence of so-called "small colony variants" that may be more difficult to isolate by routine cultures [59,60]. Vortexing-sonication of CIEDs with semiquantitative culture of the resultant sonicate fluid results in a significant increase in the sensitivity of culture results, compared with swab or tissue cultures, as has been shown by several cohort studies (**table 4**).

Table 4. Literature review of comparison between sonication and conventional cultures in CIED infection.

	N	Sonicate fluid	Swab/tissue culture
Napgal [61]	35	54%	9-20%
Oliva [62]	20	67%	50%
Mason [60]	16	94%	75-81%
Rohacek [59]	6	100%	67%

1.7.1.3 Molecular biology

To overcome limitations of traditional culture approaches, molecular methods have emerged. One of these is polymerase chain reaction (PCR) and sequencing targeting the 16S ribosomal RNA (rRNA) gene, which is universally present in bacteria. Its utility has also been described for other specimen types in which an infection is suspected but cultures are negative [63]. 16S rRNA PCR/sequencing has advantages compared with culture, including potential identification of

fastidious/nonculturable organisms and nondividing bacteria present because of host response or antibiotic therapy. Moreover, if rapidly performed, it may provide faster results than culture-based approaches, expediting antibiotic de-escalation and early discharge. However, there are challenges with this, including cost, lack of standardized criteria for interpretation of results, risk of exogenous DNA contamination leading to false-positive results, and lack of provision of susceptibility data. Recent reports also suggest the potential utility of this method as an antimicrobial stewardship tool [64].

This method has been incorporated into the diagnostic algorithm for infective endocarditis given its higher sensitivity compared with culture when performed on extracted valvular tissue [48].
Review of the current literature has uncovered only one study regarding the utility of the 16S rRNA PCR/sequencing method in diagnosing CIED infection. Esquer-Garrigos et al. showed that 16S rRNA PCR/sequencing has higher sensitivity than sonicated fluid culture and, therefore, could be considered in cases of suspected CIED infection, especially when no microbial growth is detected in intraoperative cultures after 48 hours of incubation [65].
More studies are needed to prove the high sensitivity and specificity of 16S rRNA PCR/sequencing in CIED infection, mainly including sonication methods.
In their international consensus document, the EEHRA made several recommendations for the microbiological approach procedure for CIED infections (**table 5)**.

Table 5. Summary of comprehensive recommendations from 2019 EHRA consensus document for microbiological diagnosis of CIED infections [10].

RECOMMENDATIONS FOR DIAGNOSIS OF CIED INFECTIONS BY CLINICAL FINDINGS AND MICROBIOLOGY	
Consensus statement	**Statement class**
At least three sets of blood cultures should be acquired in case of clinically suspected CIED endocarditis	**Recommended / indicated (E, O)**
Samples from the pocket should be cultured but only if acquired during removal and not passing through the sinus	**Recommended / indicated (E, O)**

Suspect CIED infections in case of vertebral osteomyelitis and/or embolic pneumonia (clinical signs and symptoms of CIED systemic infections may be difficult to recognize as only fever may be present)	**Recommended / indicated (E, O)**
Cultures of extracted CIED should be performed	**Recommended / indicated (E, O)**
PCT may be useful in case of infective endocarditis and embolism and/or in case of *S. aureus* CIED-related infective endocarditis	**May be used or recommended (E, O)**
Increased incubation time (10–14 days) for slowly-growing microorganism may be considered in case of CIED-related infective endocarditis and persistent negative blood cultures	**May be used or recommended (E)**
The usefulness of sonication of CIED to enhance microbial detection during removal/extraction is still under evaluation but may be used with caution when interpreting results	**May be used or recommended (E, O)**
Cultures from the sinus of the CIED pocket or from parts of the device exposed.	**Should NOT be used or recommended (E)**

Abbreviations: CIED: cardiac implantable electronic device; E: expert opinion; O: observational studies; PCT: procalcitonin.

1.7.2 Imaging diagnosis

1.7.2.1 Echocardiography

Echocardiography should be the first imaging tool in the assessment of patients with CIED infection to identify lead vegetations and valvular involvement. Transthoracic (TTE) and transesophageal echocardiography (TEE) are both recommended in case of suspected CIED infections [10,46,48,49]. While TTE better defines pericardial effusion, ventricular dysfunction, and pulmonary vascular pressure, TEE is superior for the detection and sizing of vegetations especially in the right atrium-superior vena cava area and in regions less well visualized by TTE (**figure 13**). In the absence of typical vegetations of measurable size, both TTE and TEE may be false negative in CIED-related infective endocarditis. Lead masses in asymptomatic CIED carriers may be observed on TTE/TEE and do not predict CIED-related infective endocarditis over long-term follow-up. Therefore, once a lead mass is identified, careful clinical assessment to rule out either infection or nonbacterial lead-thrombotic endocarditis is needed, including serial TTE/TEE or additional imaging tests [66].

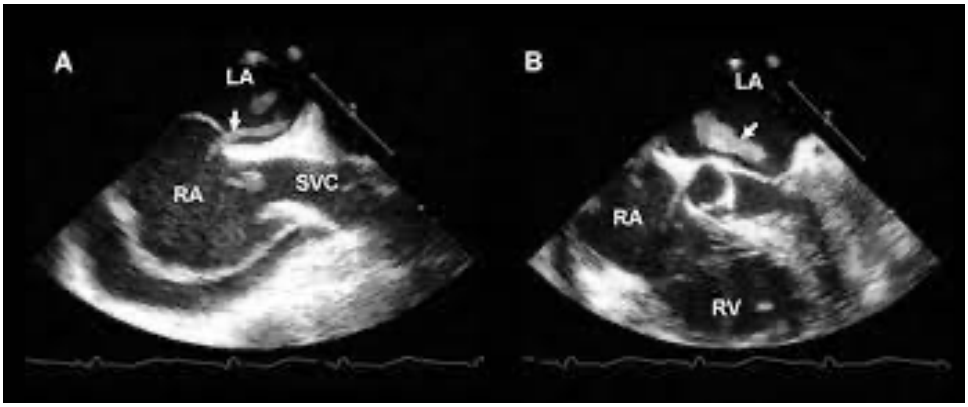


Figure 13. Vegetations detected by echocardiography in patients with systemic CIED infection. **A.** Small 0.8-cm vegetation (arrow) was detected in a patient with *S. aureus* CIED lead infection. **B.** Large 2.4-cm vegetation (arrow) was detected on the proximal portion of the left atrial (LA) (courtesy of Dr. B. Vidal).

1.7.2.2 18F-FDG positron emission tomography and computerized tomography

18F-Fluorodeoxyglucose-Positron Emission Tomography/Computed Tomography ([18F] FDG-PET/CT) has improved the diagnostic evaluation of prosthetic valve endocarditis and has been incorporated as a major diagnostic criterion [48]. Regarding CIED infections, [18F] FDG-PET/CT distinguishes between early-onset superficial surgical site infection and a true generator pocket infection, as well as differentiates between superficial and deep pocket infections [67–69]. When patients present systemic infection without signs of local infection at the generator pocket, the diagnosis of device lead infection can be challenging. Nevertheless, a [18F] FDG PET/CT in this situation is useful for the diagnosis of local infection due to its pooled specificity and sensitivity of 93% (95% CI 84–98%) and 98% (95% CI 88100%), respectively, and AUC of 0.98 at ROC analysis (see **figure 14)** [70]. In case of CIED infective endocarditis, [18F] FDG PET/CT is very specific when tracer uptake is visualized, although a negative result does not completely exclude the presence of small vegetations with low metabolic activity (i.e., limited sensitivity and negative predictive value). A recent meta-analysis by Mahmood et al. evaluated the role of PET-

CT for diagnosis of CIED infection in 14 studies involving 492 patients. Overall, the pooled sensitivity and specificity of PET-CT for diagnosis of CIED infection was 83% and 89%, respectively. PET-CT demonstrated higher sensitivity and specificity of 96% and 97%, respectively, for diagnosis of pocket infections. However, the diagnostic accuracy for systemic CIED infections (i.e., lead infections or CIED-related endocarditis) was lower, with pooled sensitivity of 76% and specificity of 83% (**table 6**) [71].

Table 6. Comparison of diagnostic accuracy of [18F] FDG-PET/CT for local CIED infection vs systemic CIED infection according to principal published studies.

Study (reference)	Local infection	Systemic infection
Mahmood et al meta-analysis [71]	**N=66**	**N=78**
- Sensitivity	96%	76%
- Specificity	97%	83%
Jerónimo et al [72]	**N=14**	**N=13**
- Sensitivity	72%	38.5%
- Specificity	95.6%	98%
Bensihmon et al [73]	**N=5**	**N=10**
- Sensitivity	100%	60%
- Specificity	100%	100%
Cautela et al [70]	**N=15**	**N=13**
- Sensitivity	86%	31%
- Specificity	100%	62%

[18F] FDG PET/CT also has the ability of whole-body evaluation, and thus has proven particularly useful for the identification of unexpected embolic localizations and metastatic infections, including mycotic aneurysms, spleen and lung embolisms, and spondylodiscitis, though not brain emboli [74]. This impacts the Duke criteria, the diagnostic certainty, and therapeutic management.

Additionally, PET/CT imaging may also contribute to mortality risk stratification assessment after lead extraction. Patients with definite CIED infection without pocket involvement on [18F] FDG PET/CT had unfavorable outcome, suggesting that the presence of an endovascular infection stemming from an unrecognized/distant site is associated with poor prognosis [75].

There is a lack of evidence on how [18F] FDG-PET/CT could improve the diagnosis in all topographical regions of CIEDs, including in endovascular leads, which TEE cannot access. Moreover, studies exploring how to differentiate between local and systemic CIED infection, including new approaches of [18F] FDG-PET/CT guiding the management of CIED infections, are needed.

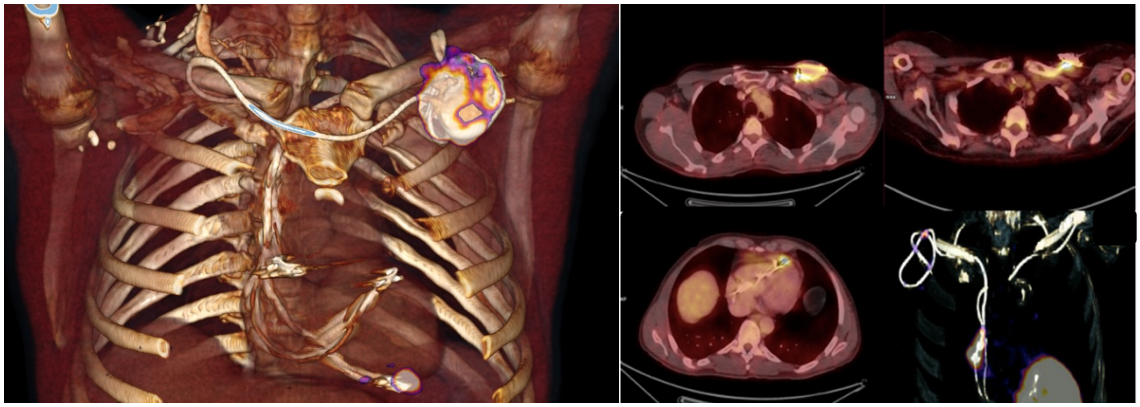


Figure 14. Left shows positive FDG infected pocket uptake in visual 3D representation. Right shows axial fused PET/CT imagen and 3D representation from 78-year-old man showing increased FDG activity at pocket and lead of CIED, most consistent with infection.

1.7.2.3 Other imaging diagnostic tests

Intracardiac echocardiography (ICE) is effective and has a high sensitivity for the detection of vegetations in cardiac devices. Therefore, a vegetation seen with ICE may be considered a major criterion for diagnosis. Recently, transvenous biopsy, guided by TEE, was shown to be useful to differentiate vegetation from thrombus [76].

Radiolabeled leucocyte (WBC) scintigraphy and 18F FDG PET/CT are complementary tools for the diagnosis of CIED-related infections and related complications in complex cases. Both imaging techniques provide additional diagnostic value, particularly in the subset of possible CIED infections, and may distinguish between early-onset superficial surgical site infection and a true generator pocket infection or, in the latter case, differentiate between superficial and deep pocket infection. White blood cell scintigraphy including single-photon emission tomography/computerized tomography (SPECT/CT) has shown high sensitivity and specificity for the detection and localization of CIED-related infections, 94% and 100%, respectively [77].

The EHRA accomplished in their international consensus document several recommendations for the diagnosis of CIED infections by imaging (**table 7**).

Table 7. Summary of global recommendations for imaging approach to diagnose CIED infection based on 2019 EHRA consensus document [10].

RECOMMENDATIONS FOR DIAGNOSIS OF CIED INFECTIONS BY IMAGING	
Consensus statement	**Statement class**
TTE is recommended as the first-line imaging modality in patients with suspected CIED-related IE	**Recommended / indicated (O)**
A chest X-ray should be performed in all patients with suspected CIED infection	**Recommended / indicated (E)**
TEE is recommended in suspected CIED infection with positive or negative blood cultures, independent of TTE results before an extraction, to evaluate CIED infection and IE	**Recommended / indicated (O)**
Repeat TTE and/or TEE within 5–7 days is recommended in case of initially negative examination when clinical suspicion of CIED-related IE remains high	**Recommended / indicated (O)**
TEE should be performed in CIED patients with *S. aureus* bacteremia	**Recommended / indicated (O)**
ICE may be considered if suspected CIED-related IE, with positive blood cultures and negative TTE and TEE results	**May be used or recommended (O, E)**
[18 F] FDG PET/CT scanning or radiolabeled WBC scintigraphy or contrast enhanced CT are recommended if suspected CIED-related IE, positive blood cultures, and negative echocardiography (attention in imaging interpretation early after device implant)	**Recommended / indicated (O, M)**
[18 F] FDG PET/CT should be performed in case of *S. aureus* bacteremia in CIED patients	**Recommended / indicated (O, E)**

[18 F] FDG PET/CT, radiolabeled WBC scintigraphy and/or contrast enhanced CT is recommended for identification of unexpected embolic localizations (i.e. lung embolism) and metastatic infections	**Recommended / indicated (O, M)**
The identification of the infection portal of entry may be considered by [18 F] FDG PET/CT and WBC imaging in order to prevent IE relapse	**May be used or recommended (O, E)**
Pulmonary CT angiography is recommended in patients with recurrent pneumonia	**Recommended / indicated (O, E)**
In patients with CIED infection treated with percutaneous lead extraction, TTE/ TEE before hospital discharge are recommended to detect presence of retained segments of pacemaker lead, and to assess tricuspid valve function, RV function, and pulmonary hypertension	**Recommended / indicated (O)**
In case of persistent sepsis after device extraction: - TEE is recommended to identify residual insulation material and local complications - [18 F]FDG PET/CT, radiolabeled WBC scintigraphy and/or contrast enhanced CT for better assessment of local extension of the infection and whole body assessment A multidisciplinary team (the Endocarditis Team) is recommended for evaluation of imaging results	**Recommended / indicated (O, M)**

Abbreviations: CIED: cardiac implantable electronic device; TTE: transthoracic echocardiography; TEE: transesophageal echocardiography. CT, computerized tomography; ICE, intracardiac echocardiography; WBC: white blood cell; E: expert opinion; O: observational studies; M: metanalysis.

1.7.3 Classification of CIED infections: Diagnostic criteria

The recommendations for diagnosis of CIED infections and/or infective endocarditis are based on the diagnostic Duke criteria [47] (in IE cases) and Novel International CIED Infection criteria consensus published in 2019 [10] (**table 8**).

Table 8. Diagnosis criteria of CIED infections based on International CIED Infection Criteria [10] and Duke Endocarditis criteria [47].

Consensus statement		Statement Class	Reference
Definite CIED clinical local infection = generator pocket shows swelling, erythema, warmth, pain, and purulent discharge OR deformation of pocket, adherence, and threatened erosion OR exposed generator OR proximal leads. **Definite CIED-SI/IE** = presence of either two major criteria or one major + three minor criteria **Possible CIED-SI/IE** = presence of either one major criteria or one major + one minor criteria or just three minor criteria **Rejected CIED-SI/IE** = patients who did not meet the criteria for IE.			
Microbiology	A. Blood cultures positive for typical microorganisms found in CIED infection and/or IE (CoNS, *S. aureus*)	**Recommended/indicated based on scientific evidence that a treatment or**	[48]

	B. Microorganisms consistent with IE from 2 separate blood cultures: a) Viridans streptococci, *Streptococcus gallolyticus*, HACEK group, *S. aureus*; or b) Community-acquired enterococci, in the absence of a primary focus C. Microorganisms consistent with IE from persistently positive blood cultures: a. >_2 positive blood cultures of blood samples drawn >12 h apart; or b. All of 3 or a majority of >_4 separate cultures of blood (first and last samples drawn >_1 h apart); or c. Single positive blood culture for *Coxiella burnetii* or phase I IgG antibody titre >1:800	**procedure is beneficial and effective: at least one randomized trial or large observational studies. (E)**	
Imaging positive for CIED infections and/or CIED-SI/IE	D. Echocardiogram (including ICE) positive for: a. CIED infection: i. Clinical pocket/generator infection ii. Lead-vegetation b. Valve IE i. Vegetations ii. Abscess, pseudoaneurysm, intracardiac fistula iii. Valvular perforation or aneurysm iv. New partial dehiscence of prosthetic valve E. [18 F] FDG PET/CT (caution should be taken in case of recent implants) or radiolabeled WBC SPECT/CT detection of abnormal activity at pocket/generator site, along leads or at valve site F. Definite paravalvular leakage by cardiac CT	**Recommended/indicated based on scientific evidence that a treatment or procedure is beneficial and effective: at least one randomized trial or large observational studies. (E)**	[48]
Minor criteria	a. Predisposition such as predisposing heart condition (e.g. new onset tricuspid valve regurgitation) or injection drug use b. Fever (temperature >38 —————————— C) c. Vascular phenomena (including those detected only by imaging): major arterial emboli, septic pulmonary embolisms, infectious (mycotic) aneurysm, intracranial haemorrhage, conjunctival haemorrhages, and Janeway's lesions d. Microbiological evidence: positive blood culture which does not meet a major criterion as noted above or serological	**Recommended/indicated based on scientific evidence that a treatment or procedure is beneficial and effective: at least one randomized trial or large observational studies. (E)**	[48]

	evidence of active infection with organism consistent with IE or pocket culture or leads culture (extracted by non-infected pocket)		

Abbreviations: CIED: cardiac implantable electronic device; CT: computerized tomography; E: expert opinion; ICE: intracardiac echocardiography; IE: infective endocarditis; M: meta-analysis; O: observational studies; R: randomized trials; SPECT: single-photon emission tomography; WBC: white blood cell.

1.8 Medical and surgical management

1.8.1. General management of CIED infections

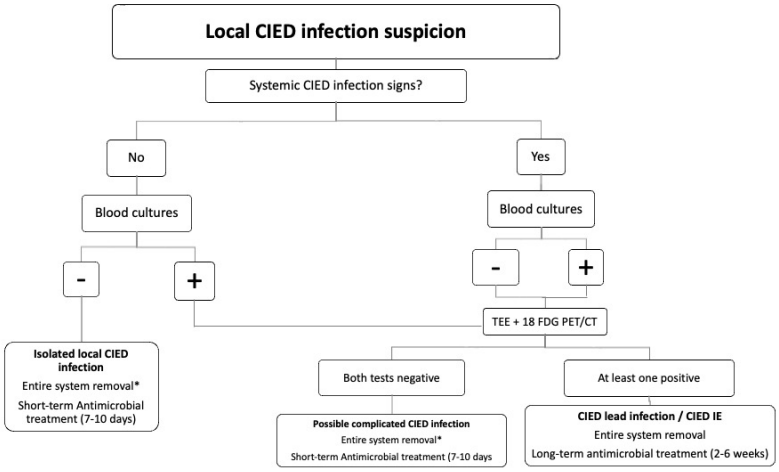
The key aspect to successful treatment of definite CIED infections is complete removal of all parts of the system and transvenous hardware, including the device and all leads (active, abandoned, epicardial as well as lead fragments). This treatment concept applies to local CIED infection (first clinical scenario algorithm, **figure 15A**) and systemic CIED infections (second clinical scenario algorithm, **figure 15B**). The timing of the extraction procedure should be without unnecessary delay after the diagnosis of CIED infection [53,78,79].

Focusing on the management algorithm, the first clinical scenario is based on suspicion of local CIED infection with or without systemic signs of infection (**Figure 15A**). In these cases, blood cultures should be performed to determine whether there were signs of systemic infection. On the assumption that blood cultures were negative, and without signs of systemic infection, an isolated local CIED infection should be considered, and removal of the entire device is recommended. However, the extraction of solely the generator without leads, could be considered in patients with advanced age, extreme frailty, comorbidities, long-term lead implantation, and high surgical risk for open surgery.

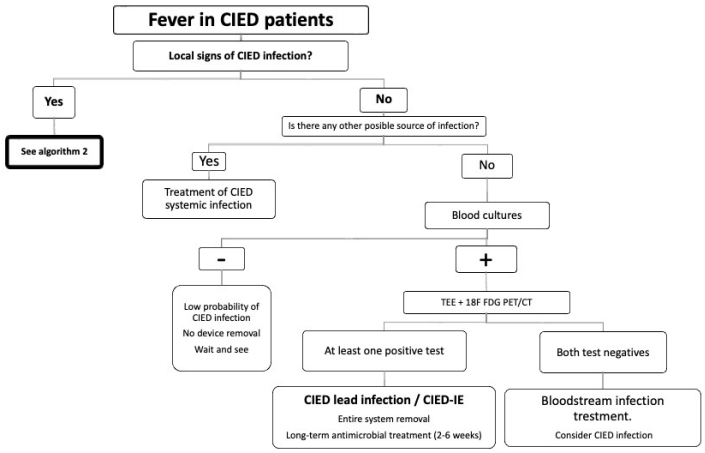
On the other hand, if the blood cultures were positive and/or there were signs of systemic infection, a TEE and cardiac [18F] FDG-PET/CT would be recommended. If both were negative, the patient would be less likely to have a systemic CIED infection. Nonetheless, in those cases

with typical CIED microorganism isolation (e.g., *S. aureus, S. epidermidis*, other CoNS, and *P. aeruginosa*) complete device removal and short antibiotic treatment should be considered. Conversely, in cases where one or both diagnostic tests were positive, there would be high suspicion of CIED infective endocarditis (lead or valve), and the device would require complete removal and an additional two to six weeks of antibiotic treatment would be recommended.

15A.



15B.



Abbreviations: CIED: cardiac implantable electronic device; TEE: transesophageal echocardiography.
*For Patients with older age, comorbidities, fragility, and high risk in device removal procedure, the removal could undergo incomplete or be dismissed. These clinical situations might need chronic antibiotic suppression to avoid relapses.

Figure 15. Algorithm for diagnosing and management of CIED infections based on two common clinical scenarios: **A.** Local CIED infection suspicion and, **B**. fever in CIED patients.

The second clinical scenario describes managing fever cases in patients with CIED without signs of local CIED infection (**Figure 15B**). In these cases, if there were a focus (e.g., urinary tract infection), it should be treated, and, in general, the patient would be unlikely to have a CIED infection. However, in cases with no source of infection, blood culture results would be necessary before further action was taken. Negative blood cultures imply a low probability of CIED infection, whereas positive results added to the absence of a clinical source, advocate the performance of a TEE and [18F] FDG-PET/cardiac CT to make definite diagnosis. If one or both tests were positive, the patient would have a high risk of CIED infective endocarditis (lead or valve), and the entire system should be removed. Thus, prolonged antibiotic treatment (i.e., 2 to 6 weeks) should also be administered. If both were negative and there was no evident source of infection, the withdrawal of the entire system should nevertheless be considered. One potential explanation for a low blood culture positivity rate that must be considered is outpatient-clinic antibiotic therapy administered prior to commencement of the diagnosis procedure [53,78,79]. Finally, if complete device removal were not possible in either of the two scenarios, sequential antibiotic treatment, taking into account chronic antibiotic suppression to avoid relapses, is recommended [80].

1.8.1.1 Other clinical scenarios of CIED infection

Removal is mandatory to cure all clinical types of infection:

- Complete CIED removal should be performed when patients undergo valve replacement or repair for *left-side infective endocarditis*, insofar as the CIED could serve as a nidus for relapsing infection and subsequent seeding of the surgically treated heart valve.
- Infection can occur in patients with *surgical epicardial leads* and/or *patches* that are connected to a *pectoral or abdominal generator*. Complete removal of infected epicardial leads and patches is recommended to eradicate the infection after balancing the risk of surgery and mortality from infection [46].

1.8.2 Antimicrobial therapy

A broad empirical antimicrobial therapy to cover both gram-positive and gram-negative microbes is recommended until the causative organism is identified. Ninety-seven percent or more of patients presenting with either pocket infection or endocarditis can be cured after combined lead extraction and antibiotic therapy, (**table 9)** [53]. Antibiotics should be started after taking samples of local or blood cultures. Cases without fever and low severity can await microbiological isolation for effective targeted therapy.

A complete course of antibiotics is recommended to treat the device pocket and/or bloodstream infection and valvular endocarditis. After device and lead removal, antibiotics are more effective in eradicating the infection. Selection of the appropriate antimicrobial agent should be based on identification and in vitro susceptibility testing results [46], (**table 10)**. Given that staphylococci are the most common microorganism, and nearly half of these are methicillin resistant, currently guidelines recommend vancomycin. Patients with infections due to methicillin-susceptible staphylococcal strains can treated with cefazolin or nafcillin, with discontinuation of vancomycin [49]. Vancomycin or in some cases daptomycin (last guidelines recommendations, (see **table 9** and **table 10**) should be continued in patients with infection due to methicillin-resistant staphylococci [48,49].

Although no clinical trials have tested the minimal duration of antibiotic therapy, in general, a two-week antibiotic therapy after lead extraction is currently recommended for CIED pocket infection, whereas ten days are recommended for pocket erosion. For patients with bloodstream infection without valvular involvement, a minimum of two weeks of parenteral antimicrobial therapy is recommended after extraction of the infected CIED. The duration of antimicrobial therapy should be at least four to six weeks for complicated infection, including endocarditis, septic thrombophlebitis, osteomyelitis, and persistent bacteremia, despite device removal and appropriate initial antimicrobial therapy. In general, the duration of antimicrobial therapy should be calculated from the day of lead extraction or negative blood cultures (whichever occurred last).

Patients with staphylococcal bacteremia need repeated blood cultures to document the clearance of infection [53].

Table 9. British scientific societies empirical treatments suggestions for treating CIED infections [53].

Diagnosis/scenario	Antimicrobial	Dose/route[a]	Comment
Early post-implantation inflammation	Flucloxacillin	0.5-1 g q6h po	Benefit of and need for antimicrobial therapy is unclear
Early post-implantation inflammation in penicillin-allergic or MRSA-colonized patient	Doxycycline OR Linezolid OR Clindamycin	100 mgq12h po 600 mg q12h po 450 mg q6h po	Benefit of and need for antimicrobial therapy is unclear
Uncomplicated CIED local infection	Vancomycin OR Daptomycin OR Teicoplanin	1 g q12h iv[b] 4 mg/kg q24h iv 6 mg/kg to a maximum of 1 g given at 0, 12 and 24 h and then q24h	If possible, avoid clindamycin in patients at risk of *Clostridium difficile* infection
CIED-SI or CIED-IE or complicated generator pocket infection pending blood cultures, e.g., in severe sepsis	Vancomycin OR Meropenem OR Daptomycin AND Meropenem	1 g q12h iv [b] 1 g q8h iv 8-10 mg/kg q24h iv 1 g q8h iv	Appropriate spectrum but risk nephrotoxicity Gentamycin (high dose, according to local guidelines) or other agents may be appropriate depending on local epidemiology less risk of nephrotoxicity than vancomycin
CIED-SI or CIED-IE or generator pocket with negative blood cultures	Vancomycin AND Gentamicin [c] OR Daptomycin AND Gentamicin [c]	1 g q12h iv [b] 1 mg/kg q12h iv 8-10 mg/kg q24h iv 1 mg/kg q12h iv	Appropriate spectrum but risk or nephrotoxicity

Abbreviations: iv: Intravenous; po: per os; q6h: every 12 h; q8h: every 8 h; q24h: every 24 h.

[a]All doses require review if renal function is impaired. [b] or dose vancomycin according to local protocols. Use daptomycin in glycopeptide-intolerant patient or when nephrotoxicity is a concern. [c] Aim for pre-dose levels < 1 mg/L and post-dose levels 3-5 mg/L. Meropenem is an alternative to gentamicin.

Table 10. Targeted antimicrobial regimens for local CIED infections or systemic CIED (including CIED-IE) assuming device removal [53].

Pathogen	Antimicrobial	Oral switch (depending on susceptibility) usually after device removal [a]
Staphylococcus spp. (methicillin-susceptible isolate)	Flucloxacillin 2 g q6h	Flucloxacillin 1 g q6h
Staphylococcus spp. (methicillin-resistant isolate or penicillin-allergic patient)	Vancomycin 1 g q12h iv[b] OR Teicoplanin 6 mg/kg to a maximum of 1 g given at 0, 12 and 24 h and then q24h OR Daptomycin 4 mg/kg q24h iv	Linezolid 600 mg q12h po OR Clindamycin 450 mg q6h po OR Doxycycline 100 mg q12h po
Streptococcus spp. (methicillin-susceptible isolate)	Benzyl penicillin 1.2 g q4h	Amoxicillin 1 g q6h
Streptococcus spp. (methicillin-resistant isolate or penicillin-allergic patient)	Vancomycin 1 g q12h iv[b] OR Teicoplanin 6 mg/kg to a maximum of 1 g given at 0, 12 and 24 h and then q24h	Linezolid 600 mg q12h po
Enterococcus spp. (amoxicillin susceptible isolate)	Amoxicillin 2 g 6qh	Amoxicillin 1 g 6qh
Enterococcus spp. (amoxicillin resistant, but vancomycin susceptible or penicillin-allergic patient)	Vancomycin 1 g q12h iv[b] OR Teicoplanin 6 mg/kg to a maximum of 1 g given at 0, 12 and 24 h and then q24h	Linezolid 600 mg q12h po
Enterococcus spp. (amoxicillin resistant, but vancomycin resistant, daptomycin-susceptible isolate)	Daptomycin 4 mg/kg q24h iv OR Linezolid 600 mg q12h po	Linezolid 600 mg q12h po
Entobacteriaceae (coliforms)	Case-by-case depending on susceptibility, monotherapy advised.	Case-by-case depending on susceptibility, monotherapy advised.

Abbreviations: iv: Intravenous; po: per os; q6h: every 12 h; q8h: every 8 h; q24h: every 24 h.

[a]All doses require review if renal function is impaired. [b] or dose vancomycin according to local protocols. Use daptomycin in glycopeptide-intolerant patient or when nephrotoxicity is a concern. After device removal, residual infection is a skin and soft tissue infection, hence lower dosing regimens.

1.8.2.1 New alternatives in antimicrobial therapy

According to IE guidelines, vancomycin has been the antibiotic of choice for empirical approach and targeted treatment of methicillin-resistant staphylococcal and the emerging enterococcal CIED infections. However, vancomycin has poor bactericidal activity, poor diffusion within vegetation, and toxicity [81–83]. Therefore, guidelines must be updated, including the recent antimicrobial therapies incorporated into daily clinical practice as a safe and effective alternative.

Daptomycin (DAP) is a lipopeptide antibiotic that targets gram-positive bacteria. It functions by binding to the bacterial membrane and disrupting its integrity, leading to inhibition of cell wall synthesis and bacterial cell death (**figure 16**) [84]. This mechanism of action makes it effective against a range of gram-positive pathogens, including methicillin-resistant *S. aureus* and CoNS. Daptomycin has been described as more effective than vancomycin for treating experimental biofilm-producing foreign-body and systemic infections [85–87]. It has a favorable safety profile and is commonly used as a treatment for various infections, including skin and soft tissue infections, bacteremia, and endocarditis.

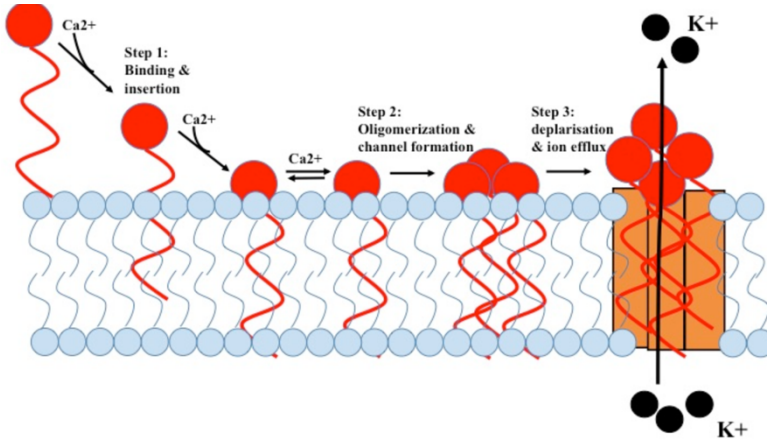


Figure 16. Daptomycin mechanism of action. Daptomycin binds and inserts into cell membrane. 2. Aggregates cell membrane. 3. Alters shape of cell membrane to form hole in the cell, allowing ions in and out of cell easily [84].

Whereas daptomycin monotherapy has been associated with microbiological failures in the treatment of *S. aureus* bacteriemia and right-side-IE in clinical trial [88] and in enterococci experimental endocarditis models[89], about potential failures in the treatment of MRSE there is no data. *Dhand* et al. have demonstrated that the combination of daptomycin plus the anti-staphylococcal β-lactams, nafcillin, or oxacillin was synergistic and effective for treating patients with refractory methicillin-resistant *S. aureus* (MRSA) bacteremia [90]. However, it is unknown if these combinations are also effective for treating MRSE.

Ceftaroline (CTL) is a broad-spectrum fifth generation cephalosporin antibiotic with activity against both gram-positive and gram-negative bacteria. It works by inhibiting bacterial cell wall synthesis through binding to penicillin-binding proteins, leading to bacterial cell death. Ceftaroline is highly active against methicillin-resistant *S. aureus* and has good activity against other gram-positive pathogens such as *Streptococcus pneumoniae* and *Streptococcus pyogenes*, as well as against selected gram-negative pathogens including *Haemophilus influenzae* and *Klebsiella pneumoniae*. Moderate activity against *E.* faecalis (MIC_{90} of 8 mg/dL). There is limited information regarding the efficacy of ceftaroline (CTL) for treating CoNS in in vitro and in vivo

models [85,92]. Regarding combination therapies, Dhand et al. have demonstrated that the combination of daptomycin plus the anti-staphylococcal β-lactams, nafcillin, or oxacillin was synergistic and effective for treating patients with refractory MRSA bacteremia [90]. Also, daptomycin plus ceftaroline has been shown active for MSSA [93]. However, we do not know if these combinations are also effective for treating MRSE and vancomycin resistant *S. epidermidis* (VRSE).

Dalbavancin is a lipoglycopeptide antibiotic that is approved by the FDA for the treatment of acute bacterial skin and skin structure infections caused by gram-positive bacteria [94–96]. However, recent studies have shown that dalbavancin may also be effective in treating other types of infections, including cardiac implantable electronic device (CIED) infections. The current standard of care for CIED infections is to remove the infected device and treat the infection with antibiotics. However, this approach can be challenging in some cases, as device removal may be difficult or impossible due to patient factors or device-related issues. Dalbavancin has several properties that make it an attractive option for the treatment of CIED infections. It has a long half-life, allowing for once-weekly dosing, which can be more convenient for patients and reduce the risk of treatment failure due to missed doses. It also has excellent activity against gram-positive bacteria, which are the most common pathogens associated with CIED infections. Several studies have reported on the use of dalbavancin for the treatment of CIED infections. These studies have generally shown good clinical outcomes, with high rates of infection resolution and low rates of treatment failure and recurrence. However, larger randomized controlled trials are needed to confirm these findings and establish the optimal dosing and duration of treatment [97,98, 107].

1.8.3. Surgical management: CIED removal

Extractions can be successfully completed using a variety of approaches and tools, including simple manual traction, locking stylets, telescoping sheaths, femoral snares, mechanical cutters, laser sheaths or open surgery. Median time from CIED infection diagnosis to device extraction

wavered between cohorts. The most recent data has been developed in a study from medical centers across Western New York from 2010 to 2021 that reported a median time to lead extraction from diagnosis of 10.9 days [99]. Also, the Mayo Clinic cohort reported a median time for removal of 10.5 days, (IQR 7-16.8 days) [100].

1.8.3.1 Transvenous lead extraction

Simple traction with either a standard or locking stylet is usually attempted first. This approach is generally successful in removing leads that move freely within the vein but remain attached at the tip to the myocardium, which can be observed with infected leads or those with a short lead dwell time. Traction-only has been used since 1989 (**figure 17**) and continues to be successful in some cases. It was initially the only transvenous method available. This method was occasionally enhanced with the use of a cord tied to the lead and then run over a pulley to a hanging one-pound weight to provide constant controlled traction to a recalcitrant lead [101].

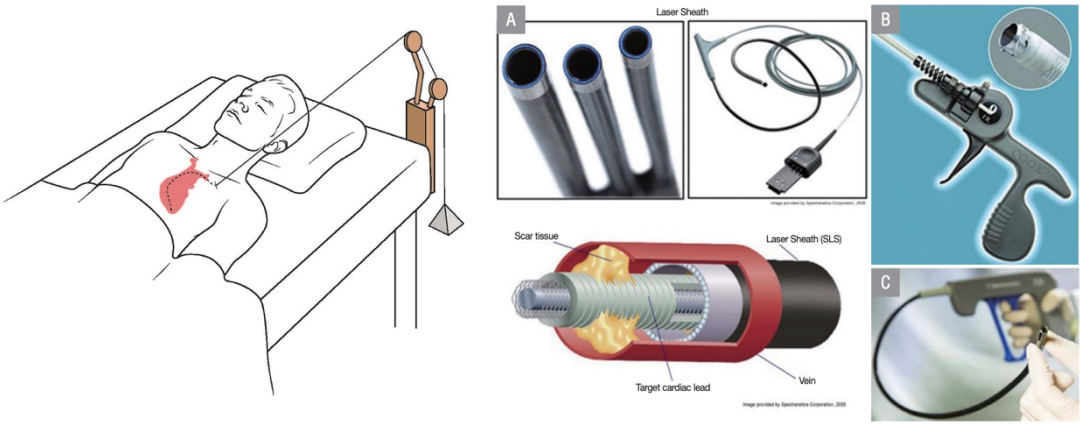


Figure 17. Historical perspective: left simple manual traction surgery schema [101]. Right powered transvenous lead extraction tools: A: laser sheath. B: Cook evolution lead extraction sheath. C: Spectranetics Tight-Rail ® rotating dilator sheath

Presently, the choice of technique used will depend on the specific characteristics of the lead and the patient's anatomy. In some cases, multiple techniques may be used in combination to ensure a successful extraction. The most common ones are described below these lines.

Simple traction: This technique involves manually pulling the lead out of the vein in which it is implanted. It is only used for leads that are not firmly attached.

Countertraction: This technique involves the use of an opposing force to pull the lead out. This is done by placing a sheath around the lead and using it to apply pressure while the lead is being pulled out.

Mechanical dilatation: This technique involves the use of special tools, such as dilators and sheaths, to expand the vein and create space for the lead to be removed.

Laser-assisted lead extraction: This technique uses laser energy to break down scar tissue around the lead, allowing it to be removed more easily.

Powered mechanical extraction: This technique uses a device that mechanically rotates and pulls the lead out.

Hybrid techniques: These techniques combine elements of two or more of the above techniques to achieve the best possible outcome.

The high success rate and low complication rate reported by high-volume, specialized centers cannot be expected by centers with less operator experience or with smaller procedural volume [102].

1.8.3.1.1 Complications of lead extraction

Despite advances in techniques for percutaneous lead extraction, there are still considerable risks associated with this procedure. The most common complications reported include tearing of the tricuspid valve, damage to the myocardium, venous lacerations, bleeding with cardiac tamponade or hemothorax, pulmonary embolism, lead tip fracture resulting in incomplete removal, and pocket hematoma (see **figure 18).** Factors that increase the risk of these complications are a) the size of the vegetation (if present), b) the time from implantation, c) and the total number of leads.

Large vegetations are more susceptible to fragmentation and septic embolism. Old leads are embedded in dense fibrous tissue, and consequently their removal by direct traction carries a higher risk of bleeding, myocardial perforation, valve tearing and venous laceration [102-104].

1.8.3.2 Open chest incision removal of leads

There is no universally agreed-upon size limit for vegetation that requires open surgery for lead extraction. The decision to perform open surgery is made on a case-by-case basis, after a thorough evaluation of the patient's clinical history, the location and size of the vegetation, and the overall risks and benefits of the procedure. Open chest surgical extraction is most suggested when lead vegetations >2-3 cm is present, when severe tricuspid valve endocarditis is associated, when percutaneous extraction has been technically impossible or incomplete, or in cases of concomitant cardiac disease requiring surgical treatment. In cases of leads >12 months old, in which percutaneous extraction can be considered safe only in specialized centers using appropriate equipment, surgical extraction is the only alternative in centers nonspecialized, but with cardiothoracic surgery available. In any case, the good exposure of cardiac cavities, that open heart surgery offers, permits their direct exploration. Consequently, all manipulations on the leads are totally controlled. Another important advantage of surgical extraction is the possibility of immediate permanent epicardial pacemaker leads implantation. The new generator can be easily implanted behind the rectus sheath, an area that is easily accessible from the sternotomy incision, without the need of additional dissection (i.e., which would be the case if the device is implanted in the right subclavian area) [101].

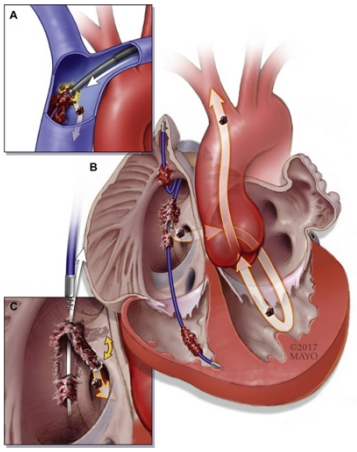


Figure 18. A: Transvenous lead removal may lead to dislodgment of endocardial lead vegetation. B: Paradoxical embolism of vegetation across patent foramen oval into systemic circulation. C: Even after removal of pacemaker lead, mobile cast may remain, leading to persistent risk of embolization [105].

The long-term impact of epidemiological changes of CIED population on the extraction type procedure has been poorly studied. Durante-Mangoni et at. conducted an observational unicentric cohort study comparing the best assessing strategy for removal between transvenous lead extraction, open chest surgery and conservative treatment (**figure 19**). The showed lower mortality rate with transvenous lead extraction (transvenous lead extraction 4.4% vs. 22.5% with open chest surgery; p=0.03). Specifically, patients with a higher Charlson index who were also treated with transvenous lead extraction presented a survival rate not significantly different from those managed with medical therapy only. They conclude that long-term benefits of transvenous lead extraction are diminished by comorbidities. In cases of CIED-IE with high comorbidities, a more conservative approach might be an option [106].

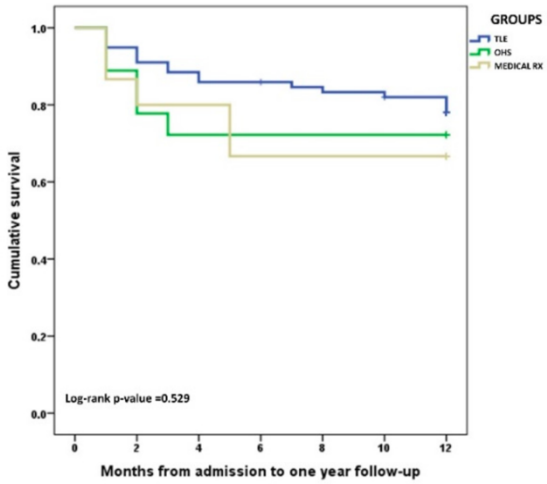


Figure 19. Kaplan–Meier curves describing survival probability, after one year follow-up, according to three therapeutic approaches used for CIED-related endocarditis: medical only, transvenous lead extraction (TLE), and open-heart surgery (OHS) [106].

1.8.3.3 Rates of incomplete or no device removal

The proportion of patients without complete CIED removal has also been reported in several studies. The MEDIC registry described 12.2% of patients who did not undergo complete device removal [79], Mayo Clinic cohort 16% [80], and Kalot et al of 5% [99]. Due to the increasing high-risk procedures and mentioned complications, some of the patients will not undergo device removal. This number of patients has been growing during the last decades due to the elderly, more comorbidities, complex and enduring devices. It is unknown whether epidemiological, demographical, and clinical evolution over the last decades has impacted the proportion of patients without complete CIED removal.

1.8.4 Device reimplantation

Performing an evaluation before implanting the device is important to ensure that patients do not have clinical signs of infection. The implantation should be postponed if signs of infection are present [46]. Reassessment of the need for a new CIED is imperative after removal of an infected

CIED. Some patients might have had interval improvement in rhythm or cardiac function and no longer meet a guideline indication for permanent pacemaker, ICD, or CRT, or a patient might not wish to receive a new device. The MEDIC registry reported over 30% of patients without reimplant a new device after removal [79].

There are no prospective trial data on the timing of new device replacement and risk of relapsing infection. A new implantation can reasonably be postponed until blood cultures are negative for 72 hours, although implantation should be delayed if the patient has another undrained source of infection [10,25,46]. Replacement device implantation should be performed in an alternative location such as the contralateral side, the iliac vein, or using epicardial or subcutaneous implantation. For pacemaker-dependent patients, temporary pacing is required as a bridge to reimplanting a new permanent device. This approach allows patients to safely await implantation of a new device for the recommended 72 hours to 14 days, depending on clinical status. For ICD patients with a high risk of short-term, sudden cardiac death, the wearable defibrillator is an option to bridge to reimplantation and, subcutaneous-ICD to avoid infection.

As above mentioned, the optimal timing of device replacement is unknown. MEDIC registry reported a median time of 10 days with an IQR of 6 to 19 days, but in their cohort 23 patients were reimplanted on the same day that their original devices were removed [79]. Another single-center study from Spain have suggested that same-day implantation is feasible for patients with isolated pocket infections and is not associated with adverse outcomes [108]. On the contrary, a study from Mayo Clinic cohort showed that a 14-day delay between CIED extraction and re-implantation in cases of CIED-IE was associated with a survival benefit, but longer length of hospital stays following re-implantation [100].

There is considerable variation between cohorts, even across the study population in a single center, regarding when to reimplant the new device safely. The optimal timing for removal, reimplanting, and the assurance of a one-time procedure strategy remains unknown; more studies to deeply brighten these questions are essential.

1.8.4. 1 Novel devices

A. Leadless Pacemaker

Leadless pacemakers have been developed to address limitations related to pulse generator pocket and transvenous leads of conventional pacemaker systems. Leadless pacemakers are inserted percutaneously through the femoral vein with a customized delivery system and placed in the right ventricle. Compared to conventional VVI pacemakers, leadless pacemakers significatively decrease the percentage of chronic and acute complications [109,110]. Second generation of leadless pacemakers provides atrioventricular synchronous pacing by sensing atrial contraction and pacing the right ventricle [111]. Although transvenous pacemakers are expected to have an infection rate ranging from 0.77% to 2.08%, no cases of pacemaker infection have been reported in clinical trials enrolling more than 3000 patients. The prevalence of leadless device infections is low as the principal sources of infection (i.e., pocket and pacemaker lead) are absent. This factor together with other factors like reduced skin and glove contact, size, location, and the device material could explain the extremely low incidence of infection in this type of devices. Current pacing guidelines recommended the implant of headless pacemakers in patients with no superior vascular access or when risk of device pocket infection is particularly high, such as previous infection and patients on hemodialysis [112].

B. Subcutaneous implantable cardiac defibrillator

A subcutaneous implantable cardiac defibrillator (S-ICD) is a type of implantable cardiac device that is positioned beneath the skin, typically in the patient's chest region, to detect and treat life-threatening heart rhythm disturbances, such as ventricular fibrillation and ventricular tachycardia. It uses a subcutaneous electrode that does not penetrate the heart, making it an alternative to traditional transvenous implantable cardioverter defibrillators (ICDs) that are positioned within the heart itself (**figure 20**). Subcutaneous ICD systems do not bear the risk of blood-stream infection or endocarditis seen with traditional transvenous ICD systems. They could be attractive

for patients not needing bradycardia or anti-tachycardia pacing and at particularly high risk of CIED infection.

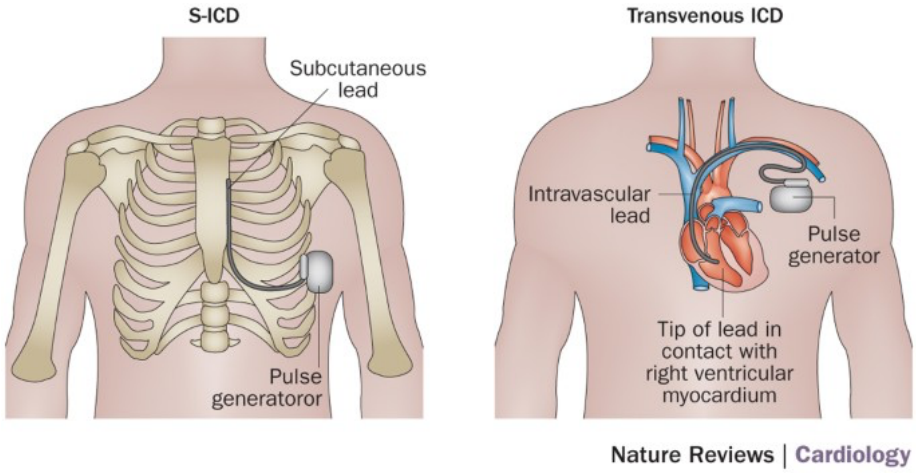


Figure 20. | Comparison between S-ICD and transvenous ICD [113].

Few studies have compared S-ICD vs. transvenous ICD (TV-ICD). One retrospective study compares long-term clinical outcomes of S-ICD and TV-ICD therapy in a propensity-matched cohort. They stated that infections occurred in 4.1% of the S-ICD group and in 3.6% of the TV-ICD group; p=0.36. There were two patients with bacteremia in the TV-ICD group and one in the S-ICD group, who also had a concomitant transvenous pacemaker. S-ICD patients had more nonlead-related complications (pocket erosion, defibrillation threshold testing failure, and device failure) than TV-ICD patients [114]. S-ICD has shown only to reduce the lead-related complications significantly at the cost of non-lead-related complications significantly at the cost of non-lead related complications, thus decreasing the risk of re-intervention to implant a new ICD lead. A randomized study has demonstrated the non-inferiority of S-ICD compared to TV-ICD. Nowadays S-ICD should be considered as an alternative to TV-ICD in patients with an indication for an ICD when pacing therapy for bradycardia support, cardiac resynchronization or ant tachycardia pacing is not needed [115].

1.9 Prognosis and outcomes

CIED infection is associated with high patient morbidity and a mortality rate of up to 20%, but in cases without device removal can rise to 30-60% [50,80,115–117]. In a large CIED infection cohort, the 30-day mortality rate was 5.5%, and 1-year mortality was 14.6%. A multivariate analysis indicated a 7-fold increase in 30-day mortality if the CIED was not removed [118]. Although CIED removal resulted in fatal complications, the mortality associated with delayed removal was significantly higher. Therefore, CIED-associated infections are the strongest indication for complete CIED system removal and should not be delayed, regardless of the timing of the start of antimicrobial therapy. Furthermore, infection relapse could occur due to retained hardware. Athan el at. showed in their analysis the impact on the prognosis of four different clinical scenarios: CIED-IE without device removal had the worst prognosis but followed by CIED infection without removal (**figure 21**). They showed in their investigation that removal is the key for survival.

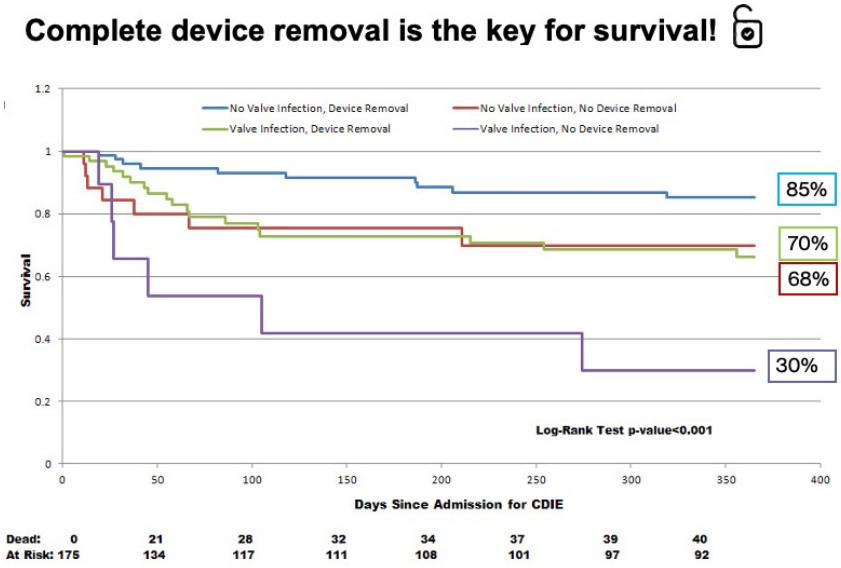


Figure 21. Survival regarding type of CIED infection and removal or not removal. [115]

1.9.1. Predictors of survival

Early diagnosis of CIED infection, including pocket abscess, erosion, and performing lead extraction within three days of diagnosis are associated with lower in-hospital mortality.[46] On the other hand, the risk of mortality significantly increased in patients with respiratory failure (odds ratio: 13.58; 95% confidence interval [CI]: 12.88 to 14.3), renal failure (odds ratio: 4.28; 95% CI: 4.04 to 4.53), heart failure (odds ratio: 2.71; 95% CI: 2.54 to 2.88) but decreased slightly in patients with diabetes (odds ratio: 0.91; 95% CI: 0.86 to 0.96) ($p < 0.001$) [52]. Kalot et al in their study reported the following factors associated with increased risk of mortality were referral from the regional facility (**figure 22**), hypertension, right ventricular dysfunction, immunosuppression, septic shock as a complication of CIED infection, and time-duration since the last device-related procedures [99].

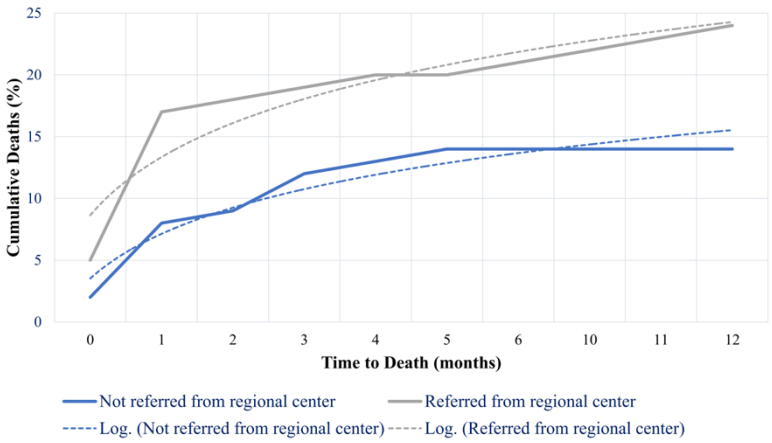


Figure 22. Line diagram (with and without log transformation) comparing the time-dependent cumulative frequencies of deaths in CIED infections with or without concomitant valvular vegetations. Mortality was disproportionately higher in vegetation groups during first 3 months, but one-year mortality was 17% vs. 11%, p=0.01.[100]

1.9.2. Long-term antibiotic suppression in patients without complete device removal

Unfortunately, some patients may not be candidates for device removal due to multiple comorbidities, limited life expectancy, or personal preference. If these patients clinically improve with initial antimicrobial therapy and demonstrate clearance of bacteremia, if present, then they may be candidates for chronic antimicrobial suppression (CAS). This long-term antimicrobial suppressive therapy and local wound care strategies are used as a palliative therapy in selected patients with CIED infection who are excessively high-risk candidates for device removal. The choice of antimicrobial therapy and its dosing are empirical, given the limited available study results. Long-term antimicrobial suppression therapy should be the last option compared with the recommended curative lead extraction approach and its outcome is unknown.

Only one previous study analyzed the reasons for no removal in CIED infections. Peacok et al. describe a CIED infection cohort with a 52.2% prevalence of CIED-IE. They reported Staphylococcal infections and high-risk procedures due to excessive medical comorbidities as the main reasons for incomplete removal. However, they did not analyze predictors of non-removal [119].

The MEDIC cohort prospectively enrolled subjects with cardiovascular-implantable electronic device infections at multiple institutions in the United States and abroad between 2009 and 2012. The proportion of patients without complete device removal was 12.2%. The most common factor was that the procedure was not felt necessary/ not considered, followed by risk considered too high. Most repeat infections occurred in the 53 patients who did not undergo CIED removal. Only 18 patients (34%) treated in this fashion remained free of infection through 6 months in the absence of chronic suppression. There was an 11.3% recurrence or relapse rate in that group versus 1.3% among patients whose treatment included device removal [80].

The other study which has reported their experience on long-term antibiotic suppression in non-complete device removal patients was Mayo Clinic cohort [80]. Tan et al reported patients with

CIED infection who did not undergo device removal were elderly (median age, 78 years; range, 34–92 years) and had multiple comorbidities (median CCI = 4). Cardiac device retention was associated with a high rate of CIEDI relapse (18%, 6/33) and mortality (44%, 21/48) at 1 year of follow-up. Sixty-three percent of cases involved gram-positive cocci, and beta-lactams were the most frequently (39.2%) used antimicrobial. CAS duration ranged from three months to ten years. Three of 41 (7.32%) patients developed signs of relapsing infection upon follow-up. Three other patients reported medication-related adverse effects. The study concluded that CAS was well tolerated and efficacious in preventing relapse. [80] There was no reported data on when to stop CAS therapy and other follow-up strategies.

Hence, the proper management strategies, treatment, and follow-up approaches are poorly studied when removal is not performed. Chronic oral suppression has been proposed to treat this population, increasing survival rates slightly. However, there is limited information on the prevalence, risk factors and outcomes of CIED-IE without complete removal.

1.9.3 Reinfection

There is a scarcity in the literature exploring the risk of reinfection. One of the largest contemporary prospective cohorts tracking CIED infections found a repeat infection risk of 1.8% among patients who were reimplanted [79]. The first systematic review and meta-analysis to assess the CIED reinfection rate showed to be higher when the time to reimplantation was >72 hours. May be this was due to an increased number of comorbid conditions in the corresponding study populations, or a high proportion of systemic CIED infections requiring additional time to clear the bloodstream of bacteremia. However, it is noteworthy that other studies, such as the Mayo Clinic cohort, showed a benefit in 14-day delayed reimplantation with no impact on hospital readmission or relapse rates [100].

1.10 Economical burden of CIED infections

The cost of care for managing CIED infections remains substantially high. Most of the incremental cost of care in infection cases compared to the device implantation cost in cases without infection was attributed to the requisite of monitoring such patients in a critical care setting and medications, including parenteral antibiotics. According to one estimate, the average cost of combined medical and surgical treatment of CIED infection in the United Sates was ≈$35,000 (PPM, $25,000; ICD, $50,000). A more precise cost estimate, adjusted for comorbid conditions, was reported in the 2007 Medicare Standard Analytic File study. Investigators estimated that adjusted incremental cost of admission for an episode of CIED infection was $15,893 for ICDs, $16,208 for PPMs, $14,360 for cardiac resynchronization devices without a defibrillator, and $16498 for cardiac resynchronization devices with a defibrillator [120].

Greenspon et al, analyzed the infection burden associated with the implantation of cardiac implantable electrophysiological devices (CIEDs) in the United States for the years 1993 to 2008.They described an increased infection burden associated with higher financial costs and inpatient mortality (**figure 23**). In-hospital charges have increased of 47%-decade [52].

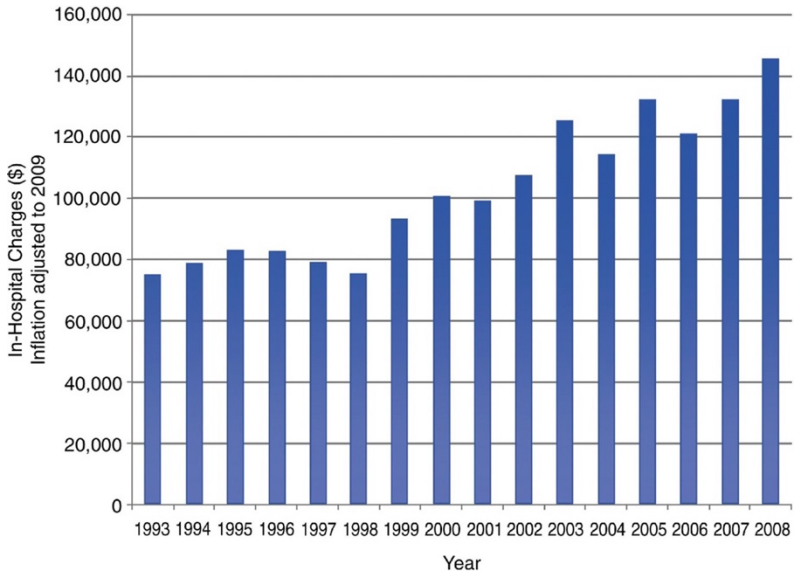


Figure 23. In-Hospital Charges Associated with CIED Infection (Inflation Adjusted to 2009) [52].

Recent Spanish registries reported the implantation rates of conventional and low-energy resynchronization pacemakers were 759 and 31 units per million population, in 2020 and 2021 respectively. In all, 520 leadless pacemakers were implanted, 70 with atrioventricular synchrony. The mean age at implantation was high (78.8 years), and the most frequent electrocardiographic change was atrioventricular block. There was a predominance of dual-chamber pacing mode, but VVI/R single-chamber pacing was used in 19% of patients in sinus rhythm, depending on age and sex. Remote monitoring capability was present in 18.5% of implanted conventional pacemakers and 45.6% of low-energy resynchronization pacemakers, although registration in this system increased by 53% in 2020. The Spanish implantable CIED registry for 2021 recorded an increase in the number CIED implantations, reflecting the recovery of hospital activity after the initial impact of the COVID-19 pandemic in 2020 [121,122]. This increasing in implantation will develop an increase in the economic burden for treating the consequently higher prevalence of CIED infection.

1.11 Prevention

1.11.1 General pre-, intra-, and post-surgical measures

Preoperative considerations

Further strategies have been proposed as beneficial in the reduction of CIED infections, especially for patients at high risk. Surgical area sterilization and antiseptic preparation of the skin at the surgical site and systemic antibiotic prophylaxis are standard therapies and should be administered before the surgical incision.

Randomized studies have demonstrated alcoholic 2% chlorhexidine to be superior to povidone-iodine (with or without alcohol) for skin preparation prior to surgery or intra-vascular catheter insertion, but no randomized data exist regarding CIED implantation [123]. For elective procedures, *S. aureus* colonization can be detected by nasal swabs. Nasal treatment with mupirocin and chlorhexidine skin washing can reduce colonization and has been shown in some

surgical studies to reduce the risk for infection [124], but there are no studies relating specifically to CIED interventions.

Intra-operative prophylaxis

Observational studies have consistently found that perioperative systemic antibiotics delivered one hour before the procedure significantly reduced the incidence of device infection compared with no antibiotics, with a relative risk reduction of 40%–95% [125,126]. A first generation cephalosporin, such as cefazolin (within 1 hour before the incision) or vancomycin (within 2 hours before the incision), is commonly administered. Vancomycin or clindamycin are alternatives to a first-generation cephalosporin for patients who are allergic to cephalosporins. Using an antibiotic solution to irrigate the device pocket has not been shown to decrease device pocket infection when compared with saline irrigation [127]. Postoperative antibiotic therapy is not currently recommended, because there are no convincing data to support the administration of postoperative antibiotic therapy. Furthermore, there is a potential risk of adverse drug events and selection of drug-resistant organisms. The recent PADIT trial, with its cluster cross-over design, tested the clinical effectiveness of incremental perioperative antibiotics to reduce device infection. The conventional treatment was a single-dose preoperative cefazolin infusion vs. a combination of pre-procedural cefazolin plus vancomycin, intra-procedural bacitracin pocket wash, and 2-day postoperative oral cephalexin in almost 20,000 patients undergoing CIED implantation. The primary outcome of 1-year hospitalization for device infection in the high-risk group was not statistically significant (non- significant 20% reduction of infection). The device infection rates were low. As there are no data supporting this practice, it is not recommended to administer postoperative antibiotic therapy.

Finally, the predominance of staphylococci as pathogens in CIED infection rather than oral flora suggests that antibiotic prophylaxis for dental procedures is of little or no value. Antimicrobial prophylaxis is not recommended for dental or other invasive procedures not directly related to device manipulation to prevent CIED infection [46].

1.11.2. Antibacterial envelope prophylaxis

The Tyrx Envelope is an antibacterial envelope releasing minocycline and rifampin in the generator pocket after CIED implantation. The most recent version is bio-absorbable and disappears within nine weeks after implantation (**figure 24**). This envelope eliminates staphylococcal species and prevents biofilm formation on implanted pacing devices in animal studies and reduces CIED infections in high-risk patients in observational studies [128]. The World-wide Randomized Antibiotic Envelope Infection Prevention trial (WRAP-IT trial) reported a 40% reduction in major cardiac implantable electronic device (CIED) infections within 12 months of the procedure with the use of an antibacterial-eluting envelope [129]. The effects of the TYRX envelope on the reduction of the risk of CIED infection are sustained beyond the first-year post procedure, without an increased risk of complications [130-131].

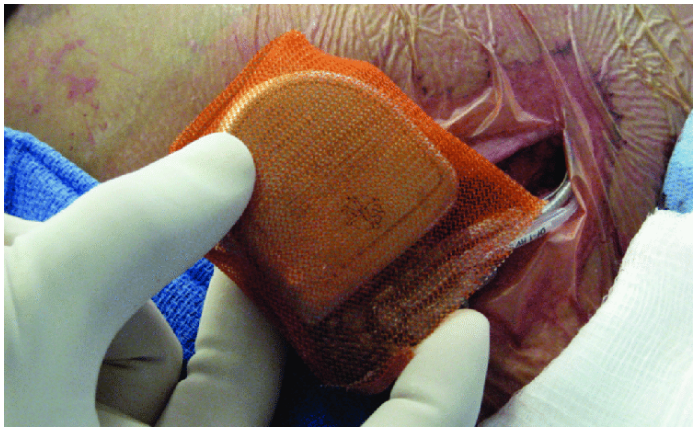


Figure 24. Tyrx Envelope (Medtronic) is an antibacterial envelope releasing minocycline and rifampin in generator pocket after CIED implantation [128].

All these studies have proved that in patients identified as at high risk for CIED infection, using a commercially available antibacterial envelope was associated with a marked reduction in CIED infections. However, the wide implementation of absorbable envelopes is limited by its cost-effectiveness, which is only balanced in patients with a specific risk profile.

1.12 Summary gaps in evidence to justify this thesis.

Gaps in clinical epidemiology of CIED-IE

- There is limited information on the historical evolution of the epidemiology, clinical presentation, microbiology, and outcomes of CIED-IE episodes covering recent decades.
- Life expectancy has improved during these decades, and the age of patients and the number of comorbidities has increased, as has the need for new and more complex CIEDs. However, these changes have not been very well studied.
- It is unknown whether the rate of CIED-IE among all types of IE is the same across all European regions or whether this percentage has increased in the 21st century.

Gaps in microbiology of CIED-IE

- In recent decades, due to antibiotic pressure, multi-resistant microorganisms that cause infections in humans have increased. There is a lack of information on the evolution of resistance to antibiotics in patients with CIED-IE and on whether aging and comorbidities have changed their microbial etiology.

Gaps in diagnosis of CIED-IE

- There is need for more studies to determine the diagnostic yield of 16S rRNA PCR in CIED infections in sonicated and non-sonicated cultures.
- Most studies performed with [18F] FDG-PET/CT have analyzed pocket and intracardiac lead regions. However, there are no studies analyzing the subcutaneous and the intravascular segments of CIED-IE.
- There is a need to study the usefulness of combining TEE and [18F] FDG-PET/CT for the diagnosis of CIED-IE. TEE explores the intracardiac segment very capably, as [18F] FDG-PET/CT does the endovascular and subcutaneous segments, hence their combination could be useful for diagnosing CIED-IE.
- There is a need to know the role of [18F] FDG-PET/CT for guiding the treatment duration, of CIED infections in general and particularly in CIED-IE, in patients with non-removed leads who are on chronic oral antimicrobial suppression therapy.

Gaps in medical treatment of CIED-IE

- New therapeutical and safer antibiotic alternatives to vancomycin are needed for treating staphylococcal CIED infections. Daptomycin and ceftaroline are very active against methicillin-susceptible and methicillin resistant staphylococci. However, their role in monotherapy or combination therapy against methicillin- or vancomycin-resistant *Staphylococcus epidermidis* CIED-IE is unknown.
- More evidence is needed from treating staphylococcal biofilm infections based on animal endocarditis-biofilm experimental models to identify more effective strategies for eradicating resting bacteria and curing these infections without resorting to surgical device removal.
- To determine the mid- and long-term efficacy and safety of chronic oral antimicrobial suppression in patients with CIED infections without device removal.

Gaps in surgical treatment of CIED-IE

- The optimal timing for removal and reimplantation, ensuring a one-time procedural strategy for non-virulent infections, remains unknown; more studies to shed light on these parameters are essential.
- Due to aging, comorbidities and more complex devices, the number of patients without complete removal of an infected CIED has been growing in recent decades. However, the prevalence, justifications and predictors for non-device removal are not well characterized nor are the outcomes.

2 Hypothesis

Hypothesis 1

1.1. As life expectancy has improved in recent decades, the age of patients, their comorbidities, and the need for new and more complex CIEDs have also increased. As a result, the prevalence of CIED-IE has increased and the epidemiological, clinical, and microbiological profile has changed over the last four decades.

1.2. Due to aging and increased comorbidity and device complexity in recent decades, short- and mid-term survival has worsened in recent years.

1.3. The same is true for infective endocarditis, and we will find no differences among the rates of surgery and mortality in different European regions.

Hypothesis 2

2.1 The sensitivity of [18] FDG PET/CT will be very high for diagnosing pocket CIED infections and will descend progressively in other lead segments (subcutaneous, endovascular, and intracardiac) although the specificity will remain very high in all topographical regions.

2.2 The combination of [18] FDG PET/CT and TEE will improve sensitivity for diagnosing systemic (lead) CIED infections without losing specificity.

2.2 Increases in [18] FDG PET/CT spleen and bone marrow metabolism will allow us to distinguish between local and systemic CIED infections.

2.4 The disappearance of [18] FDG PET/CT uptake in local and lead infections could be a safe indicator for stopping chronic oral antimicrobial suppresion therapy in patients with CIED infections without complete device removal.

Hypothesis 3

3.1 Due to increases in age, comorbidities and device complexity in recent years, high-risk device removal procedures have augmented, and the proportion of patients without device removal has also increased in recent decades.

3.2 The risk factors for not removal the device will depend more on host-dependent factors rather than on the complexity of the implanted devices.

3.3 Chronic oral antibiotic suppression will be safe and effective in patients with CIED-IE without device removal and will increase their survival.

Hypothesis 4

4.1 The *in vitro* activity (MIC/MBC) of daptomycin and ceftaroline will be similar to vancomycin against methicillin-resistant *Staphylococcus epidermidis* (MRSE) and will be superior to vancomycin against a vancomycin-resistant *S. epidermidis* (VRSE) strain.

4.2. The *in vitro* combination of daptomycin plus ceftaroline will be synergistic and bactericidal against MRSE and VRSE strains.

4.3 The combination of daptomycin plus ceftaroline will be effective and more active than monotherapies for treating MRSE and VRSE experimental endocarditis in the rabbit model.

4.4. The addition of ceftaroline to daptomycin will prevent the *in vitro* and *in vivo* development of resistance to daptomycin.

3 Objectives

The main objective of this thesis is to study changes in epidemiology, diagnosis, and antibiotic treatment of cardiac implantable electronic device infections. This overarching objective can be divided into four specific objectives:

Objective 1

1.1 To determine the epidemiological, clinical and outcomes changes in infective endocarditis (IE) in Europe during the 21st Century and to analyze potential inter-regional differences.

1.2 To study the epidemiological, clinical, microbiological, surgical and in-hospital and one-year mortality changes of cardiac implantable electronic device (CIED) IE over the last four decades and to identify one-year mortality prognostic factors.

Objective 2

2.1 To study the overall diagnostic yield of cardiac [18] FDG PET/CT in CIED-IE and in each of the four different topographical regions (pocket, subcutaneous, endovascular, and intracardiac lead) through a case-control design.

2.2 To determine the diagnostic yield of combining cardiac [18] FDG PET/CT and TEE in diagnosing systemic CIED infections.

2.3 To study whether the spleen and bone marrow hypermetabolism can distinguish local from systemic CIED infections.

2.4 To determine whether cardiac [18] FDG PET/CT is useful for safely stopping chronic oral antibiotic suppression therapy in patients with CIED infections without complete device removal who progress to negative [18] FDG PET/CT during the follow-up.

Objective 3

3.1 To study the prevalence, clinical characteristics, and outcomes of patients with CIED-IE without complete device removal and to identify the risk factors associated with not removing devices.

3.2 To determine the efficacy and safety of chronic oral antibiotic suppression in patients with CIED-IE without device removal.

Objective 4

4.1 To determine the *in vitro* activity (MIC/MBC) of daptomycin and ceftaroline in comparison with vancomycin in five MRSE and one VRSE strains.

4.2 To study whether the combination of daptomycin and ceftaroline is synergistic and bactericidal against five MRSE and one VRSE strains.

4.3 To study the *in vivo* efficacy of the combination of daptomycin plus ceftaroline for the treatment of MRSE and VRSE experimental endocarditis in rabbits.

4.4 To determine whether the combination of daptomycin plus ceftaroline is able to prevent the *in vitro* and *in vivo* development of resistance to daptomycin in MRSE and VRSE strains.

4. Material, methods, and results

The material and methods and results obtained in this thesis are presented as a compendium of research articles:

1. Ambrosioni J*, **Hernández-Meneses M*,** Durante-Mangoni E, Tattevin P, Olaison L, Freiberger T, Hurley J, Hannan M.M, Chu V, Hoen B, Moreno A, Llopis J, Cuervo G, Miró JM. and International Collaboration for Endocarditis (ICE) investigators. Epidemiological Changes and Improvement in Outcomes of Infective Endocarditis in Europe in the 21st Century. Infect Dis Ther. 2023 Mar 15. doi: 10.1007/s40121-023-00763-8. Online ahead of print. PMID: 36922460.

   *These authors contributed equally.

   Objective 1.1

2. **Hernández-Meneses M**, Llopis J, Sandoval E, Ninot S, Almela M, Falces C, Pericàs JM, Vidal B, Perissinotti A, Marco F, Mestres CA, Paré C, García de la María C, Cuervo G, Quintana E, Tolosana JM, Moreno A, Miró JM; Hospital Clinic Infective Endocarditis Team Investigators. Forty-Year Trends in Cardiac Implantable Electronic Device Infective Endocarditis. Open Forum Infect Dis. 2022 Oct 14;9(11): ofac547. doi: 10.1093/ofid/ofac547. PMID: 36381626; PMCID: PMC9648563.

   Objectives 1.1 and 1.2

3. **Hernández-Meneses M*,** Perissinotti A*, Páez-Martínez S, Llopis J, Dahl A, Sandoval E, Falces C, Ambrosioni J, Vidal B, Marco F, Cuervo G, Moreno A, Bosch J, Tolosana JM, Fuster D, Miró JM. Reappraisal of [18F] FDG-PET/CT for diagnosis and management of cardiac implantable electronic device infections. Accepted in Revista Española Cardiología, March 2023.

*These authors contributed equally.

Objectives 2.1, 2.2, 2.3 and 2.4

4. **Hernández-Meneses M,** Llopis J, Sandoval E, Cuervo G, Ninot S, Fernández M, Falces C, Vidal B, Perissinotti A, Marco F, Garcia-de-la-Maria C, Quintana E, Tolosana JM, Moreno A, Miro JM. Prevalence, risk factors and impact of chronic antibiotic suppression in patients with cardiac implantable electronic device infective endocarditis without device removal. Manuscript submitted to Microorganisms.

   Objectives 3.1 and 3.2

5. C. García-de-la-Mària*, **Marta Hernández-Meneses***, A. Cañas-Pacheco*, Guillermo Cuervo, J. García-González, J.M. Miró. Effectiveness of Daptomycin plus Ceftaroline in the treatment of methicillin-resistant and vancomycin resistant *Staphylococcus epidermidis* Experimental Endocarditis. Manuscript in preparation.

   *These authors contributed equally.

   Objectives 4.1, 4.2, 4.3 and 4.4.

Study 1

4.1 Epidemiological Changes and Improvement in Outcomes of Infective Endocarditis in Europe in the 21st Century

Juan Ambrosioni*, Marta Hernández-Meneses*, Emmanuel Durante-Mangoni, Pierre Tattevin, Lars Olaison, Thomas Freiberger, Hurley, Margaret Hannan, Vivian Chu, Bruno Hoen, Asunción Moreno, Guillermo Cuervo, Jaume Llopis, Jose M. Miró, and International Collaboration for Endocarditis (ICE) investigators. Infect Dis Ther. 2023 Mar 15. doi: 10.1007/s40121-023-00763-8. Online ahead of print. PMID: 36922460.

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ORIGINAL RESEARCH

Epidemiological Changes and Improvement in Outcomes of Infective Endocarditis in Europe in the Twenty-First Century: An International Collaboration on Endocarditis (ICE) Prospective Cohort Study (2000–2012)

Juan Ambrosioni · Marta Hernández-Meneses · Emanuele Durante-Mangoni · Pierre Tattevin · Lars Olaison · Tomas Freiberger · John Hurley · Margaret M. Hannan · Vivian Chu · Bruno Hoen · Asunción Moreno · Guillermo Cuervo · Jaume Llopis · José M. Miró

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ABSTRACT

Introduction: Infective endocarditis (IE) has undergone important changes in its epidemiology worldwide.
Methods: The study aimed to compare IE epidemiological features and outcomes according to predefined European regions and between two different time periods in the twenty-first century.
Results: IE cases from 13 European countries were included. Two periods were considered: 2000–2006 and 2008–2012. Two European regions were considered, according to the United Nations geoscheme for Europe: Southern (SE) and Northern–Central Europe (NCE). Comparisons were performed between regions and periods. A total of 4195 episodes of IE were included, 2113 from SE and 2082 from NCE;

Juan Ambrosioni and Marta Hernández-Meneses equally contributed as first authors.

Jaume Llopis and José M. Miró equally contributed as senior authors.

The ICE investigators are listed in the "Acknowledgements" section.

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2787 cases were included between 2000 and 2006 and 1408 between 2008 and 2012. Median (IQR) age was 63.7 (49–74) years and 69.4% were males. Native valve IE (NVE), prosthetic valve IE (PVE), and device-related IE were diagnosed in 68.3%, 23.9%, and 7.8% of cases, respectively; 52% underwent surgery and 19.3% died during hospitalization. NVE was more prevalent in NCE, whereas device-related IE was more frequent in SE. Higher age, acute presentation, hemodialysis, cancer, and diabetes mellitus all were more prevalent in the second period. NVE decreased and PVE and device-related IE both increased in the second period. Surgical treatment also increased from 48.7% to 58.4% ($p < 0.01$). In-hospital and 6-month mortality rates were comparable between regions and significantly decreased in the second period.

Conclusions: Despite an increased complexity of IE cases, prognosis improved in recent years with a significant decrease in 6-month mortality. Outcome did not differ according to the European region (SE versus NCE).

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Graphical Abstract:

Epidemiological Changes and Improvement in Outcomes of Infective Endocarditis in Europe in the 21st Century

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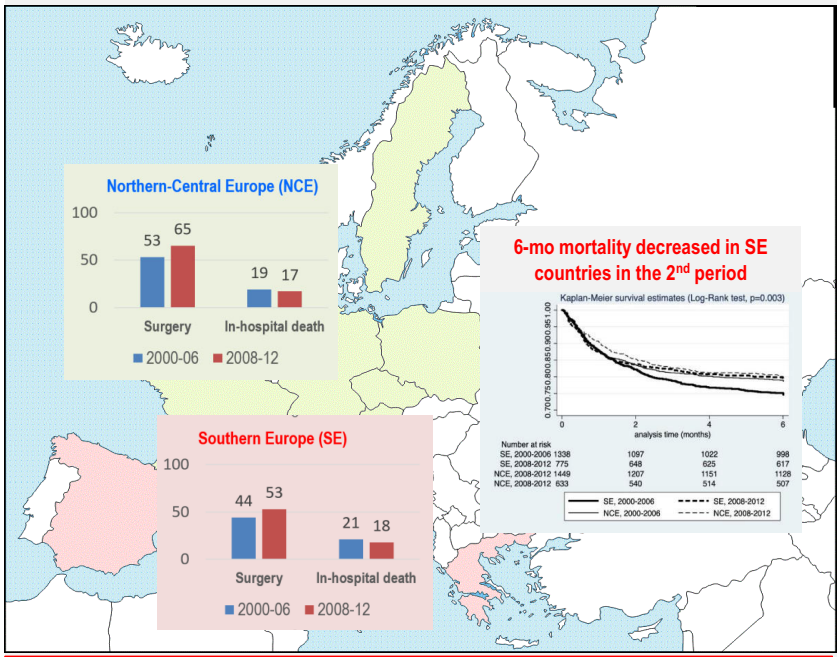
Adis

PEER-REVIEWED FEATURE

Hypothesis: The epidemiology and outcomes of infective endocarditis (IE) in Europe could have experienced substantial variations according to predefined regions [Southern (SE) and Northern and Central Europe (NCE)] and throughout the first 12 years of this Century.

Objectives: The study aimed to compare IE epidemiological features and outcomes according to predefined European regions (NCE vs. SE) and between two different time periods (2000-06 vs. 2008-12) in this Century.



Main conclusions:

- The complexity of IE cases has increased in Europe between 2000 and 2012 with a rise in the proportion of patients who benefit from surgical treatment.
- Although the percentage of in-hospital and 6-month mortality decreased modestly, this may represent a significant improvement in the overall management and prognosis of IE in Europe.

Keywords: Infective endocarditis; Europe; Epidemiology; Cardiac surgery; Mortality

Key Summary Points

In recent decades, the epidemiology and outcomes of infective endocarditis (IE) have undergone important changes worldwide, but these changes are poorly characterized in the European regions.

The study aimed to identify the epidemiological and clinical features of 4,195 episodes of IE in the 13 European countries through the International Collaboration on Endocarditis (ICE) registry, comparing two regions (Southern [SE] vs. Northen-Central Europe [NCE] and two periods of time (2000–2006 vs. 2008–2021) in the twenty-first century.

The study revealed an increase in the complexity of the IE profile over time in both of these European regions, including a significant rise in the proportion of patients benefitting from surgical treatment (from 49% to 58%; $p < 0.01$). In-hospital (19%) and six-month (22%) mortality rates were similar between the regions and significantly decreased in recent years, mainly in the SE countries (from 21% to 18%, $p < 0.01$).

We have learned that, despite the increase in patients´ comorbidities and a more complex endocarditis profile, modestly decreasing in-hospital and six-month mortality may reflect a significant improvement in the overall management and prognosis of IE in Europe.

DIGITAL FEATURES

This article is published with a digital feature (a graphical abstract). To view digital features for this article go to https://figshare.com/s/e98d8be0814c0d2b240e.

INTRODUCTION

Infective endocarditis (IE) has undergone important changes in its epidemiology worldwide. In high-income countries, the proportion of IE related to prior rheumatic disease has decreased significantly and has been replaced proportionally by cases related to degenerative valvulopathies, prosthetic valves, and cardiovascular implantable electronic devices [1]. IE incidence seems to be on the rise in high-income countries [2, 3]. Indeed, community-acquired, nosocomial, and [4] healthcare-related cases have risen in recent years. The proportion of IE caused by staphylococci and the median age of patients have also augmented, which may be partially justified by better reporting of cases. In low-income countries, in contrast, IE remains related to classic risk factors, such as rheumatic disease [5], and streptococci remain the most frequent causative agents [1].

A changing profile of IE has been described in several European countries [6–8]. European regions have large disparities in terms of access to care [3]. Moreover, in regions with comparable access to care, practices vary considerably in different countries (and even within the same country). In the early twenty-first century, IE has been described to be more often an acute disease, characterized by a high rate of *Staphylococcus aureus* infection, and to affect patients with more comorbid conditions [9]. In parallel, significant improvements in the management of IE, such as larger availability of cardiac surgery when it is indicated [10, 11] or the creation of multidisciplinary IE teams [12], have expanded in recent years. The paradox of a mortality rate that has remained relatively stable may be explained by this parallel increase in the complexity of cases and progress in care. The Euro-Endo registry is a recent prospective registry of IE cases, mainly from Europe, but also from abroad [13]. In the Euro-Endo registry initial report, in-hospital and overall 1-year mortality were 17.1% and 23.1%, respectively [14]. However, there are no reliable reports of previous years to put Euro-Endo registry information in context [15].

It is also unknown whether the epidemiological factors, complications, and outcome associated with IE differ across European regions with different healthcare systems and medical practices. The aim of this study was to compare IE epidemiological variables and outcomes in Europe according to predefined regions and across two different time periods in the twenty-first century, using data from the International Collaboration on Endocarditis (ICE) prospective cohort study (2000–2012).

METHODS

This observational study was based on data within the ICE Prospective Cohort Study and the ICE-Plus databases. The ICE Prospective Cohort Study (ICE-PCS) database contains prospective data on 5591 patients with definite and possible IE from 64 sites in 28 countries collected between January 1 2000 and December 31 2006. The ICE-Plus database contains prospective data on 2124 patients with IE from 34 sites in 18 countries collected between September 1 2008 and December 31 2012 [16]. For the purpose of this study, cases from the 28 European centers were included in the main study, and to overcome the issue of differences in practices between centers, a specific subanalysis was performed only with the 12 European centers reporting cases in both periods of time (see Fig. 1 and Supplementary Fig. 1).

Briefly, sites of the ICE cohort had a minimum enrollment of 12 cases per year in a center with access to cardiac surgery, patient identification procedures in place to ensure consecutive enrollment and to minimize ascertainment

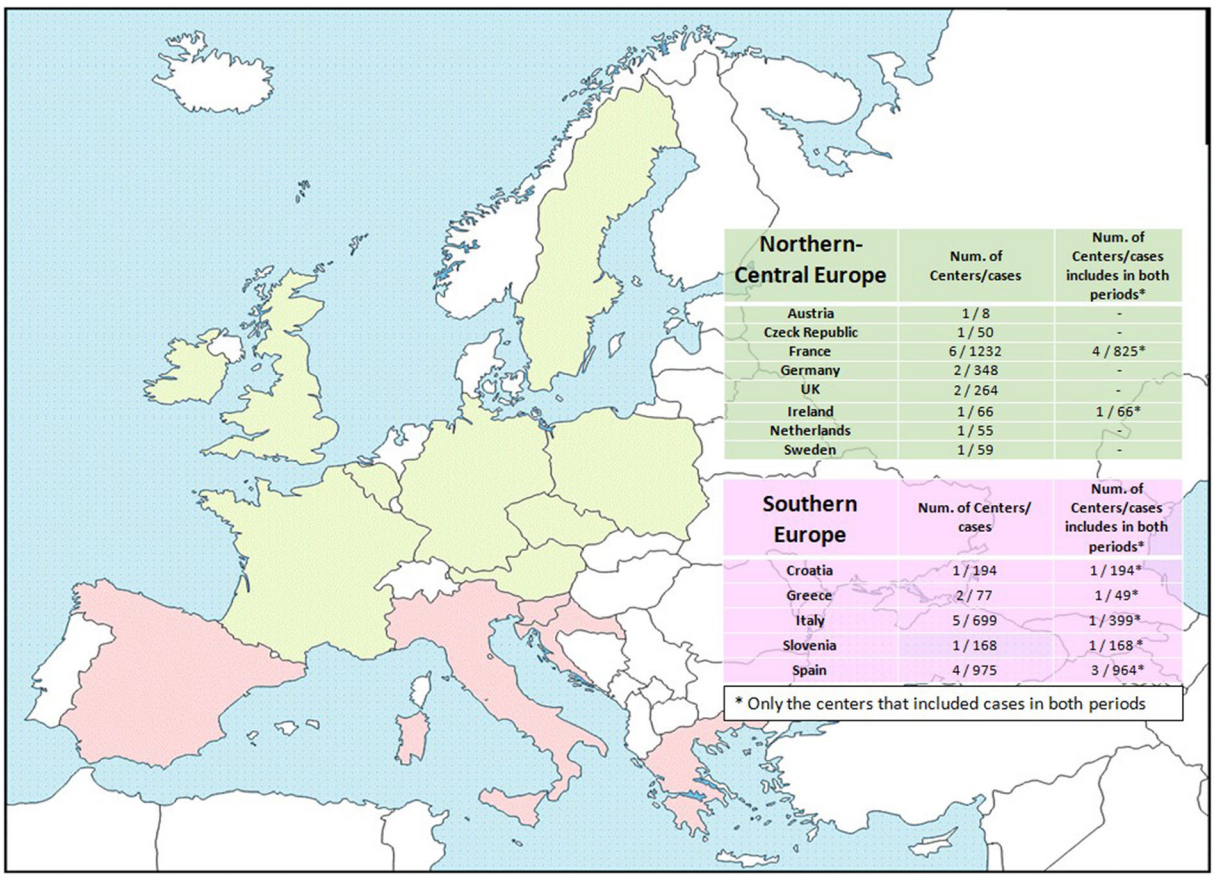


Fig. 1 Countries, centers, and cases from ICE cohort included in the study. Green: Northern–Central European countries included in the study. Red: Southern European countries included in the study

bias, high-quality data, and an institutional review board and/or ethics committee approval.

The ICE registry was funded for two periods: 2000–2006 and 2008–2012, and these two periods were arbitrarily chosen for comparing epidemiological changes and outcomes of early and late IE in the first two decades of the 21st century.

For analyses purposes, two periods were considered: 2000–2006 (early) and 2008–2012 (late), according to data collection in the ICE cohorts. Centers were grouped according to the United Nations geoscheme for Europe [14]. Two European regions were considered for analysis: Southern (SE) and Northern and Central Europe (NCE). Due to very limited data (only two ICE centers, one from Romania and one from Russia, with less than 30 IE cases reported in total), Eastern Europe could not be considered for analysis. Comparisons were performed between both periods (2000–2006 versus 2008–2012) and the two regions (SE versus NCE), including epidemiological factors, microbiology, clinical aspects, echocardiographic findings, and outcome.

The variables included in the study are presented in Tables 1, 2, and 3, and were collected using an standardized case report form. Definitions have been previously described [4]. Definitions for the place of infection were as follows: (a) Cases were considered community-acquired if they were diagnosed within 48 h of admission, and if signs or symptoms consistent with IE developed in a patient without extensive out-of-hospital contact with healthcare interventions or systems; (b) cases were considered nosocomial healthcare associated if they occurred in a patient hospitalized for more than 48 h prior to the onset of signs or symptoms consistent with IE; and (c) cases were considered non-nosocomial healthcare associated if they were diagnosed within 48 h of admission, and if signs or symptoms consistent with IE developed prior to hospitalization in patients with extensive out-of-hospital contact with healthcare interventions or systems, defined as: (1) receipt of intravenous therapy, wound care, or specialized nursing care at home within the 30 days prior to the onset of native valve endocarditis; (2) receipt of hemodialysis or intravenous chemotherapy in the 30 days before the onset of native valve endocarditis; (3) hospitalization for 2 or more days in the 90 days before the onset of native valve endocarditis; or (4) residence in a nursing home or long-term care facility [4].

The American and European IE guidelines for the indications of surgery were followed, as was the classification of emergent, urgent, and elective surgery [17, 18].

Compliance with ethics guidelines

The Institutional Review Board (IRB) of the Hospital Clinic of Barcelona approved the implementation of this study (ERB number HCB/2004/4629). 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.

Statistical Analysis

Continuous variables are presented as medians with 25th and 75th percentiles. Categorical variables are presented as frequencies and percentages of the specified group. The chi-square test was used to compare categorical variables, and the Mann–Whitney or Kruskal–Wallis tests were used, as appropriate, to compare continuous variables. Multivariable analysis was performed to identify variables independently associated with in-hospital and 6-month mortality. We did select the variables using a bivariate analysis. Those with a p-value < 0.20 were considered as candidates for the multivariable analyses. In addition, those variables with an important clinical relevance (e.g., age and gender) were also included in the model. We used both forward stepwise and backward elimination subset selection methods to identify variables independently associated with mortality. The significance level for entering effects was < 0.1, and the significance level for removing effects was < 0.05. Multicollinearity was calculated using the Belsley, Kuh, and Welsch test and principal component analysis [19]. Interaction tests between the Charlson score and the period of time or the European

Table 1 Baseline characteristics and predisposing conditions of overall cohort

	Total *N* = 4195	**NCE** *N* = 2082	**SE** *N* = 2113	***p*-Value**	**Early period (2000–2006)** *N* = 2787	**Later period (2008–2012)** *N* = 1408	***p***
Baseline characteristics							
Age (years, median, IQR) (*N* = 4195)	63.7 (49–74)	62.8 (48–74)	64.1 (48–74)	< 0.01	63.2 (47–73)	64.8 (51–75)	< 0.01
Male gender (*N* = 4186)	2904 (69.4%)	1441 (69.4%)	1463 (69.3%)	0.92	1922 (69.1%)	982 (69.8%)	0.64
First sign to admission < 1 month (*N* = 3848)	3180 (83%)	1533 (82.2%)	1647 (83.1%)	0.48	1995 (79.4%)	1185 (88.8%)	< 0.01
Hemodialysis (*N* = 3287)	194 (5.9%)	93 (5.7%)	101 (6.1%)	0.56	136 (4.9%)	58 (11%)	< 0.01
Diabetes (*N* = 4098)	776 (18.9%)	357 (17.9%)	419 (20%)	0.08	464 (17.1%)	312 (22.6%)	< 0.01
Cancer (*N* = 4099)	469 (11.4%)	242 (12.1%)	227 (10.8%)	0.22	278 (10.3%)	191 (13.8%)	< 0.01
HIV positive (*N* = 4127)	88 (2.1%)	13 (0.6%)	75 (3.6%)	< 0.01	66 (2.4%)	22 (1.6%)	0.09
Predisposing conditions							
Previous IE (*N* = 4172)	343 (8.2%)	159 (7.7%)	184 (8.7%)	0.22	235 (8.5%)	108 (7.8%)	0.44
Native valve predisposition[a] (*N* = 4034)	1137 (28.2%)	605 (29.7%)	532 (26.6%)	0.03	799 (29.1%)	338 (26.2%)	0.05
Congenital heart disease (*N* = 4078)	373 (9.4%)	208 (10.3%)	165 (8%)	0.01	229 (8.5%)	144 (10.5%)	0.04
CIED (*N* = 4160)	517 (12.4%)	226 (11%)	291 (13.8%)	< 0.01	352 (12.7%)	165 (12%)	0.51
Intravenous drug use (*N* = 4160)	324 (7.8%)	138 (6.7%)	186 (8.8%)	0.01	245 (8.9%)	79 (5.7%)	< 0.01
CA-IE (*N* = 3879)	2910 (75%)	1450 (79%)	1460 (71.5%)	< 0.01	1965 (75.7%)	945 (73.7%)	0.18

Table 1 continued

	Total $N = 4195$	NCE $N = 2082$	SE $N = 2113$	p-Value	Early period (2000–2006) $N = 2787$	Later period (2008–2012) $N = 1408$	p
N-IE ($N = 3879$)	726 (18.7%)	272 (14.8%)	454 (22.2%)	< 0.01	470 (18.1%)	256 (20%)	0.17
HA-IE ($N = 3879$)	243 (6.3%)	114 (6.2%)	129 (6.3%)	0.89	162 (6.2%)	81 (6.3%)	0.95
IE type							
Native ($N = 4123$)	2816 (68.3%)	1458 (70.9%)	1358 (65.7%)	< 0.01	1909 (70%)	907 (64.9%)	< 0.01
Prosthetic ($N = 4123$)	985 (23.9%)	482 (23.4%)	503 (24.3%)	0.49	619 (22.7%)	366 (26.2%)	0.01
CIED endocarditis ($N = 4123$)	322 (7.8%)	117 (5.7%)	205 (9.9%)	< 0.01	198 (7.3%)	124 (8.9%)	0.08

NCE Northern and Central European countries; *SE* Southern European countries; *HIV* human immunodeficiency virus; *IE* infective endocarditis; *CA* community acquired; *N* nosocomial, *HA* healthcare-associated; *CIED* cardiovascular implantable electronic devices

[a]Including aortic regurgitation, aortic stenosis, mitral regurgitation, and mitral stenosis

Table 2 Microbiologic etiology comparative analyses between the two predefined regions and two periods of overall cohort

	Total ***N*** **= 4195**	**NCE** ***N*** **= 2082**	**SE** ***N*** **= 2113**	***p*-Value**	**Early period (2000–2006)** ***N*** **= 2787**	**Later period (2008–2012)** ***N*** **= 1408**	***p*-Value**
Staphylococcus aureus (*N* = 3882)	1039 (26.8%)	506 (26.2%)	533 (27.2%)	0.59	711 (27.2%)	328 (26.3%)	0.61
Viridans group Streptoccoci (*N* = 3882)	655 (17.4%)	295 (15.9%)	360 (18.2%)	0.16	443 (18%)	212 (16.7%)	0.39
Coagulase negative *Staphylococcus* (*N* = 3882)	510 (13.6%)	219 (10.8%)	291 (14.9%)	< 0.01	327 (12.5%)	183 (14.8%)	0.09
Enterococcus spp. (*N* = 3882)	427 (10.5%)	202 (10.1%)	225 (10.8%)	0.60	269 (8.9%)	158 (12.5%)	< 0.01
Streptococcus gallolyticus (*N* = 3882)	330 (9%)	173 (12.3%)	157 (7.3%)	< 0.01	221 (8.8%)	109 (9%)	0.90
Other streptococci[a] (*N* = 3882)	257 (7.2%)	143 (10.1%)	144 (5.8%)	< 0.01	159 (6.4%)	98 (8.1%)	0.11
Gram negative (not HACEK[b]) (*N* = 3882)	132 (4%)	59 (3.1%)	73 (3.7%)	0.37	83 (3.2%)	49 (3.9%)	0.25
Polymicrobial (*N* = 3882)	85 (1.6%)	59 (2.6%)	26 (1.2%)	< 0.01	44 (0.5%)	41 (3%)	< 0.01
HACEK[b] (*N* = 3882)	50 (1.2%)	28 (1.5%)	22 (1.1%)	0.46	35 (1.3%)	15 (1.1%)	0.68
Fungi (*N* = 3882)	53 (1.2%)	22 (1.2%)	31 (1.2%)	0.99	36 (1.3%)	17 (1.2%)	0.96
Negative culture (*N* = 3882)	235 (4.9%)	124 (2.6%)	111 (5.9%)	< 0.01	219 (8%)	16 (1.1%)	< 0.01
Other (*N* = 3882)	109 (2.6%)	53 (2.5%)	56 (2.7%)	0.73	78 (3%)	31 (2.2%)	0.20

[a]Other *Streptococci* including *Streptococcus pneumoniae*, beta hemolytic group Streptococci, etc.
[b]HACEK group includes *Haemophilus* species, *Aggregatibacter actinomycetemcomitans*, *Aggregatibacter aphrophilus* (formerly *Haemophilus aphrophilus* and *Haemophilus paraphrophilus*), *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* species.

regions were also performed. Kaplan–Meier curves were built to compare 6-month mortality between periods and region. Prognostic factors for in-hospital and 6-month mortality were analysed using a logistic regression model, with comparisons reported with odds ratios (ORs) with 95% confidence intervals (CIs). For all tests, a p-value < 0.05 was considered significant. Statistical analyses were performed using Stata statistical package v.14 (Stata Corporation LLC).

Table 3 Echocardiographic findings, complications, treatment, and outcome of overall cohort

	Total $N = 4195$	NCE $N = 2082$	SE $N = 2113$	*p*-Value	Early period (2000–2006) $N = 2787$	Later period (2008–2012) $N = 1408$	*p*-Value
Vegetation present							
Intracardiac vegetation ($N = 4146$)	3450 (83.2%)	1650 (80.3%)	1800 (86.1%)	< 0.01	2301 (83.5%)	1149 (82.7%)	0.50
Aortic valve ($N = 4135$)	1590 (38.5%)	776 (37.7%)	814 (39.2%)	0.35	1035 (37.7%)	555 (39.9%)	0.18
Mitral valve ($N = 4135$)	1546 (37.4%)	781 (38%)	765 (36.8%)	0.42	1030 (37.6%)	516 (37.1%)	0.76
Tricuspid valve ($N = 4131$)	384 (9.3%)	176 (8.6%)	208 (10%)	0.11	280 (10.2%)	104 (7.5%)	< 0.01
Pulmonary valve ($N = 4124$)	43 (1%)	21 (1%)	22 (1.1%)	0.91	26 (1%)	17 (1.2%)	0.43
Complications							
Stroke ($N = 4107$)	719 (17.5%)	373 (18.6%)	346 (16.5%)	0.08	455 (16.8%)	264 (19%)	0.08
Embolization non-stroke ($N = 4096$)	1136 (27.7%)	530 (26.4%)	606 (29%)	0.07	660 (24.4%)	476 (34.2)	< 0.01
CHF ($N = 4093$)	1305 (31.9%)	578 (28.9%)	727 (34.7%)	< 0.01	793 (29.3%)	512 (37%)	< 0.01
Persistent positive blood culture[a] ($N = 4027$)	293 (7.3%)	130 (6.5%)	163 (8%)	0.06	171 (6.3%)	122 (9.2%)	< 0.01
Intracardiac abscess ($N = 4122$)	698 (16.9%)	386 (19%)	312 (14.9%)	< 0.01	392 (14.3%)	306 (22.1%)	< 0.01
Treatment/outcome							
Surgical therapy[b] ($N = 4162$)	2163 (52%)	1177 (56.9%)	986 (47.1%)	< 0.01	1349 (48.7%)	814 (58.4%)	< 0.01
Time elapsed between admission and surgery ($N = 2163$) (days)	1899 (87.8%)	15 (6–30)	18 (9–32)	< 0.01	17 (8–32)	15 (6–29)	< 0.01

Table 3 continued

	Total $N = 4195$	NCE $N = 2082$	SE $N = 2113$	*p*-Value	Early period (2000–2006) $N = 2787$	Later period (2008–2012) $N = 1408$	*p*-Value
In-hospital death[c] ($N = 4169$)	806 (19.3%)	387 (18.7%)	419 (19.9%)	0.34	558 (20.1%)	248 (17.8%)	0.06
Six-month mortality ($N = 4187$)	939 (22.4%)	439 (21.2%)	500 (23.7%)	0.05	649 (23.4%)	290 (20.6%)	0.04
Relapses ($N = 1973$)	109 (5.5%)	45 (4.6%)	64 (6.4%)	0.08	70 (5.6%)	39 (5.5%9	0.18

NCE Northern and Central European countries; *SE* Southern European countries; *CHF* congestive heart failure

[a]Persistent blood cultures were defined as blood cultures that remained positive after 7 days of effective therapy

[b]In the NCE region, the rates of cardiac surgery in the periods 2000–2006 and 2008–2012 were 53.05% ($N = 766$) and 63.34% ($N = 411$), respectively. In the SE region they were 43.83% ($N = 583$) and 52.75% ($N = 403$) in the same time periods

[c]In the NCE region, the in-hospital mortality rates in the periods 2000–2006 and 2008–2012 were 19.25% ($N = 279$) and 17.06% ($N = 411$), respectively. In the SE region they were 20.85% ($N = 279$) and 18.06% ($N = 140$) in the same time periods

RESULTS

The distribution of countries according to the predefined regions, and the relative proportion of cases and centers provided by each country are shown in Fig. 1. There were 2782 cases in the early period (2000–2006) and 1408 cases in the later period (2008–2012), see Fig. 2. Most cases from the SE region were provided by Spanish (975 cases from four centers) and Italian (699 cases from five centers) centers, whereas most cases from the NCE region were provided by French sites (1232 cases from six centers). In all, 4195 episodes of IE were included in the final analysis, 2113 from SE and 2082 from NCE. Overall, median (IQR) age was 63.7 (49–74) years and 69.4% were males. Native valve IE (NVE), prosthetic valve IE (PVE), and cardiac implantable electronic device-related IE were diagnosed in 68.3%, 23.9%, and 7.8% of cases, respectively; 52% underwent surgery and 19.3% died during hospitalization.

Baseline Characteristics and Predisposing Conditions

Baseline characteristics and predisposing conditions of patients are presented in Table 1. Human immunodeficiency virus (HIV) infection was more prevalent in SE centers. Native valve involvement was more prevalent in NCE, whereas device-related IE was more frequent in SE ($p < 0.01$ for all comparisons). When comparing time periods, patient age increased ($p < 0.01$) and acute presentation, hemodialysis, cancer, and diabetes mellitus was all more prevalent in the second period ($p < 0.01$ for all comparisons). Intravenous drug use became less prevalent ($p < 0.01$). Native valve IE decreased ($p < 0.01$) and prosthetic ($p = 0.01$) and device-related IE both increased, although the latter not significantly ($p = 0.08$).

Microbiological Findings

Microbiological features are presented in Table 2. Overall, *S. aureus* was the most prevalent microbial etiology, in 26.8% of cases and it was equally distributed in NCE and SE

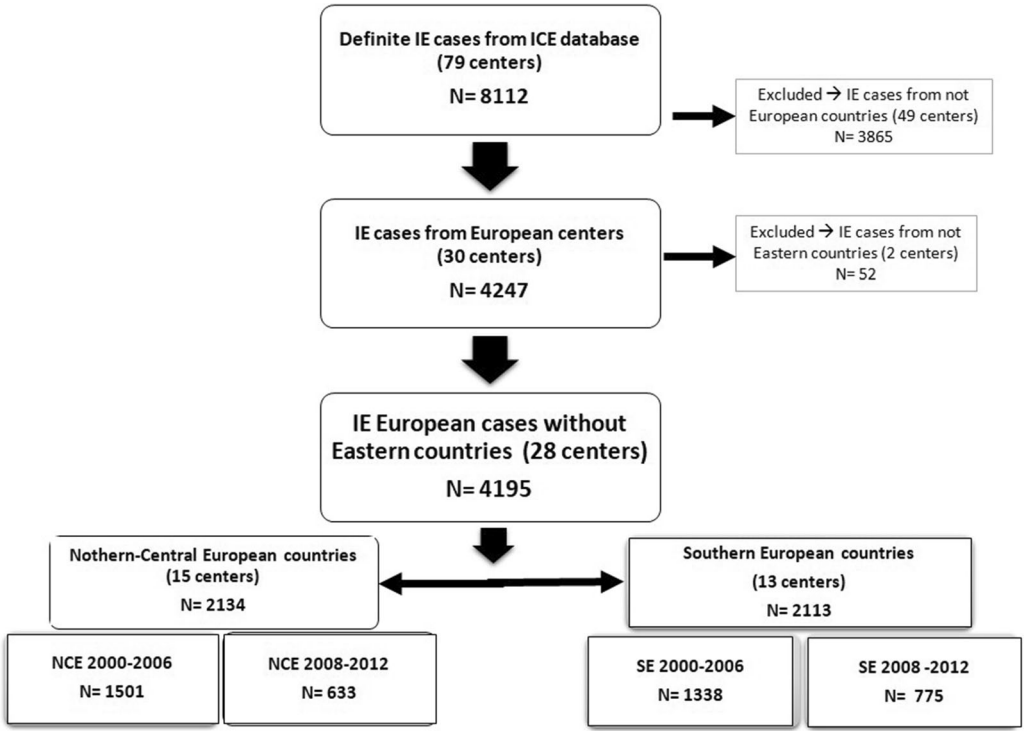


Fig. 2 Flow chart of cases included in the study. *NCE* Northern and Central European countries (according to the UN geoscheme), *SE* Southern European countries (according to the UN geoscheme)

countries. Coagulase-negative staphylococci (CoNS) IE was more frequent in SE, viridans group *Streptococcus* (VGS) and *Enterococcus* spp. were equally distributed, and *S. gallolyticus* (formerly *S. bovis*) was more frequent in NCE countries. When comparing time periods, *Enterococcus* spp. increased with no other relevant difference among microorganisms. Notably, the proportion of culture negative cases was extremely low in the second period, accounting for only 1.1% of cases.

Echocardiographic Findings, Treatment, and Outcome

Echocardiographic findings, complications, treatment, and outcome are presented in Table 3. Valve involvement was not different between regions. Stroke and intracardiac abscesses were more prevalent in NCE, while systemic embolization was more prevalent in SE, although not statistically significant. Stroke ($p = 0.08$), congestive heart failure, systemic embolization, persistently positive blood cultures, and intracardiac abscesses increased in the second period ($p < 0.01$ for all comparisons). Surgical treatment was applied significantly more often in NCE countries, and regarding time periods, increased from 48.7% to 58.4% ($p < 0.001$). Stratified by group, surgery recourse remained stable in NCE countries in both periods (61.7% versus 64.6%, $p = 0.39$), but significantly increased in the SE countries (44.8% versus 50.1%, $p = 0.03$). In-hospital and 6-month mortality were comparable between regions and significantly decreased at 6 months in the second period from 23.4% to 20.6% ($p = 0.04$). When analyzed by period and by region, a more pronounced decrease in mortality was observed in SE countries (Fig. 3).

Multivariable analysis of factors associated with in-hospital mortality is presented in Table 4. The multicollinearity index was weak (maximum of 3.22). Classic IE prognostic factors (such as Charlson score, PVE, *Staphylococcus aureus* etiology, congestive heart failure,

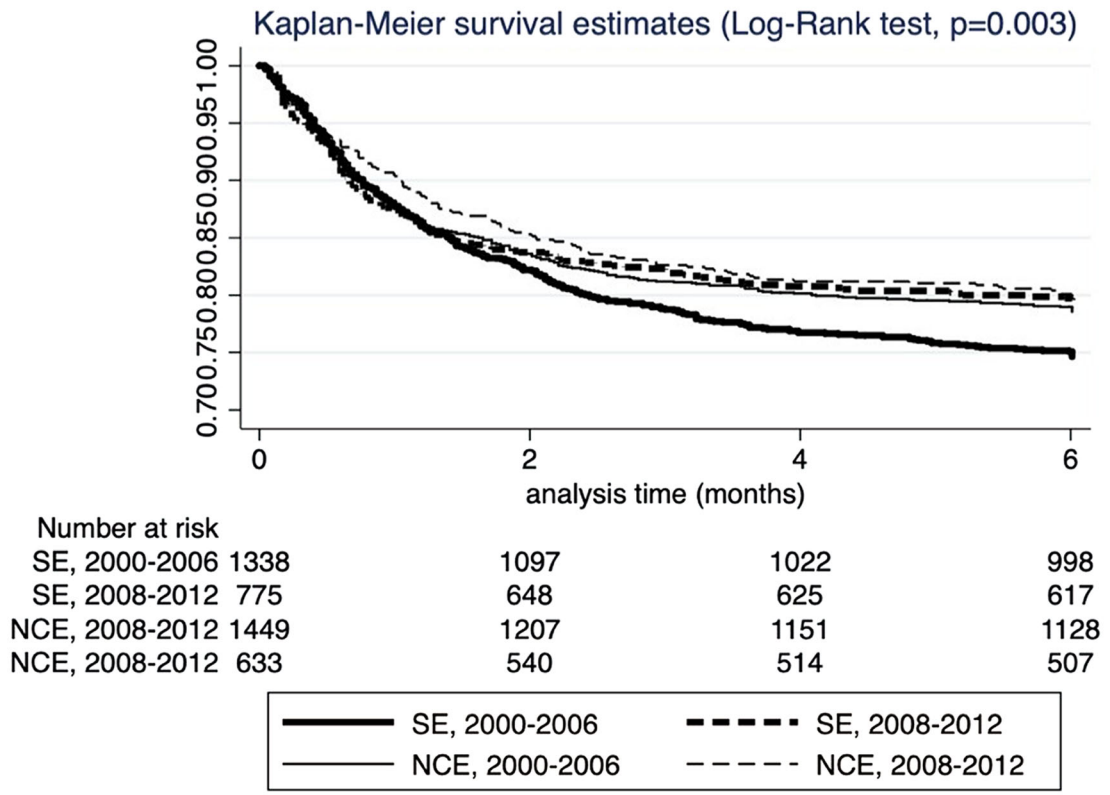


Fig. 3 Kaplan–Meir curves of 6-month mortality for 4195 IE cases included in the study, according to pre-established regions and periods. *SE* Southern-European Countries; *NCE* Northern–Central European Countries

stroke, persistently positive blood cultures, or paravalvular complications), were independently related to increased mortality. VGS etiology and surgery were protective factors. Surgery was also protective when we excluded the patients who died before 2 weeks without surgery, with an OR (95%CI) of 0.67 (0.57, 0.80). The region (NCE versus SE) was unrelated to both in-hospital and 6-month mortality, but being diagnosed in the second period was a protective factor (OR of 0.54 and 0.53, respectively, for in-hospital and 6-month mortality).

A subanalysis was performed with Charlson co-morbidity index (Fig. 4), showing that 6-month mortality was consistently lower in the second period for a given Charlson score, without interaction between variables (interaction test $p = 0.08$).

The specific subanalysis performed only with centers reporting cases in both periods ($N = 2665$ cases, from 12 centers) showed no major differences in results, compared with the entire cohort (Supplementary Fig. 1 and Supplementary Tables 1–4).

DISCUSSION

In recent decades, the epidemiology of IE in developed countries has shown a trend toward a higher comorbidity index, and increased complexity of cases, and therefore, a shift in the microbiological causes, favoring staphylococcal etiology [1]. Despite these recognized changes of IE in recent years, no study has compared different European regions or has evaluated prognosis trends over time. Our study shows an overall improvement in outcomes in Europe, despite the increased complexity of cases (shown by the higher rates of comorbidities

Table 4 Multivariable analysis of factors associated with in-hospital mortality and 6-month mortality of overall cohort

	In-hospital mortality			Six-month mortality		
	Multivariate OR	CI 95%	*p*-Value	Multivariate OR	CI 95%	*p*-Value
Charlson score	1.36	(1.24, 1.50)	< 0.01	1.34	(1.01, 1.66)	0.04
Prosthetic valve IE	1.62	(1.26, 2.10)	< 0.01	1.68	(1.30, 2.17)	< 0.01
Staphylococcus aureus[a]	1.82	(1.43, 2.34)	< 0.01	1.72	(1.32, 2.24)	< 0.01
ConS[a]	1.59	(1.17, 2.21)	< 0.01	1.48	(1.07, 2.09)	< 0.01
Viridans group Streptoccoci[a]	0.38	(0.21, 0.72)	< 0.01	0.64	(0.44, 0,92)	0.02
Intracardiac vegetation	1.57	(1.14, 2.19)	< 0.01	1.59	(1.15, 2.19)	< 0.01
Stroke	2.47	(1.91, 3.18)	< 0.01	2.31	(1.79, 3.01)	< 0.01
CHF	2.79	(2.24, 3.49)	< 0.01	2.77	(2.21, 3.46)	< 0.01
Persistent positive blood culture	2.69	(1.91, 3.78)	< 0.01	2.65	(1.84, 3.81)	< 0.01
Paravalvular complications	1.83	(1.43, 2.32)	< 0.01	1.81	(1.42, 2.32)	< 0.01
N IE and HA IE versus CA IE	1.89	(1.56, 2.27)	< 0.01	1.30	(1.01, 1.66)	0.04
In-hospital surgery	0.69	(0.55, 0.87)	< 0.01	0.68	(0.54, 0.86)	< 0.01
European region (SE versus NCE)	1.33	(0.88, 1.45)	0.18	1.33	(0.91, 1.41)	0.27
Period (2008–2012 versus 2000–2006)	0.54	(0.40, 0.76)	< 0.01	0.53	(0.39, 0.73)	< 0.01

This analysis was adjusted by age and gender

NCE Northern and Central European countries; *SE* Southern European countries; *IE* infective endocarditis; *CHF* congestive heart failure; *N* nosocomial; *HA* healthcare associated; *CA* community acquired; *IE* infective endocarditis

[a]The reference group is the rest of the etiological microorganisms

such as hemodialysis or diabetes mellitus). Moreover, as shown in Fig. 4, for a given Charlson score, mortality was always lower in the second period.

The reasons for this overall better prognosis in the later period are not completely understood, although they may reflect several factors such as the increased proportion of early surgery (although not performed faster after admission in the second period); the better management of IE complications such as CNS emboli, or the utilization of more effective, better tolerated, and active antimicrobial agents; and the multidisciplinary approach by IE teams, among other factors. Although these data were not analyzed in our article, the role of newer antimicrobials or newer combinations of drugs in Europe may have had an impact. In fact, although recommended treatment regimens have remained almost unchanged for decades [15, 20], antimicrobial management of IE in reference centers frequently differ from the recommendations, even in centers whose clinical specialists have co-written the international management guidelines [21] The creation of specific teams dedicated to the management of these increasingly complex cases (so-called IE teams) [12], might have also impacted the observed global improvement. These teams, an integration of ID specialists, clinical microbiologists, cardiologists, cardiac surgeons, nuclear medicine, and radiology specialists, among others, have been shown to significantly reduce the mortality of IE cases [22], and have become more frequent in many centers recently.

Regarding geographical trends among regions, during the early period, prognosis was slightly better in NCE countries, and was

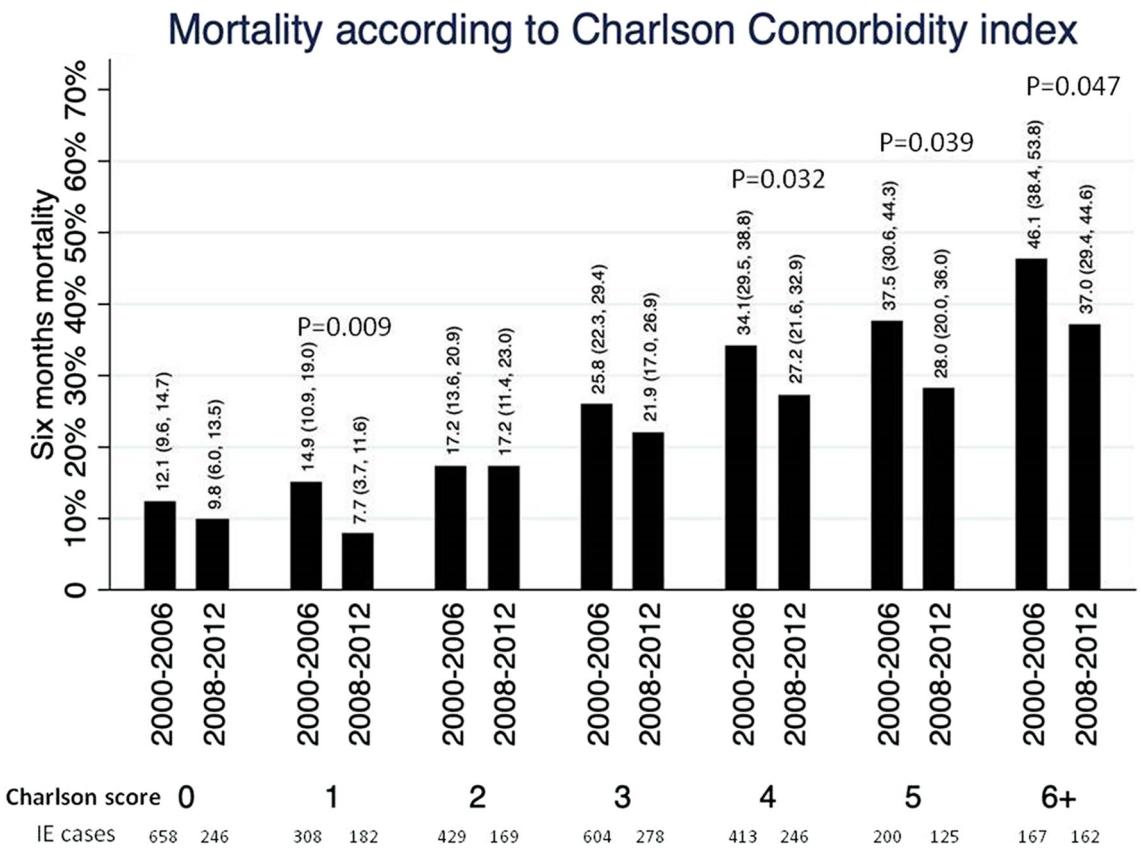


Fig. 4 Analysis of mortality rate according to Charlson score, stratified by period (2000–2006 and 2008–2012)

associated with higher rates of cardiac surgery. As shown in Fig. 3, in the most recent chronological period these differences in mortality were not observed among regions, and overall mortality has decreased in association with an increase in the proportion of IE patients treated by cardiac surgery in SE countries. Unfortunately, we were unable to analyze the situation of IE in Eastern Europe, where access to care may be more limited and where intravenous drug use has importantly risen recently, with HIV and IE related to intravenous drug use becoming a major concern [23]. In this context, we would expect a quite different epidemiological and microbiological profile, with a higher proportion of right-sided IE and higher prevalence of co-morbidities such as HIV and HCV co-infection [24].

We did not identify major microbiological relevant differences between regions or periods, apart from a significant increase in the proportion of enterococcal IE, which may be related to the progressive aging of patients with IE [25] and the increasing prevalence of colorectal pathology in the general population [26]. Enterococcal IE is expected to rise even more, considering that *Enterococcus* spp. is the main cause of IE in transcatheter aortic valve replacement (TAVR) cases, and the number of TAVR cases is also expected to increase in the future, due to expanding indications [25–28]. *S. aureus* and CoNS IE, on the rise during in recent decades, remained stable during the two periods of our study.

However, the reduction in mortality shown in our study represents a modest but positive trend in the field of IE. Putting our data in context, with respect to the Euro-Endo registry, in hospital mortality in our study was 20.1% for the first period and 17.8% for the second, compared with 17% in the Euro-Endo registry [14, 29, 30]. Thus, it seems to continue with a

trend towards a lower mortality, but these data should be confirmed at 6-month of follow-up. Unfortunately, as with the ICE cohort, the majority of hospitals reporting to the Euro-Endo registry are tertiary reference centers, and consequently may not accurately reflect the overall epidemiology of IE in Europe (including smaller hospitals from smaller cities, with no cardiac surgery).

Our study has several strengths. First, the large number of episodes allows a reliable analysis and provides adequate statistical power. Moreover, no previous large studies of this type have been performed in Europe since the Euro-Endo registry cannot compare two periods of time. To avoid the bias of different prognosis being related to a center's experience, we have performed a subanalysis with centers participating in both periods, and the main results did not change.

Our article also has several limitations. Firstly, the UN geoscheme for Europe is a statistical and not a meaningful healthcare classification. Most of the countries included in our study belong to the World Health Organization (WHO) regions with low or extremely low childhood mortality, and thus, no comparison was possible between countries with high and low sanitary standards. Moreover, the classification of Southern versus Northern–Central is arbitrary. As a multicenter study, the use of health administrative data would have eliminated the bias due to the selective reporting of cases from reference centers, although it would likely have yielded less granular data. Moreover, there are large differences in practices even within the same country; for instance, a center from Marseille could have been considered as part of SE if only a geographical classification was applied. Conversely, a center from Milan could have been considered as part of the NCE region [14]. Furthermore, some countries are largely over-represented (such as France, Spain, or Italy), and the situation in other countries of the same region may be different. Unfortunately, Eastern Europe was excluded due to lack of data, which might have impacted on the epidemiology and outcomes of IE, as previously discussed. In addition, the retrospective nature of the study and the missing data existing for some variables may affect results of the analyses, particularly the subanalysis with the centers reporting cases in both periods due to the attrition in the number of cases. However, this is a problem observed with all retrospective cohorts. There is a bias of IE selection cases, since mostly large university tertiary centers provided data to ICE. The microbiology, predisposing conditions, and outcome of IE in smaller centers in the same countries or regions could differ considerably. Last but not least, data collection in the ICE cohort finished in 2012, more recent data was not available.

CONCLUSION

The complexity of IE cases increased in Europe between 2000 and 2012, accompanied by an increase in the proportion of patients undergoing surgical treatment. Survival improved in the latest period, particularly in SE countries. Although the percentage decrease of in-hospital and 6-month mortality is modest, considering the increased age and case complexity of patients with IE, it may represent a significant improvement in the overall treatment, prognosis, and potential public health implications for the management IE in Europe.

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Guillermo Cuervo, Jaume Llopis and José M. Miró contributed to the design and development of the study and to the acquisition, analysis, and interpretation of the results. All authors contributed to producing the article, by drafting the work or revising it critically. All authors have had access to the final version and have approved it to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were properly investigated and resolved.

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Compliance with Ethics Guidelines. The Institutional Review Board (IRB) of the Hospital Clinic of Barcelona approved the implementation of this study (ERB number HCB/2004/4629). 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.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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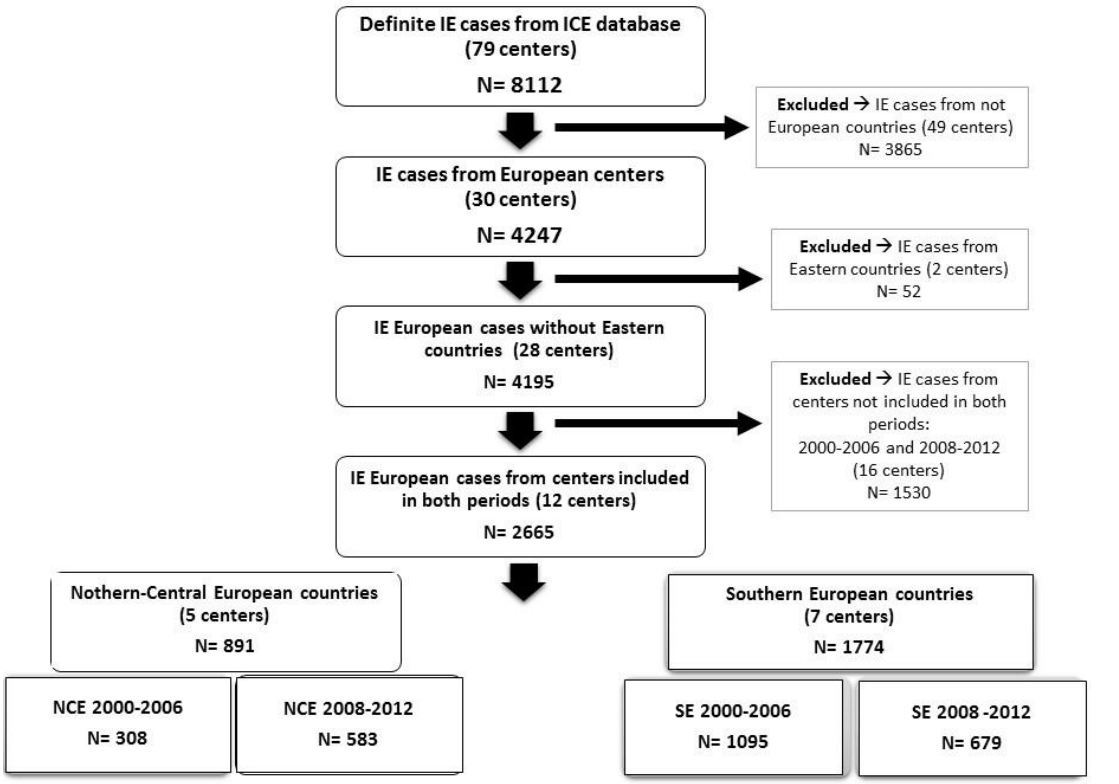
Publisher's Note

Supplementary Figure 1. Patient flowchart for the specific sub-analysis performed only with centers reporting cases in both periods (N=2665 cases, from 12 centers)



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Supplementary table 1. Baseline characteristics and predisposing conditions of all cases from the centers included in both periods.

	Total N= 2665	NCE N= 891	SE N=1774	p	Early period (2000-2006) N= 1403	Later period (2008-2012) N= 1262	p
Baseline characteristics							
Age (years, median IQR) (N=2665)		63 (50 – 74)	63.6 (48-74)	0.18	62.8 (47-73)	63.7 (51-74)	0.02
Male gender (N=2662)	1861 (69.9%)	636 (71.5%)	1225 (69.1%)	0.21	978 (69.8%)	883 (70.1%)	0.86
First sign to admission < 1 month (N=2467)	2048 (83%)	683 (84.6%)	1365 (82.2%)	0.13	974 (76.9%)	1074 (89.5%)	<0.01
Hemodialysis (N= 1879)	119 (6.3%)	24 (4.7%)	95 (6.9%)	0.06	64 (4.6%)	55 (11.5%)	<0.01
Diabetes (N= 2632)	523 (19.9%)	160 (18.4%)	363 (20.6%)	0.17	239 (17.1%)	284 (23%)	<0.01
Cancer (N= 2641)	261 (9.9%)	124 (10%)	137 (7.8%)	<0.01	140 (10%)	121 (9.7%)	0.78
HIV positive (N= 2631)	60 (2.3%)	5 (0.6%)	55 (3.1%)	<0.01	43 (3.1%)	17 (1.4%)	<0.01
Predisposing conditions							
Previous IE (N=2649)	192 (7.2%)	36 (4.1%)	156 (8.8%)	<0.01	108 (7.7%)	84 (6.7%)	0.32
Native valve predisposition* (N= 2563)	714 (27.9%)	257 (30%)	457 (26.8%)	0.10	412 (29.9%)	302 (25.5%)	0.01
Congenital heart disease (N= 2587)	243 (9.4%)	102 (11.8%)	141 (8.2%)	<0.01	105 (7.7%)	138 (11.2%)	<0.01
CIED (N= 2077)	322 (15.5%)	74 (10.8%)	248 (17.9%)	<0.01	167 (19.3%)	155 (12.8%)	<0.01
Intravenous drug use (N= 2647)	178 (6.7%)	37 (4.2%)	141 (8%)	<0.01	115 (8.2%)	63 (5%)	<0.01
IE Type							
CA-IE (N=2665)	1899 (75.5%)	678 (86.3%)	1221 (70.6%)	<0.01	1046 (77.3%)	853 (73.5%)	0.02
N-IE (N=2665)	471 (18.7%)	80 (10.2%)	391 (22.6%)	<0.01	234 (17.3%)	237 (20.4%)	0.04
HA-IE (N=2665)	144 (5.8%)	28 (3.5%)	116 (6.8%)	<0.01	74 (5.4%)	70 (6.1%)	0.55
Native (N= 2614)	1769 (67.7%)	622 (70.8%)	1147 (66.1%)	0.02	961 (70.5%)	808 (64.6%)	<0.01
Prosthetic (N= 2614)	626 (19.5%)	219 (24.9%)	407 (23.5%)	0.41	299 (21.9%)	327 (26.1%)	0.01
CIED endocarditis (N= 2614)	219 (8.4%)	38 (4.3%)	181 (10.4%)	<0.01	103 (7.6%)	116 (9.3%)	<0.01

*Including aortic regurgitation. aortic stenosis. mitral regurgitation and mitral stenosis.

Abbreviations: NCE: Northern and Central European countries; SE: Southern European countries; HIV. human immunodeficiency virus; IE: infective endocarditis; CA: communited adquired; N: nosocomial, HA: healthcare-associated CIED: cardiovascular implantable electronic devices.

Supplementary table 2. Microbiologic etiology comparative analyses between the two predefined regions and two periods of all cases from the centers included in both periods.

	Total N=2665	NCE N= 891	SE N=1774	P	Early period (2000-2006) N= 1403	Later period (2008-2012) N= 1262	p
Staphylococcus aureus (N= 2493)	669 (26.8%)	210 (26.2%)	459 (27.2%)	0.59	370 (27.2%)	299 (26.3)	0.61
Viridans group Streptoccoci (N= 2493)	435 (17.4%)	128 (15.9%)	307 (18.2%)	0.16	245 (18%)	190 (16.7)	0.39
Coagulase negative Staphylococcus (N= 2493)	338 (13.6%)	87 (10.8%)	251 (14.9%)	<0.01	170 (12.5%)	168 (14.8)	0.10
Enterococcus spp. (N= 2493)	263 (10.5%)	81 (10.1%)	182 (10.8%)	0.60	121 (8.9%)	142 (12.5%)	<0.01
Streptococcus gallolyticus (N= 2493)	222 (9%)	99 (12.3%)	123 (7.3%)	<0.01	120 (8.8%)	102 (9%)	0.90
*Other streptococci** (N= 2493)	179 (7.2%)	81 (10.1%)	98 (5.8%)	<0.01	87 (6.4%)	92 (8.1%)	0.11
Gram negative (not HACEK**) (N= 2493)	97 (4%)	33 (4.1%)	64 (3.8%)	0.70	53 (3.9%)	44 (3.9%)	0.97
Polymicrobial (N= 2493)	41 (1.6%)	21 (2.6%)	20 (1.2%)	0.02	7 (0.5%)	34 (3.9%)	<0.01
*HACEK*** (N= 2493)	31 (1.2%)	12 (1.5%)	19 (1.1%)	0.46	18 (1.3%)	13 (1.1%)	0.68
Fungi (N= 2493)	31 (1.2%)	10 (1.2%)	21 (1.2%)	0.99	17 (1.3%)	14 (1.2%)	0.97
Negative culture (N= 2493)	121 (4.9%)	21 (2.6%)	100 (5.9%)	<0.01	109 (8%)	12 (1.1%)	<0.01
Other (N= 2493)	66 (2.6%)	20 (2.5%)	46 (2.7%)	0.73	41 (3%)	25 (2.2%)	0.20

*Other *streptococci* includes: *Streptococcus pneumoniae*. betahemolitic group streptococci. etc.

**HACEK group includes: *Haemophilus* species. *Aggregatibacter actinomycetemcomitans*. *Aggregatibacter aphrophilus* (formerly *Haemophilus aphrophilus* and *Haemophilus paraphrophilus*). *Cardiobacterium hominis*. *Eikenella corrodens* and *Kingella* species.

Abbreviations: NCE: Northern and Central European countries; SE: Southern European countries.

Supplementary table 3. Echo findings, complications, treatment and outcome of all cases from centers included in both periods.

	Total N=2665	NCE N= 891	SE N=1774	P	Early period (2000-2006) N= 1403	Later period (2008-2012) N= 1262	p
Vegetation findings							
Intracardiac vegetation (N= 2634)	2241 (85%)	720 (81.7%)	1521 (86.8%)	<0.01	1210 (87.1%)	1031 (82.8%)	<0.01
Aortic valve (N=2623)	1062 (40.5%)	362 (41.1%)	700 (40.2%)	0.63	562 (40.8%)	500 (40.2%)	0.75
Mitral valve (N=2622)	989 (37.7%)	352 (40%)	637 (36.5%)	0.08	528 (38.4%)	461 (37%)	0.45
Tricuspid valve (N=2618)	222 (8.5%)	59 (6.7%)	163 (9.4%)	0.02	132 (9.6%)	90 (7.2%)	0.11
Pulmonary valve (N= 2614)	27 (1%)	9 (1%)	18 (1%)	0.99	10 (0.7%)	17 (1.4%)	0.11
Complications							
Stroke (N=2635)	500 (19%)	202 (23.1%)	298 (16.9%)	<0.01	255 (18.4%)	245 (19.6%)	0.42
Embolization non-stroke (N= 2632)	830 (31.5%)	316 (36.1%)	514 (29.3%)	<0.01	387 (27.9%)	443 (35.6)	<0.01
CHF (N= 2628)	921 (35%)	319 (36.6%)	602 (34.3%)	0.24	470 (33.8%)	451 (36.4%)	0.17
Persistent positive blood culture* (N= 2571)	215 (8.4%)	73 (8.4%)	142 (8.4%)	0.98	111 (8%)	104 (8.7%)	0.53
Intracardiac abscess (N= 2629)	515 (19.6%)	238 (27.2%)	277 (15.8%)	<0.01	228 (16.4%)	287 (23.1%)	<0.01
Treatment/outcome							
Surgical therapy (N= 2641)	1385 (52.4%)	564 (63.6%)	821 (46.8%)	<0.01	676 (48.5%)	709 (56.9%)	<0.01
In-hospital death (N= 2651)	516 (19.5%)	141 (15.9%)	375 (21.2%)	<0.01	295 (21.1%)	221 (17.7%)	0.03
One-year follow up							
One-year mortality (N=2201)	681 (30.9%)	191 (25.2%)	490 (33.9%)	<0.01	401 (29.6%)	280 (33.1%)	0.09
Relapses (N= 1365)	79 (5.8%)	25 (4.1%)	54 (7.2%)	0.01	42 (5.6%)	37 (6.1%)	0.70

*Persistent blood cultures were defined as blood cultures that remained positive after 7 days of effective therapy.

Abbreviations: NCE: Northern and Central European countries; SE: Southern European countries; CHF: congestive heart failure

Supplementary table 4. Multivariable analysis of factors associated with inhospital mortality and one-year mortality of all cases from centers included in both periods.

	In-hospital mortalily			One-year mortality		
	MULTIVARIATE OR	CI 95%	p	MULTIVARIATE OR	CI 95%	p
Charlson	1.31	(1.18, 1.45)	<0.01	1.33	(1.18, 1.50)	<0.01
Prosthetic valve IE	1.40	(0.97, 1.29)	0.07	1.41	(0.98, 1.97)	0.08
*Staphylococcus aureus**	1.68	(1.34, 2.10)	<0.01	1.73	(1.25, 2.40)	<0.01
*ConS**	1.41	(0.91, 2.20)	0.12	1.55	(1.03, 2.35)	0.04
Viridans group *Streptoccoci**	0.59	(0.47, 0.74)	<0.01	0.63	(0.41, 0,95)	0.03
Intracardiac vegetation	2.11	(1.33, 3.38)	<0.01	1.35	(0.89, 2.07)	0.16
Stroke	2.72	(1.98, 3.72)	<0.01	1.86	(1.35, 2.56)	<0.01
CHF	3.12	(2.35, 4.14)	<0.01	2.48	(1.88, 3.27)	<0.01
Persistent positive blood culture	2.66	(1.76, 4.04)	<0.01	2.24	(1.45, 3.47)	<0.01
Paravalvular complications	2.69	(1.91, 3.78)	<0.01	1.87	(1.38, 2.54)	<0.01
N IE and HA IE vs CA IE	1.64	(1.31, 2.08)	<0.01	1.15	(0.82, 1.43)	0.42
In-hospital surgery	0.59	(0.44, 0.88)	<0.01	0.55	(0.41, 0.74)	<0.01
European region (NCE vs SE)	0.63	(0.44, 0.88)	<0.01	0.72	(0.52, 1.02)	0.06
Period (2008-2012 vs 2000-2006)	0.63	(0.44, 0.88)	0.01	0.97	80.66, 1.44)	0.90

*The reference group is the rest of the etiological microorganisms.

Abbreviations: NCE: Northern and Central European countries; SE: Southern European countries; IE: infective endocarditis; CHF: congestive heart failure; CA: community adquired; N: nosocomial; HA: health-care associated; IE: infective endocarditis.

Study 2

4.2 Forty-Year Trends in Cardiac Implantable Electronic Device Infective Endocarditis

Marta Hernández-Meneses, Jaume Llopis, Elena Sandoval, Salvador Ninot, Manel Almela, Carlos Falces, Juan M. Pericàs, Bárbara Vidal, Andrés Perissinotti, Francesc Marco, Carlos A. Mestres, Carlos Paré, Cristina García de la María,1 Guillermo Cuervo, Eduard Quintana,3, José M. Tolosana, Asunción Moreno, José M. Miró and *Hospital Clínic of Barcelona* Infective Endocarditis team Investigators. Open Forum Infect Dis. 2022 Oct 14;9(11): ofac547. doi: 10.1093/ofid/ofac547. PMID: 36381626; PMCID: PMC9648563.

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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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[a]The Hospital Clinic Infective Endocarditis Team Investigators are listed in the Appendix.

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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 (^{18}FDG-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 ^{18}FDG-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}FDG-PET/CT was described only for the second period, as it was only introduced in 2014; 29 patients underwent ^{18}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}FDG-PET/CT at the pocket ± 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}FDG-PET/CT	29 (21)	0	29 (25.7)	<.01	2 (3.6)	27 (47.4)	<.01
Positive ^{18}FDG-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
Staphylococcus aureus	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
Enterococcus 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				.09			
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: ^{18}FDG-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 1*A* summarizes the proportion of CIED-IE compared with overall IE episodes over the 4 decades. Figure 1*B* 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, ^{18}FDG-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

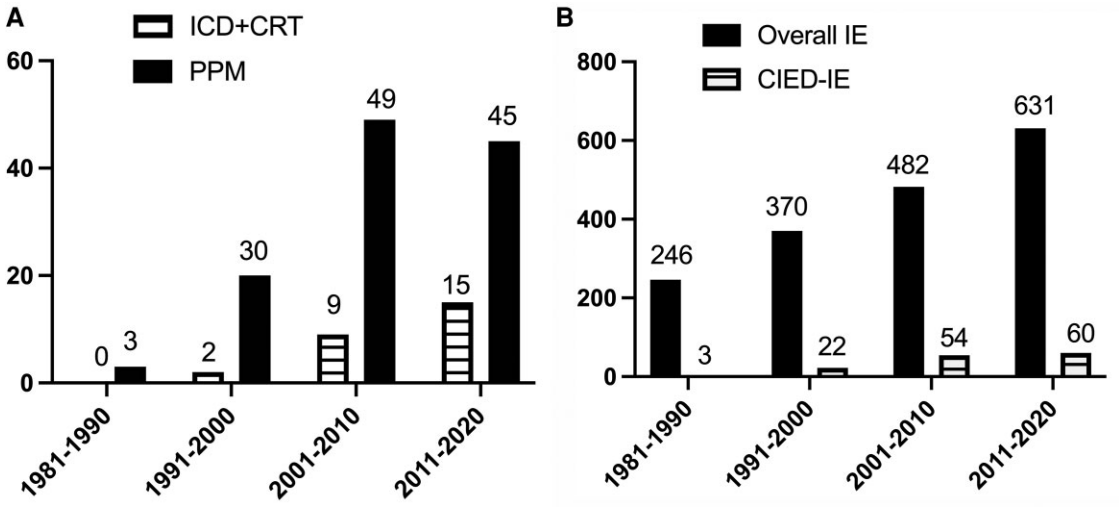

Figure 1. *A*, Evolution of cardiac implantable electronic device infective endocarditis (CIED-IE) incidence according to device type: pacemaker (PPM), implantable cardioverter-defibrillator (ICD), and cardiac resynchronization therapy (CRT) over 4 decades. *B*, Evolution of CIED-IE incidence compared 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, peripherical 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 2*C*), 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 2*A*) and the comparison of survival curves between the 2 studied periods (1981–2000 vs 2001–2020) (Figure 2*B*), among the 3 groups of valve vegetations (Figure 2*C*), and in patients with and without device removal (Figure 2*D*).

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
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: ^{18}FDG-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.

[a]There 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.

[b]Patients 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 ^{18}FDG-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}FDG-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
Staphylococcus aureus	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
Enterococcus 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
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: ^{18}FDG-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; 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

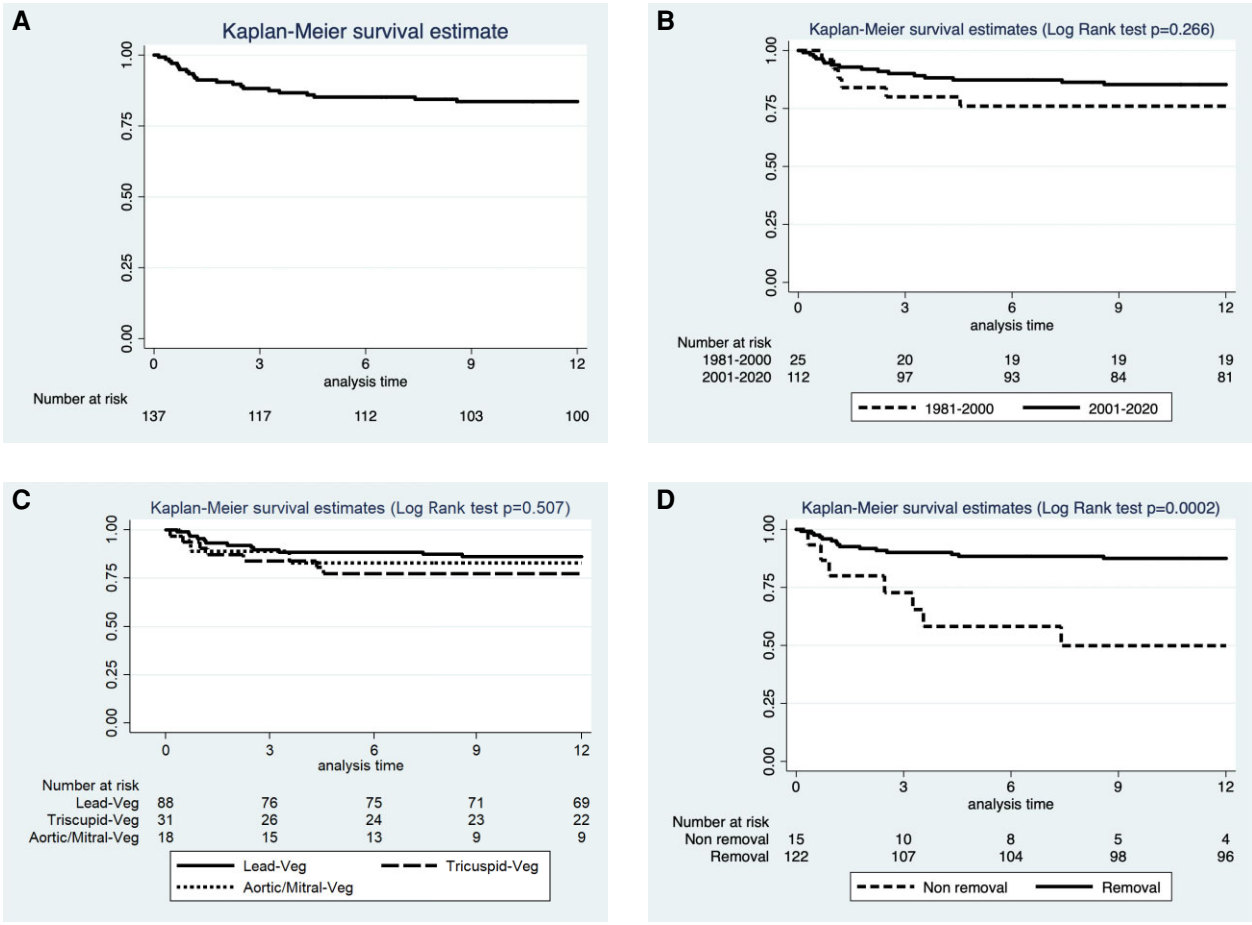

Figure 2. *A,* Kaplan-Meier survival curve for 1-year mortality in patients with cardiac implantable electronic device infective endocarditis (CIED-IE). *B,* Comparison of Kaplan-Meier survival curve for 1-year mortality according to the 2 periods (1981–2000 vs 2001–2020). *C,* Comparison of Kaplan-Meier 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

	Univariate			Multivariate		
Variable	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, ^{18}FDG-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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Table S1. Comparison of CIED-IE according to the timing of presenting symptoms: early and late.

Variable	Early (<1 year) (N=39)	Late ≥1 year) (N=99)	*P*
Age, years (median, IQR)	71 (63 -76.5)	70 (58 – 75)	0.41
Male gender	33 (84.6%)	83 (83.8%)	0.91
Fever	21 (53.8%)	73 (73.7%)	**0.03**
Concomitant pocket infection	20 (51.3%)	35 (35.4%)	0.09
Interval implant/exchange - diagnosis <60 days	86 (41 - 72)	2115 (873 - 3969)	**< 0.01**
Study period			
1981-2000	11 (28.2%)	14 (14.1%)	0.06
2001-2020	28 (71.8%)	85 (85.9%)	
Place of acquisition			
Community	16 (41%)	64 (64.6%)	**0.01**
Nosocomial	10 (25.7%)	9 (9.1%)	**0.03**
HCA-infections	13 (33.3%)	26 (26.3%)	0.42
Transferred from other hospital	13 (33.3%)	36 (36.4%)	0.73
Type of Cardiac Device			
PPM	34 (87.2%)	80 (80.8%)	0.34
ICD	5 (12.8%)	18 (18.2%)	0..42
CRT	0	1 (1%)	0.31
Type of CIED-IE			
Early (<1 year)	39 (100%)	0	NA
Late (>1 year)	0	99 (100%)	NA
CIED-IE only	27 (69.2%)	62 (62.6%)	0.45
CIED-IE + Valve infection	12 (30.8%)	37 (37.4%)	0.45
Charlson comorbidity index (Median IQR)	4 (4.0 – 6.0)	4 (4.0 – 6.0)	0.38
Diabetes mellitus	15 (38.5%)	31 (31.3%)	0.43
Chronic kidney disease (CKD)	6 (15.4%)	13 (13.1%)	0.73
Coronary heart disease	13 (33.3%)	30 (30-3%)	0.73
Previous heart failure	11 (28.2%)	18 (18.2%)	0.22
Echocardiography			
Vegetation on device	39 (100%)	99 (100%)	1
Tricuspid valve vegetation	3 (7.7%)	28 (28.3%)	**<0.01**
Other	8 (15,4%)	7 (7%)	0.44
Valve vegetation size, Median (IQR)	10.0 (7.0 – 14.0)	10.0 (8.0 – 20.0)	0.31
^{18}F-PET/CT	5 (12.8%)	24 (24.2%)	0.09

Microbiology			
Positive blood cultures or lead/valve culture	39 (100%)	99 (100%)	**1**
16S-RNA PCR	9 (23.1%)	21 (21.2%)	0.46
Positive 16S-RNA PCR result	6/9 (66.7%)	11/21 (529.4%)	0.46
S. aureus	15 (38.5%)	31 (31.1%)	0.43
MRSA	5 (12.8%)	8 (8.1%)	0.43
Coagulase-negative Staphylococcus	16 (41%)	46 (46.5%)	0.56
MR-CoNS	3 (7.7.%)	12 (12.1%)	0.41
Enterococcus	1 (2.6%)	5 (5.1%)	0.31
VGS	0	1 (1%)	0.32
Gram negatives	4 (10.3%)	6 (6.1%)	0.44
Polymicrobial	0	7 (7.1%)	**<0.01**
Others	3 (7.6%)	3 (3.1%)	0.85
Complications	18 (46.2%)	57 (57.6%)	0.23
Pulmonary embolism	1 (2.6%)	11 (11.1%)	**0.04**
Heart failure	12 (30.8%)	23 (23.2%)	0.38
Sepsis/shock	5 (12.8%)	10 (10.1%)	0.66
Persistent bacteremia	0	3 (3%)	0.08
Treatment			
Removal of cardiac device system	36 (92.3%)	87 (87.9%)	0.41
Type of removal			
Traction	28 (77.8%)	67 (77%)	0.92
Open surgery	8 (22.2%)	19 (21.8%)	0.96
Reimplant	22 (61.1%)	62 (71.3%)	0.26
Interval removal-reimplantation (days, median, IQR)	16.5 (13-25)	15 (10-22)	0.25
ABS in patients without removal of cardiac device system	2 (5.1%)	11 (11.1%)	0.21
In-hospital Mortality	7 (17.9%)	11 (11.1%)	0.32
One-year follow up			
Surgery	4 (10.3%)	4 (4%)	0.24
Mortality	8 (20.5%)	15 (15.2%)	0.47
Relapses	1 (2.6%)	7 (7.1%)	0.21

*Abbreviations: PPM Pacemaker, ICD implantable cardioverter-defibrillator, CRT cardiac resynchronization therapy. HCA healthcare-associated; ABS antibiotic suppressive therapy, ^{18}F-PET/CT: ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography; 16S-rRNA-PCR: 16S Ribosomal RNA gene-targeted metagenomic sequencing. CoNS: *Coagulase-negative Staphylococcus;* MR: methicillin-resistant; GVS: viridian's group streptococci. NA: not applicable.

Table S2. Comparison of CIED-IE according to the type of the device system: Pacemaker (PPM) and, implantable defibrillator device (ICD) plus cardiac resynchronization therapy (CRT).

Variable	PCM (N=114)	ICD + CRT (N=24)	*p*
Age, years (median, IQR)	72 (63 - 77)	62.5 (54 - 68)	**<0.01**
Male gender	92 (80.7%)	23 (95.8%)	**<0.01**
Fever	78 (68.4%)	16 (66.7%)	0.87
Concomitant pocket infection	43 (37.7%)	50%	0.27
Interval implant/exchange - diagnosis <60 days	1007 (233 - 3138)	1888 (510 - 3188)	0.34
Study period			
1981-2000	23 (20.2%)	2 (8.3%)	0.17
2001-2020	91 (79.8%)	22 (91.7%)	
Place of acquisition			
Community	64 (56.1%)	16 (66.7%)	0.33
Nosocomial	17 (14.9%)	2 (8.3%)	0.32
HCA-infections	33 (29%)	6 (25%)	0.69
Transferred from other hospital	38 (33.3%)	11 (45.8%)	0.26
Type of Cardiac Device			
PCM	114 (100%)	0	NA
ICD	0	23 (95.8%)	NA
CRT	0	1 (4.2%)	NA
Type of CIED-IE			
Early (<1 year)	34 (29.8%)	5 (20.8%)	0.34
Late (>1 year)	80 (70.2%)	10 (41.7%)	**0.01**
CIED-IE only	73 (63%)	16 (66.7%)	0.81
CIED-IE + Valve infection	41 (36%)	8 (33.3%)	0.81
Charlson comorbidity index (Median IQR)	4.0 (3.0 – 6.0)	4.0 (2.0 – 5.5)	0.49
Diabetes mellitus	33 (29%)	13 (54.2%)	**0.02**
Chronic kidney disease (CKD)	15 (13.2%)	4 (16.7%)	0.67
Coronary heart disease	31 (27.2%)	12 (50%)	**0.04**
Previous heart failure	18 (15.8%)	11 (45.8%)	**<0.01**
Echocardiography			
Vegetation on device	114 (100%)	24 (100%)	NA
Tricuspid valve vegetation	24 (21.1%)	7 (29.2%)	0.42
Other	14 (12.3%)	1 (4.2%)	0.81
Valve vegetation size, Median (IQR)	10.0 (8.0 – 20.0)	9.5 (7.0 – 19.0)	0.21
^{18}F-PET/CT	21 (84%)	3 (75%)	0.69

Microbiology			
Positive blood cultures or lead/valve culture	114 (100%)	24 (100%)	NA
16S-rRNA PCR	26 (22.8%)	4 (16.7%)	0.48
Positive 16S-rRNA PCR result	16 (61.5%)	1 (25%)	0.13
S. aureus	35 (30.7%)	11 (45.8%)	0.17
MRSA	10 (8.8%)	3 (12.5%)	0.61
Coagulase-negative Staphylococcus	55 (48.2%)	7 (29.3%)	0.07
MR-CoNS	13 (11.4%)	2 (8.3%)	0.63
Enterococcus	4 (3.5%)	2 (8.3%)	0.42
VGS	1 (0.9%)	0	0.32
Gram negatives	8 (7%)	2 (8.3%)	0.83
Polymicrobial	5 (4.4%)	2 (8.3%)	0.51
Others	6 (5.3%)	0	0.08
Complications	58 (50.9%)	17 (70.8%)	0.06
Pulmonary embolism	9 (7.9%)	3 (12.5%)	0.52
Heart failure	25 (21.9%)	10 (41.7%)	0.07
Sepsis/shock	13 (11.4%)	2 (8.3%)	0.63
Persistent bacteremia	3 (2.6%)	0	0.08
Treatment			
Removal of cardiac device system	78 (77.2%)	17 (77.3%)	0.99
Type of removal			
Traction	78 (77.2%)	17 (77.3%)	0.99
Open surgery	23 (22.8%)	4 (18.2%)	0.60
Reimplant	67 (66.3%)	17 (77.3%)	0.26
Interval removal-reimplantation (days, median, IQR)	14 (10 – 21)	20 (15 – 28)	0.34
ABS in patients without removal of cardiac device system	11 (9.6%)	2 (8.3%)	0.83
In-hospital Mortality	16 (14%)	2 (8.3%)	0.38
One-year follow up			
Surgery	6 (5.3%)	2 (8.3%)	0.61
Mortality	19 (16.7%)	4 (16.7%)	1
Relapses	6 (5.3%)	2 (8.3%)	0.61

*Abbreviations: PPM Pacemaker, ICD implantable cardioverter-defibrillator, CRT cardiac resynchronization therapy. HCA healthcare-associated; ABS antibiotic suppressive therapy, ^{18}F-PET/CT: ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography; 16S-rRNA-PCR: 16S Ribosomal RNA gene-targeted metagenomic sequencing. CoNS: *Coagulase-negative Staphylococcus;* MR: methicillin-resistant; GVS: viridian's group streptococci. NA: not applicable.

Table S3. Comparison of CIED-IE according to one-year mortality

Variable	Alive (N=112)	Dead (N=23)	*P*
Age, years (median, IQR)	69.5 (57.0 – 76.0)	71.0 (64.0 – 78.0)	0.13
Male gender	95 (84.8%)	19 (82.6%)	0.80
Fever	79 (70.5%)	15 (65.2%)	0.62
Concomitant pocket infection	49 (43.8%)	5 (21.7%)	**0.03**
Interval implant/exchange - diagnosis <60 days	1356 (279.5 - 3019)	1214 (86 - 3969)	0.91
Study period			
1981-2000	19 (17%)	6 (26.1%)	0.35
2001-2020	93 (83%)	17 (73.9%)	
Place of acquisition			
Community	68 (60.7%)	11 (47.8%)	0.26
Nosocomial	14 (12.5%)	5 (21.7%)	0.31
HCA-infections	30 (26.8%)	7 (30.4%)	0.73
Transferred from other hospital	44 (39.3%)	4 (17.4%)	**0.01**
Type of Cardiac Device			
PPM	92 (82.1%)	19 (82.6%)	0.96
ICD	20 (17.9%)	3 (13%)	0.54
CRT	0	1 (4.3%)	0.31
Type of CIED-IE			
Early (<1 year)	30 (26.8%)	8 (34.8%)	0.46
Late (>1 year)	82 (73.2%)	15 (65.2%)	0.46
CIED-IE only	73 (65.2%)	13 (56.5%)	0.45
CIED-IE + Valve infection	39 (34.8%)	10 (43.5%)	0.45
Charlson comorbidity index (Median IQR)	4.0 (3.0 – 5.0)	5.0 (5.0 – 8.0)	**<0.01**
Diabetes mellitus	30 (26.8%)	14 (60.9%)	**<0.01**
Chronic kidney disease (CKD)	9 (8%)	9 (39.1%)	**<0.01**
Coronary heart disease	37 (33%)	6 (26.1%)	0.50
Previous heart failure	21 (18.8%)	7 (30.4%)	0.26
Echocardiography			
Vegetation on device	112 (100%)	23 (100%)	NA
Tricuspid valve vegetation	24 (21.4%)	7 (30.4%)	0.38
Other	13 (11.7%)	2 (8.7%)	0.31
Valve vegetation size, Median (IQR)	10.0 (7.0 – 20.0)	9.0 (7.5 – 18.5)	0.64
^{18}F-PET/CT	25 (22.3%)	2 (8.7%)	0.06
Positive ^{18}F-PET/CT result	21/25 (84%)	½ (50%)	0.36

Microbiology			
Positive blood cultures or lead/valve culture	112 (100%)	23 (100%)	NA
16S-rRNA PCR	23 (20.5%)	4 (17.4%)	0.72
Positive 16S-rRNA PCR result	12/23 (52.2%)	2/4 (50%)	0.94
S. aureus	33 (29.5%)	11 (47.8%)	0.11
MRSA	10 (8.9%)	3 (13.3%)	0.56
Coagulase-negative Staphylococcus	55 (49.1%)	7 (30.4%)	0.08
MR-CoNS	13 (11.6%)	2 (8.7%)	0.66
Enterococcus	4 (3.6%)	2 (8.8%)	0.41
VGS	0	1 (4.3%)	0.15
Gram negatives	8 (7.1%)	2 (8.7%)	0.41
Polymicrobial	7 (6.3%)	0	**<0.01**
Others	5 (4.4%)	0	0.08
Complications	55 (49.1%)	19 (82.6%)	**<0.01**
Pulmonary embolism	9 (8%)	3 (13%)	0.70
Heart failure	20 (17.9%)	15 (65.2%)	**<0.01**
Sepsis/shock	5 (4.5%)	10 (43.5%)	**<0.01**
Persistent bacteremia	1 (0.9%)	2 (8.7%)	0.19
Treatment			
Removal of cardiac device system	105 (93.8%)	16 (69.6%)	**0.01**
Type of removal			
Traction	82 (78.1%)	11 (68.8%)	0.37
Open surgery	23 (21.9%)	5 (31.3%)	0.32
Reimplant	74 (70.5%)	8 (50%)	0.07
Interval removal-reimplantation (days, median, IQR)	15.0 (11.0 – 21.0)	21.2 (5.0 – 37.0)	0.65
ABS in patients without removal of cardiac device system	7 (6.3%)	5 (21.7%)	0.08
In-hospital Mortality	0	18 (78.3%)	**NA**
One-year follow-up			
Surgery	6 (5.4%)	2 (8.7%)	0.60
Mortality	0	23 (100%)	NA
Relapses	7 (6.3%)	1 (4.3%)	0.60

*Abbreviations: PPM Pacemaker, ICD implantable cardioverter-defibrillator, CRT cardiac resynchronization therapy. HCA healthcare-associated; ABS antibiotic suppressive therapy, ^{18}F-PET/CT: ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography; 16S-rRNA-PCR: 16S Ribosomal RNA gene-targeted metagenomic sequencing. CoNS: *Coagulase-negative Staphylococcus;* MR: methicillin-resistant; GVS: viridian's group streptococci. NA: not applicable.

Study 3

4.3 Reappraisal of [18F] FDG-PET/CT for diagnosis and management of cardiac implantable electronic device infections

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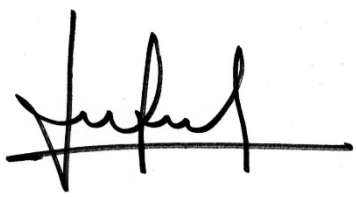
C E R T I F I C A

El manuscrito titulado «Reappraisal of [18F]FDG-PET/CT for diagnosis and management of cardiac implantable electronic device infections», cuyos autores son Marta Hernández-Meneses, Andrés Perissinotti, Silvia Páez-Martínez, Jaume Llopis, Anders Dahl, Elena Sandoval, Carlos Falces, Juan Ambrosioni, Bárbara Vidal, Francesc Marco, Guillermo Cuervo, Asunción Moreno, Jordi Bosch, José M. Tolosana, David Fuster, José M. Miró, en representación de los investigadores del *Hospital Clínic of Barcelona Infective Endocarditis Team*

HA SIDO ACEPADO PARA PUBLICACIÓN en Revista Española de Cardiología el día 17 de marzo de 2023, con el número de referencia REC-D-23-00014R2

Y para que conste a petición del interesado se firma el presente certificado en Madrid a diez y siete de marzo de dos mil veintitrés.

SOCIEDAD ESPAÑOLA DE CARDIOLOGÍA



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Reappraisal of [18F]FDG-PET/CT for diagnosis and management of cardiac implantable electronic device infections.

--Manuscript Draft--

Full Title:	Reappraisal of [18F]FDG-PET/CT for diagnosis and management of cardiac implantable electronic device infections.
Abstract:	Introduction and objectives The role of [18F]FDG-PET/CT in cardiac-implantable-electronic-device (CIED) infections require better evaluation, especially diagnosing systemic infections (SI). We aimed to determine [18F]FDG-PET/CT diagnostic accuracy in each CIED topographical region; to study [18F]FDG-PET/CT added value to transesophageal echocardiography (TEE) in diagnosing SI; spleen and bone marrow (BM) uptake in differentiating isolated-local-infections (LI) from SI; and [18F]FDG-PET/CT potential application in follow-up. Methods Retrospective-single-center study including 54 cases and 54 controls from 2014-2021. Primary endpoint was [18F]FDG-PET/CT diagnostic yield in each topographical CIED region. Secondary analyses described [18F]FDG-PET/CT performance compared with the TEE in SI; BM and spleen uptake in SI and LI, and finally, [18F]FDG-PET/CT potential application in guiding stopping chronic antibiotic suppression (CAS) when completed device removal is not performed. Results Thirteen (24%) LI and 41 (76%) SI. Overall, [18F]FDG-PET/CT specificity was 100% and sensitivity 85% (79% pocket, 57% subcutaneous-lead, 22% endovascular-lead, 10% intracardiac-lead). When combined with TEE, [18F]FDG-PET/CT could increase definite SI from 34% to 56% (p=0.04). SI with bacteremia showed higher spleen (p=0.05) and BM metabolism (p=0.04) than LI. Thirteen patients without complete device removal underwent a follow-up [18F]FDG-PET/CT with no relapses after CAS discontinuation in six cases with negative follow-up [18F]FDG-PET/CT. Conclusions The diagnostic yield of [18F]FDG-PET/CT for evaluating CIED infections showed high sensitivity in LI but much lower in SI. However, accuracy increased when [18F]FDG-PET/CT is combined with TEE in endovascular-lead-bacteremic infection. Spleen and BM hypermetabolism could differentiate bacteremic-SI from LI. Although further prospective studies are needed, a follow-up [18F]FDG-PET/CT could have a potential role in the management of CAS therapy when complete device removal is unachievable.
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Abstract

Introduction and objectives

The role of [18F]FDG-PET/CT in cardiac-implantable-electronic-device (CIED) infections require better evaluation, especially diagnosing systemic infections (SI). We aimed to determine [18F]FDG-PET/CT diagnostic accuracy in each CIED topographical region; to study [18F]FDG-PET/CT added value to transesophageal echocardiography (TEE) in diagnosing SI; spleen and bone marrow (BM) uptake in differentiating isolated-local-infections (LI) from SI; and [18F]FDG-PET/CT potential application in follow-up.

Methods

Retrospective-single-center study including 54 cases and 54 controls from 2014-2021. Primary endpoint was [18F]FDG-PET/CT diagnostic yield in each topographical CIED region. Secondary analyses described [18F]FDG-PET/CT performance compared with the TEE in SI; BM and spleen uptake in SI and LI, and finally, [18F]FDG-PET/CT potential application in guiding stopping chronic antibiotic suppression (CAS) when completed device removal is not performed.

Results

Thirteen (24%) LI and 41 (76%) SI. Overall, [18F]FDG-PET/CT specificity was 100% and sensitivity 85% (79% pocket, 57% subcutaneous-lead, 22% endovascular-lead, 10% intracardiac-lead). When combined with TEE, [18F]FDG-PET/CT could increase definite SI from 34% to 56% (p=0.04). SI with bacteremia showed higher spleen (p=0.05) and BM metabolism (p=0.04) than LI. Thirteen patients without complete device removal underwent a follow-up [18F]FDG-PET/CT with no relapses after CAS discontinuation in six cases with negative follow-up [18F]FDG-PET/CT.

Conclusions

The diagnostic yield of [18F]FDG-PET/CT for evaluating CIED infections showed high sensitivity in LI but much lower in SI. However, accuracy increased when [18F]FDG-PET/CT is combined with TEE in endovascular-lead-bacteremic infection. Spleen and BM hypermetabolism could differentiate bacteremic-SI from LI. Although further prospective studies are needed, a follow-up [18F]FDG-PET/CT could have a potential role in the management of CAS therapy when complete device removal is unachievable.

KEY POINTS

- What is known about the topic?

[18F]FDG-PET/CT has improved the diagnostic evaluation of cardiac implantable electronic device (CIED) infections and has been incorporated as a major diagnostic criterion in prosthetic valve endocarditis guidelines.

Although [18F]FDG-PET/CT diagnostic yield is high for the pocket, its accuracy in other CIED topographical regions requires better characterization.

Transesophageal echocardiography (TEE) is gold standard for diagnosis. However, it is challenging to differentiate between thrombus and vegetation. Many patients with bacteremia probably have endovascular lead infection, which TEE is not able to detect.

It has been shown recently that hypermetabolism of the spleen and bone marrow (BM) detected by [18F]FDG-PET/CT can be considered as an indirect sign of infective endocarditis on native or prosthetic valves.

There is no data on the usefulness of [18F]FDG-PET/CT in guiding the duration of chronic oral antimicrobial therapy in patients with CIED infections without complete device removal.

- What does this study add?

[18F]FDG-PET/CT has overall high specificity and sensitivity for local infections of the generator pocket but sensitivity is lower in systemic infections and other topographical sections of the CIED lead.

We demonstrate that [18F]FDG-PET/CT combined with TEE can significantly increase the definite diagnosis rate in endovascular and intracardiac lead infections.

Spleen and bone marrow hypermetabolism may help distinguish systemic bacteremia from isolated local CIED infection.

When complete device removal is unachievable, a follow-up negative [18F]FDG-PET/CT might guide physicians in stopping suppressive oral antimicrobial therapy.

Introduction

Cardiac implantable electronic devices (CIED) figure in a broad clinical spectrum of infections, such as local CIED infections, which can appear as isolated local infections (LI) or associated with systemic lead infections (SI). SI involves endovascular lead and intracardiac lead infections, including infective endocarditis (IE). General diagnosis is challenging and is based on microbiological data and cardiac imaging techniques such as transesophageal echocardiography (TEE) [1-3, 5]. ^{18}F-Fluorodeoxyglucose-Positron Emission Tomography/Computed Tomography ([18F]FDG PET/CT) has improved the diagnostic evaluation of prosthetic valve endocarditis and has been incorporated as a major diagnostic criterion in guidelines [1]. In addition, it has been recently shown that hypermetabolism of the spleen and bone marrow (BM) as detected by [18F]FDG-PET/CT can be considered an indirect sign of IE on native or prosthetic valves [4, 6].

Despite the latest evidence, the overall usefulness of [18F]FDG-PET/CT in CIED infections must be better characterized. Several cohort studies have been published [3, 5], showing high diagnostic yield for generator pocket infections but much lower performance in lead-associated infection (SI) [7]. TEE is also unable to detect lead vegetations in many patients with bacteremia which probably have an endovascular lead infection (SI) [2]. [18F]FDG-PET/CT could help to improve the diagnosis in all topographical regions of CIEDs, including in endovascular leads, which TEE cannot access.

The primary endpoint of this study was determining the diagnostic yield of [18F]FDG-PET/CT in each of the different CIED topographical regions: pocket, subcutaneous, endovascular, and intracardiac lead. Secondary endpoints were analyzing [18F]FDG-PET/CT performance compared with TEE in diagnosing SI; also defining the diagnostic value of spleen and BM hypermetabolism as an indirect sign of SI; and, finally, studying the potential utility of [18F]FDG PET/CT, in the follow-up of CIED infections without complete device removal and suppressed with chronic antibiotics to avoid relapses, guiding physicians on when to stop chronic oral suppression (CAS) therapy.

Material and methods

Study design

A retrospective case-control study was conducted at *Hospital Clínic de Barcelona*, a referral center for IE and cardiovascular infections, to evaluate the usefulness of [18F]FDG-PET/CT in the diagnosis of CIED infections. All suspected cases of CIED infection have been discussed during weekly IE-team meetings since 1986 [8]. The final diagnosis of each case was reached, through the application of the modified Duke criteria [9] and international guidelines [2], by consensus. We included all consecutive patients with definite CIED infection who met the inclusion criteria from January 2014 to January 2021. Information was gathered from the electronic medical clinical data. Consecutive cases were matched with controls by age (+/- 5 years), gender, CIED type and calendar year. All the patients were followed-up at least one year until December 2021.

Inclusion criteria

*Cases (**true positives**)*

Local and systemic infections were classified following European Heart Rhythm Association (EHRA) diagnosis criteria recommendations [2]. For suspected cases of CIED-IE, the modified Duke criteria were applied [9]. In all cases, LI and SI were evaluated by performing blood cultures, swab, pocket (device and leads when extracted) cultures and 16SrRNA-PCR, and echocardiography. For the primary objective of this study, i.e., evaluating the diagnostic accuracy of [18F]FDG-PET/CT (sensitivity, specificity, positive and negative predicted value), [18F]FDG-PET/CT results were excluded as a major diagnostic criterion of cases. All CIED infections (100%) were surveyed using this imaging modality.

The final diagnosis was achieved by consensus of the weekly IE team meetings for each case. Only patients with a definite diagnosis of CIED infection were included.

Types of CIED infection:

- Isolated local device infections (LI): local signs of infection involving the pocket generator with or without subcutaneous lead, and/or positive cultures of pocket swab, device, subcutaneous lead (and positive 16SrRNA-PCR when performed). This group includes definitions of CIED-related infection as specified in the EHRA consensus: Isolated generator pocket infection, isolated pocket erosion, pocket site infection without bacteremia/systemic signs of infection [2].

We define *isolated local device infections* as those not associated with systemic signs of infection. Patients with suspicion of SI or positive endovascular/intracardiac lead culture were systematically excluded from this group.

- Systemic infections (SI): patients with or without associated local CIED infection who also presented endovascular/intracardiac lead infection (including IE) determined by systemic signs of infection, e.g., fever, elevated CPR, leukocytosis, and positive blood cultures or endovascular/intracardiac lead cultures (and positive 16SrRNA-PCR when performed), and/or presence of vegetations on leads or the tricuspid valve, diagnosed by transesophageal echocardiography (TEE). This group includes definitions of CIED-related infection as clarified in the EHRA consensus: lead infection, pocket site infection with lead/valvular endocarditis, CIED endocarditis without pocket infection, positive blood cultures and lead or valvular vegetation(s) [2]. Patients classified as possible or probable were excluded, because they were not considered as definite true positive.

*Controls **(true Negatives)***

Patients with CIED and studied by [18F]FDG-PET/CT due to solid or hematologic neoplasms were included as controls without indication of CIED FDG uptake status. All the topographical regions of the control CIEDs were evaluated, except the intracardiac lead segment, as none of the controls underwent myocardial uptake suppression [10].

Matching criteria

All cases and controls were paired by age, sex, type of device, and similar time interval between CIED implant/replacement and [18F]FDG-PET/CT performance.

Exclusion criteria

Cases

Patients with no definite criteria of CIED infection were excluded. As mentioned above, all cases were considered as true positive; there were no false positives.

Controls

Patients with previous CIED infections or any clinical or laboratory sign of local or systemic infection within the previous or subsequent six months from the moment of [18F]FDG-PET/CT acquisition were

excluded. Patients with central intravenous lines and/or mediastinal hypermetabolic lesions that could interfere with the assessment were also excluded.

[18F]FDG-PET/CT considerations

Whole-body [18F]FDG-PET/CT studies were acquired 60 min after ^{18}F-FDG injection (4.0 MBq/kg) in a hybrid scanner (Biograph mCT 64S; Siemens) with myocardial uptake suppression protocol consisting of a fasting period of 12h and intravenous administration of 50 IU/kg of unfractionated heparin 15min before ^{18}F-FDG injection. Diabetic patients were managed as indicated by EANM/SNMMI guidelines for 18F-FDG use in inflammation and infection [6,10]. Consuming a high-fat, low-carbohydrate diet before [18F]FDG-PET/CT was not systematically introduced in all patients, given that this protocol was implemented after the study was designed.

Visual analysis

All patients underwent the body [18F]FDG-PET/CT as a part of the study protocol. The study's primary endpoint was the [18F]FDG-PET/CT result, which was assessed qualitatively by two blinded, independent nuclear medicine specialists. All images were interpreted separately by the two independent nuclear medicine specialists, and disagreements were settled by consensus with a third nuclear medicine reader. Positivity criteria was the presence of any focal or heterogeneous uptake related to each topographical region identified in both attenuation-corrected and uncorrected images to avoid attenuation-correction artifacts. [18F]FDG-PET/CT visual analysis results were also compared to those of TEE in SI.

Semiquantitative analysis

Semiquantitative analysis, supervised by both readers, was performed in all [18F]FDG-PET/CT studies by measuring the maximum standardized uptake value (SUV_{max}) of a volume of interest (VOI) sphere including the totality of the pocket and a VOI sphere placed on the most active part of each segment of the lead (subcutaneous, endovascular and intracardiac).

No semiquantitative analysis was performed in the intracardiac lead regions of control subjects as they did not undergo myocardial inhibition protocol. Hence, specificity analysis for intracardiac lead was excluded from the statistical analysis.

Spleen and bone marrow (BM) metabolism

Values of SUV_{mean} were obtained for spleen and BM to assess indirect signs of infection/inflammation as described in Boursier et al [6] by placing a spherical VOI at the center of the spleen and in one lumbar

vertebra, carefully avoiding the inclusion of any abnormal area secondary to possible lesions. For reference, descending thoracic aorta blood pool-SUV_{mean} was calculated as was liver-SUV_{mean}. SUV ratios were calculated by dividing the SUV_{max} of the area of interest by the blood pool and liver SUV_{mean} with the aim of overcoming any bias related to physiological individual fluctuations of ^{18}F-FDG distribution.

Follow-up [18F]FDG PET/CT

At least one [18F]FDG-PET/CT within the first six months after discharge was achieved in all patients whose devices could not be entirely removed. Patients had at least one [18F]FDG-PET/CT scheduled every 4-6 months; more than one [18F]FDG-PET/CT may have been performed depending on the time of follow-up completed during the study. Data on chronic antibiotic suppression (CAS) therapy, duration, and type of infection were also analyzed.

Further details regarding [18F]FDG-PET/CT methodology can be found in supplementary data.

Transesophageal echocardiography

Echocardiographic *assessment* was achieved by TEE in all cases using a GE VIVID E95 system. Any mass seen on a lead in echocardiography in the context of bacteremia was assumed to be vegetation. All echocardiography exams were validated by a second investigator, and further discrepancies by a third member of the team.

Statistical analysis

Continuous variables are presented as median (interquartile ranges) and were compared using Mann-Whitney's test. Categorical variables are presented as frequencies (percentages) and were compared using the Chi-squared test or Fisher test. For all tests, statistical significance was labeled with a p-value <0.05. Validity calculations sensitivity (Sn), specificity (Sp), positive and negative predictive values were obtained using contingency tables according to the true positive (TP) and true negative (TN), false positive (FP) and false negative (FN) obtained from [18F]FDG-PET/CT results. ROC curves were also performed from the different $SUV_{max/mean}$ values to obtain a more accurate cut-off point for the infection diagnosis. Statistical analyses were made with STATA 14.0.

Ethical considerations

The Ethical Review Board (ERB) of the *Hospital Clínic of Barcelona* approved the implementation of this study (ERB number HCB/2020/1489). The requirement for informed written consent was waived given the

retrospective nature of the study. Patient identification was encoded, complying with the requirements of the Organic Law on Data Protection 15/1999.

Results

We included 54 cases and 54 controls; the characteristics of both groups are presented in **Table 1**. In 25% of cases, less than 152 days elapsed between the implant or device change procedure and the clinical infection.

Comparison between cases with isolated local and systemic infection

Cases were divided into those with isolated LI (N=13) and those with SI with or without local infection (N=41). Baseline characteristics were similar between groups, **Table 2**. Local signs of device infection were present in 87% (47/54) cases: 100% (13/13) with isolated LI and 82.9% (34/41) from the SI group, p <0.01. Some patients with SI: 34.1% (14/41) showed a positive echocardiography result. Microbiological positivity and etiology were distributed homogeneously in both groups, with a predominance of *Staphylococcus aureus* and coagulase negative staphylococci (CNS), **(see supplementary material table S1).** The specific classification of SI in terms of the diagnosis criteria is summarized in **Table S2, supplementary material.** Patients with SI underwent significantly more removal surgery (70.7%vs.38.4%, p=0.04); patients with isolated LI received more CAS (61.5%vs.24.4%, p<0.01). There were no statistically significant differences between patients with isolated LI and SI regarding re-implant surgery, in-hospital mortality, or relapse. Otherwise, there were no differences regarding [18F]FDG-PET/CT results globally or for any topographical segment during the interval between CIED implant/replacement and [18F]FDG-PET/CT (<3 months vs. >3 months). All characteristics comparing groups and [18F]FDG-PET/CT results are summarized in **Table S3, supplementary material**.

[18F]FDG-PET/CT accuracy results

The main results can be found in **Table 3.** The overall [18F]FDG-PET/CT sensitivity with confirmed CIED infection was 85% (46/54). Pocket sensitivity was 79% (37/47), subcutaneous lead 57% (27/47), endovascular lead was 22% (9/41) and 10% (4/41) intracardiac lead. However, intracardiac lead sensitivity could be underestimated because 31.5% (17/54) of cases showed unsuccessful myocardial inhibition. Median time on antibiotic treatment before [18F]FDG-PET/CT acquisition was five (0–14) days in cases

with positive results, whereas in cases with negative results it was 13 (5–16) days, p=0.19. There was a trend, but no significant differences were found regarding the period between antibiotic was initiated and [18F]FDG-PET/CT performance. Twelve (22.2%) cases had been on antibiotic therapy prior to [18F]FDG-PET/CT acquisition with a median duration of six days (0.0–14.0).

Central illustration shows positive [18F] FDG uptake examples and sensitivity values of FDG-PET/CT in a visual 3D representation of each CIED topographical region.

Table 4 compares diagnostic performance between TEE and [18F]FDG-PET/CT in patients with systemic infection showing fever, leukocytosis and elevated CPR with positive blood cultures or positive lead cultures/16SrRNA-PCR and/or positive echo. In those patients, when [18F]FDG-PET/CT was combined with TEE, the definite diagnosis rate of infection significantly increased from 34% (14/41) to 56% (23/41) (p=0.04) due to detection of endovascular involvement, with rates higher in the bacteremic (from 38.8% ([7/18] to 66.7% [12/18]) than in the non-bacteremic form (from 30.4% ([7/23] to 47.8% [11/23]) of systemic infection (p=0.37).

ROC curves were analyzed for the median SUVmax of all four CIED topographical regions and the ratio between each SUVmax/liver-SUVmean and blood pool-SUVmean. Clinically significant values were only found in pocket uptake for SUVmax and SUVmax/SUVmean liver values, it is shown in **Figure 1.** The remaining ROC curves can be found in the supplementary data **(figures S1-5)**

Spleen and bone marrow FDG uptake

There were no differences among any semiquantitative variables in cases and controls regarding spleen or BM uptake, including between LI and SI (**Table S4**, supplementary material). However, in the bacteremia subgroup of SI, the SUV_{mean} spleen (p=0.05) and BM (p=0.04) were significantly higher than in LI, this data is summarized in **Table 5.**

Follow-up [18F]FDG-PET/CT in patients with chronic suppressive antibiotic therapy

Overall cohort flowchart focused on patients with non-complete device removal who received CAS and underwent follow-up [18F]FDG PET/CT is described in supplementary data (**Figure S6)**. Complete system removal was performed in 66.7% (36/54) cases and was significantly higher (p=0.03) in patients with SI 73.1% (30/41) than in those with isolated LI 46.2% (6/13) **(table S1).** Eighteen cases were classified as non-removal or non-complete device removal (9/18 and 9/18, respectively), the main reasons for not removing devices were: advanced age, severe comorbidities, patient frailty and high surgical risk. Device

removal was achieved in 45/54 (83.3%) of patients, and of those patients who underwent device removal, it was incomplete in 9/45 (20%). Most of cases underwent manual traction 40/45 (88.9%), whereas only 5/45 (11.1%) cases required open surgery. After hospital discharge, all patients were followed for at least six months, and 13 patients (13/18) (65%) had a follow-up [18F]FDG-PET/CT performed. Two patients, in whom the follow-up [18F]FDG-PET/CT was not performed, died during hospital admission. The other three patients were followed up in others hospital institutions without [18F]FDG-PET/CT. Except the two patients who died before discharge, all patients (13) received CAS, all characteristics of 18 patients without device removal can be found in **Table S5,** supplementary material. All patients had at least one [18F]FDG-PET/CT study performed; 4/13 patients had more than three [18F]FDG PET/CTs during the follow-up. The number of studies on each patient varied during follow-up, as they were indicated by the IE team on an individual basis for each case. Six patients switched from positive to negative FDG uptake during the follow-up, and four of them (66.7%) stopped CAS by IE Team agreement. Four patients with a previous negative [18F]FDG-PET/CT remained negative during the follow-up; two of them (50%) stopped CAS by IE Team decision. To date, there are no signs of relapse in any of these six cases**.** The median time to negative [18F]FDG-PET/CT result was two months (1-5). The median follow-up time was 38 months; patients who interrupted CAS are shown in **Table 6**.

Discussion

Several cohort studies of CIED infections have been published in recent years [7, 11-12] showing [18F]FDG-PET/CT high sensitivity and specificity values in pocket infections but lower diagnostic performance in lead-associated infections. However, to date there is no gold standard for assessing the subcutaneous and endovascular lead portion in CIED infections. Also, differentiation between LI and SI may be problematic, as intraoperative lead contamination in patients with LI might occur during device extraction [2-4, 11].

In our study, [18F]FDG-PET/CT demonstrated an overall sensitivity for CIED infections of 85%: 79% for pocket and 57% for subcutaneous lead infections. On the contrary, as has been reported in previous studies [7,12], our results show low sensitivity on endovascular (22%) and intracardiac leads (10%). [18F]FDG-PET/CT specificity was 100% for all segments except intracardiac lead, which could not be evaluated, as there were no true negatives intracardiac lead controls because none of control patients underwent myocardial uptake suppression protocol.

Spread of the infection from a contaminated generator pocket through the subcutaneous lead into the endovascular spaced has been hypothesized to be the main pathogenesis mechanism in CIED infections [4]. This mechanism may explain 83% (34/41) of our SI cases. Also, in our data, the [18F]FDG-PET/CT CIED pocket was the most frequent area of positive uptake, followed by subcutaneous lead in second place. Nonetheless, Rizwan et al. [10] suggests that CIED lead infection can also originate from a distant source, possibly explaining the remaining seven cases (17%) presenting SI without LI.,

Compared to previous studies, our work shows equivalent sensitivity and specificity values with a larger sample of patients. In our cohort, the ROC curve for pocket SUV_{max} had a cut-off point of 2.4 with sensitivity of 79.6% and specificity of 92.6% (**Figure 1a**). Other studies had similar results for diagnostic yield, for pocket CIED infections [12-15]. On the contrary, Mahmood et al. showed higher sensitivity and specificity values for SI, probably due to a meta-analysis based on several heterogeneous studies with a low number of patients, divergent designs, and the inclusion of other prosthetic infections [7].

Eight out of 47 cases with LI showed normal [18F]FDG-PET/CT results considered as FN. In all but one FN result, patients had undergone antibiotic therapy for more than 20 days before [18F]FDG-PET/CT acquisition. Several studies have suggested that antibiotic therapy for more than seven days before [18F]FDG-PET/CT acquisition can reduce its diagnostic performance [11,12,16]. However, no significant

differences were found in our cohort regarding the period between antibiotic initiation and [18F]FDG-PET/CT performance (median 13 days for FNs and 5 days for TPs, p=0.19). Nonetheless significance could be masked by the small number of cases. The absence of FP results in our cohort can be partially explained by the longer period elapsed from device implantation to [18F]FDG-PET/CT acquisition in controls, median time 6.1 (0.05–24.31) year. Jerónimo's et al [12] median time between device implantation and [18F]FDG-PET/CT was 2.3 (0.6–6.4) years. Their study as well other published works [14,15] state that FP results are caused by post-operative inflammatory activity.

Although TEE plays an essential role in the diagnosis of lead infection, it may be hard to differentiate vegetations from lead-strands or small-adhered thrombi [16]. It is commonly accepted that TEE is initially performed on patients with suspected SI, whereas [18]FDG-PET/TC should be the primary technique to confirm LI due to the lower [18F]FDG-PET/CT sensitivity for endovascular and intracardiac lead infections. Concordantly, in our cohort, TEE showed higher accuracy in diagnosing intracardiac lead infections. However, it is worth noticing that [18F]FDG-PET/CT had better performance in subcutaneous and endovascular lead infections in SI cases with bacteremia. Negative TEE result does not rule out SI [12] and considering that Pizzi et al. demonstrated an increased sensitivity of [18F]FDG-PET/CT in combination with TEE [17], our results suggest that [18F]FDG-PET/CT may be not only the test of choice to confirm an active local infection [15] but also complementary to TEE in SI cases. Our data showed that [18F]FDG-PET/CT used in combination with TEE increased the definite diagnosis rate of infection from 30.4% to 56.1% in a statistically significant manner (p=0.04) due to the detection of endovascular lead [18]FDG uptake. Furthermore, [18F]FDG-PET/CT has the additional value of being able to detect septic embolisms [14, 18-20] as occurred in two of our SI cases. This data seems to be consistent with that published by Rodríguez-Alfonso et al. They showed [18F]FDG-PET/CT correctly reclassified 57% of patients with initial suspicion of generator pocket infection by detecting lead infection with high diagnostic performance, especially in patients with initial suspicion of LI [21].

Some authors suggest that an increased the metabolic rate of the spleen and BM could be used as an indirect sign of infection [4]. Our study could not corroborate this hypothesis, as SUV_{mean} spleen and SUV_{mean} BM were similar in cases and controls and between LI and SI. However, these findings could be hampered by the fact that most control cases were oncologic patients in which spleen and/or BM uptake could be increased due to neoplastic pathology, chemotherapy or other hematological alterations. Nonetheless, we

found significative differences in spleen and BM metabolism between those patients with SI and confirmed bacteremia compared to LI cases. These results may be explained by the expected hyper-activation of the phagocytic mononuclear system in cases of bacteremia, which could be helpful in distinguishing bacteremic-lead infections from isolated local infections.

Complete device removal in CIED-IE is mandatory to cure infection [4, 22]; however, in last decades a higher number of patients cannot undergo complete CIED extraction surgery [5], even if indicated, due to the growth in comorbidities, aged patients, and more complex infections. Chronic oral suppression (CAS) has been proposed as a helpful strategy in those cases. In our cohort, patients with non-complete device removal received undefined CAS, in most cases lifelong, bearing a high burden for patients translating into side-effects, multidrug-resistant infections, and a high cost for the health system. To date there is no tool to guide clinicians on when to stop CAS. We studied six cases in which [18F]FDG-PET/CT, in combination with clinical evolution, laboratory, and microbiological findings, usefully guided physicians in discontinuing CAS in the absence of relapse for more than two years of follow-up. Although the limited number of cases in our cohort, this work supports the idea that further prospective studies could validate [18F]FDG-PET/CT as a reliable tool for stopping CAS safely during the follow-up of cases with incomplete device removal [23-24].

This study holds some limitations. First, it is a retrospective study with limitations on data interpretation; therefore, data on previous antibiotic therapy was not achieved for each case. Second, it was impossible to evaluate intracardiac leads in the [18F]FDG PET/CTs of control subjects, as they did not undergo a myocardial inhibition protocol. Thus, the specificity analysis for the intracardiac lead was excluded. Also, a high-fat, low-carbohydrate diet before [18F]FDG-PET/CT was not systematically applied to all patients. Third, comparisons between bone marrow and spleen uptake are made based on small subgroups of patients with power statistical limitations. Fourth, the control group had devices implanted for longer time compared to cases, so it was not possible to assess the accuracy of [18F]FDG-PET/CT on recently implanted CIEDs. Finally, the number of cases in which CAS therapy was stopped based on negative [18F]FDG-PET/CT was small and these preliminary results need to be confirmed in further studies with a larger set of patients.

The key findings of this study are the high sensitivity and specificity of [18F]FDG-PET/CT for identifying LI and its unique role in the assessment of the subcutaneous and endovascular lead infection which it is not possible to be evaluated by any other diagnostic technique. This work is the first to compare spleen and

BM metabolism and their potential utility in stratifying CIED infections, showing a potential role to detect bacteremic cases. Also, our cohort is the largest published case-control series and the only study evaluating [18F]FDG-PET/CT in the management of CAS therapy when complete device removal could not be achieved.

Conclusions

The diagnostic performance of [18F]FDG-PET/CT is high in local CIED infections but lower in endovascular and intracardiac lead infections. However, [18F]FDG-PET/CT is the only available technique for assessing subcutaneous and endovascular lead infection and may be complementary to TEE in cases of bacteremia, increasing the definite diagnosis of lead-infections. Moreover, spleen and BM metabolism may help to distinguish between bacteremic-lead infections and isolated LI. Although further prospective studies are needed, a follow-up [18F]FDG-PET/CT could have a potential role in the management of CAS therapy when complete device removal is unachievable.

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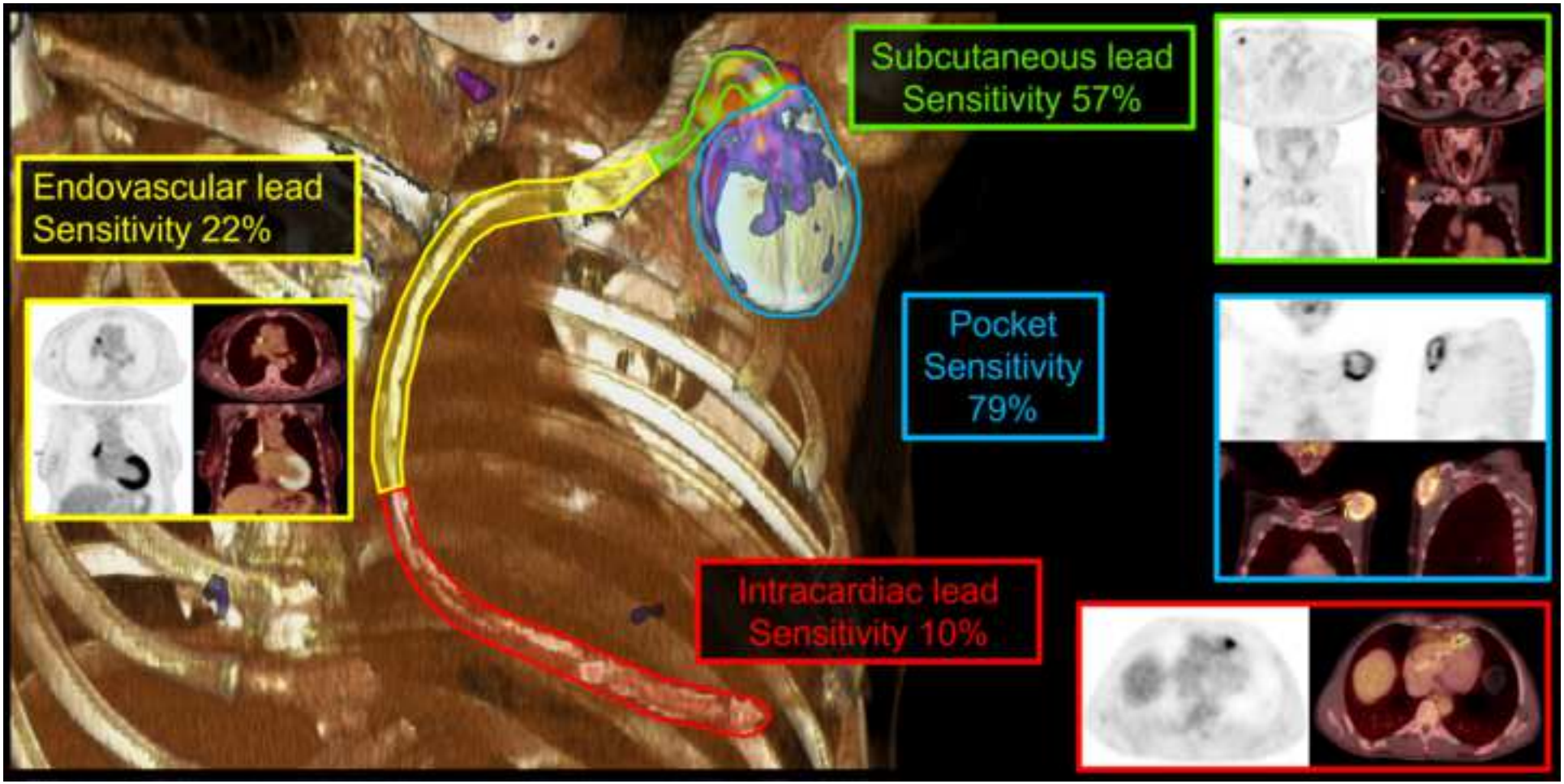
Figures legend

Central illustration shows positive FDG uptake examples and sensitivity values of [18F]FDG-PET/CT in a visual 3D representation of each CIED topographical region: pocket (blue), subcutaneous (green), endovascular (yellow) and intravascular (red).

Figures 1a. ROC curve for CIED pocket SUV_{max} cut-off point 2.35 [Sn: 79.63% Sp: 92.59%]. **1b.** ROC curve for CIED pocket SUV_{max}/SUV_{mean} liver, cut-off point 1.28 [Sn: 75.56% Sp:88.89%]

Central Illustration



Figuras (Figures)

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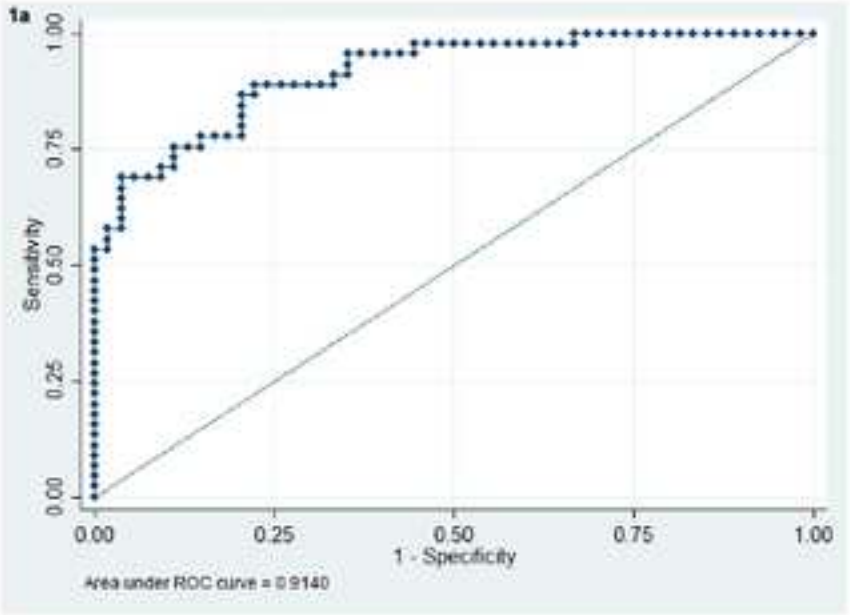

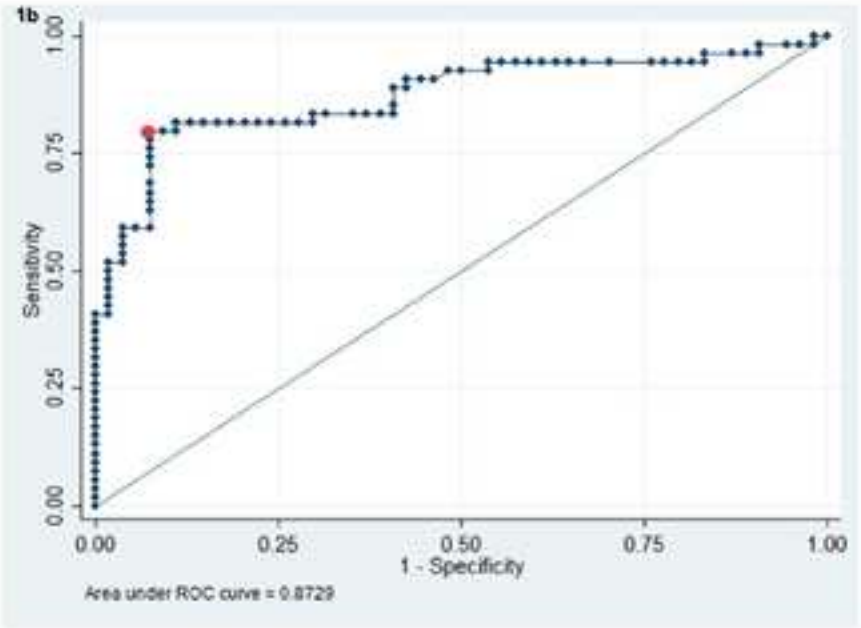

Table 1. Baseline characteristics of cases (CIED infections) and controls.

	Cases N=54	**Controls N=54**	***p***
Variables			
Age (ye	78 (69.0–85.0)	83 (77.0–88.0)	-
Female gender	16 (29.6%)	10 (18.5%)	
Days between CIED implant/replacement and [18F]FDG PET/CT	768.5 (152.0–2443.0)	1389.0 (707.0–3131.0)	**<0.01**
CIED type			
• **PPM**	41 (75.9%)	44 (81.5%)	-
• **ICD**	12 (22.2%)	10 (18.5%)	-
• **CRT**	1 (1.9%)	0	-
[18F] FDG PET/CT results			
• Positive [18F]FDG PET/CT	46 (85.2%)	0	**-**

Abbreviations. CIED Cardiac implantable electronic device; PPM: pacemaker; ICD: implantable cardiac defibrillator; CRT: cardiac resynchronization therapy.

Table 2. Comparison of patients with CIED infection according to isolated local infections of the generator pocket and/or subcutaneous lead (LI) or systemic infections with or without associated local infection (SI)

	Total	Isolated local infections N=13	Systemic infections N=41	*P* value
Baseline and matching characteristics				
Age (years, IQR)	78 (69.0–85.0)	83.0 (75.0–87.0)	77.0 (69.0–85.0)	0.35
Female gender	16 (29.6%)	4 (30.7%)	12 (29.2%)	0.91
CIED Type:				
PPM	41 (75.9%)	9 (69.2%)	32 (78%)	0.54
ICD	12 (22.2%)	4 (30.7%)	8 (19.5%)	0.42
CRT	1 (1.9%)	0	1 (2.4%)	0.31
Local infection signs	47 (87%)	13 (100%)	34 (82.9%)	**<0.01**
Echocardiography				
Echo vegetation (TTE/TEE) *	14 (25.9%)	0	14 (34.1%)	NA
Lead vegetation	14 (25.9%)	0	14 (34.1%)	NA
Tricuspid valve vegetation	2 (3.7%)	0	2 (4.8%)	NA
Mitral valve vegetation	1 (1.8%)	0	1 (2.4%)	NA
[18]FDG-PET/CT				
Positive [18F]FDG-PET/CT	46 (85.2%)	11 (84.6%)	35 (85.3%)	0.94
Pocket	37	8	29	0.54
Subcutaneous lead	27	7	20	0.75
Endovascular Lead	9	0	9	NA
Intracardiac lead	4	0	4	NA
Systemic emboli	1 (1.8%)	0	1 (2.4%)	NA
Pulmonary emboli	1 (1.8%)	0	1 (2.4%)	NA
Interval between CAS initiation and [18F]FDG-PET/CT (days, IQR)	6.0 (0.0–14.0)	6.0 (0–15.0)	8.0 (4.0–13.0)	0.38

Interval between in-hospital admission and device removal (days, IQR)	8.5 (1.5–14.0)	5.5 (1.0 – 14.0)	12.5 (6.0–14.0)	0.25

Abbreviations. CIED Cardiac implantable electronic device; PPM: pacemaker; ICD: implantable cardiac defibrillator; CRT: cardiac resynchronization therapy. NA: Not available. CAS: chronic antibiotic suppression.

*TEE: 13 (92.8%) and TTE: 1 (7.2%).

Table 3. Overall diagnostic accuracy of [18F]FDG-PET/CT according to the four topographical regions of CIED infection.

	CIED infection N= 54	Pocket infection N=47*	Subcutaneous lead N=47*	Endovascular lead N=41	Intracardiac lead N=41
Sensitivity	85% (75.5, 94.5)	79% (66.7, 90.7)	57% (43.0, 71.8)	22% (9.9, 34.9)	10% (0.5, 18.2)
Specificity	100% (93.4, 100.0)	100% (92.4, 100.0)	100% (92.4, 100.0)	100% (91.3, 100.0)	NA
Positive Predictive Value	100% (93.4, 100.0)	100% (92.4, 100.0)	100% (92.4, 100.0)	100% (91.3, 100.0)	100% (91.3, 100.0)
Negative Predictive Value	87% (77.9, 96.3)	84.4% (74.3, 94.5)	73% (60.6, 85.4)	62.8% (48.4, 77.2)	59.3% (45.7, 72.9)

* 13 isolated LI cases + 34 SI with LI.

Abbreviations. CIED: Cardiac implantable electronic device; NA: not available. LI: Isolated local infection.

Table 4. Diagnostic performance of [18F]FDG-PET/CT compared to transesophageal echocardiography in 41 patients with systemic infection with (18 patients) or without (23 patients) bacteremia.

Type of Systemic Infection	**Transesophageal Echocardiography**		
	Positive	Negative	Total
With bacteremia (N=18)			
Endovascular [18F]FDG-PET/CT			
- **Positive**	2*	5	7 (38.9%)
- **Negative**	5*	6	11
Total	7 (38.8%)	11	18
Intracardiac [18F]FDG-PET/CT			
- **Positive**	2	0	2 (11.1%)
- **Negative**	5	11	16
Total	7 (38.8%)	11	**18**
Without bacteremia (N=23)			
Endovascular [18F]FDG-PET/CT			
- **Positive**	0	2**	2 (8.7%)
- **Negative**	7*	14	21
Total	7 (30.4%)	16	**23**
Intracardiac [18F]FDG-PET/CT			
- **Positive**	0	2**	2 (8.7%)
- **Negative**	7	14	21
Total	7 (30.4%)	16	**23**

*Patients simultaneously have vegetations on the leads and/or tricuspid valve. **These were different patients.

Table 5. Comparison of spleen and BM SUV_{mean} in bacteremic cases.

	SUV_{mean} spleen	**SUV_{mean} Bone marrow lumbar column**
Bacteremia SI *vs.* LI *vs.* controls		
- Bacteremia	2.00 (1.7-2.3)	1.75 (1.6-1.9)
*p-value **vs**. LI*	**0.05**	**0.04**
*p-value **vs**. controls*	0.43	0.71

Abbreviations. SI: Systemic infection. LI: Isolated local infection.

Table 6. Patients with non-complete device removal on chronic antibiotic suppression (CAS) therapy whose treatment was stopped according to the follow-up [18F]FDG-PET/CT result*.

	Sex/ Age	**Clinical data**	**Micro-organism**	**Baseline [18F] FDG PET/CT**	**CAS therapy**	**Follow-up [18F] FDG PET/CT**	**AB Duration**	**Outcome treatment (months)**
1	Male 93	Pocket and lead CIED-IE	*MSSA*	Positive pocket-subcutaneous lead	Levofloxacin+ TMP-SMX	Negative	**Four-months**	**No relapses after 43 months-off-CAS**
2	Male 60	Pocket CIED infection	*CoNS*	Positive pocket	Linezolid	Negative	**Eight-month**	**No relapses after 44 months-off-CAS**
3	Male 89	EV-Lead CIED infection	*MSSA*	Negative	Levofloxacin+ rifampicin	Negative	**Six-months**	**No relapses after 38 months-off-CAS**
4	Female 75	Pocket CIED infection	*C. acnes*	Positive pocket-subcutaneous lead	Linezolid	Negative	**Two-month**	**No relapses after 38 months-off-CAS**
5	Female 85	Pocket and lead CIED infection	*MSSA*	Positive pocket-subcutaneous lead	Levofloxacin+ rifampicin	Negative	**Three-months**	**No relapses after 17 months-off-CAS**
6	Female 80	Pocket and lead CIED infection	*MRSA*	Negative	Linezolid	Negative	**One-month**	**No relapses after 36-months-off-CAS**

Abbreviations: CIED-IE: Cardiac implantable electronic device infective endocarditis CAS: chronic antibiotic suppression; CoNS: coagulase negative staphylococci; SC: subcutaneous lead; EV: endovascular; TMP-SMX: trimethoprim-sulfamethoxazole

*The overall non-complete device removal on CAS therapy is summarized in table S2 supplementary material.

[18]FDG-PET/CT methodological considerations

Whole-body FDG-PET/CT studies were acquired 60 min after 18F-FDG injection (4.0 MBq/kg) in a hybrid scanner (Biograph mCT 64S; Siemens) with myocardial uptake suppression protocol consisting of a fasting period of 12h and intravenous administration of 50 IU/kg of unfractionated heparin 15min before 18F-FDG injection.

Images were reconstructed using the iterative True X + TOF (Ultrahigh definition PET) algorithm (2 iterations, 20 subsets) with point spread function (PSF) and time of flight (TOF) corrections. All images included a Gaussian post-filter of 2 mm FWHM and were reconstructed into a matrix size of 200 and a voxel size of 4.1x4.1x3 mm3. CT parameters were approximately 100 kV and 120 mA, adjusted to patient morphology.

Visual analysis

The study's primary endpoint was the FDG-PET/CT result, which was assessed qualitatively by visual evaluation. Images were interpreted separately by two blinded, independent nuclear medicine specialists. Each topographical region was visually classified as positive or negative for infection. Positivity criteria were the presence of any focal or heterogeneous uptake related to each topographical region identified in both attenuation-corrected and uncorrected images. Additionally, whole-body images were carefully assessed to detect any other signs of infection, embolic event, or neoplastic lesion.

Semiquantitative analysis

A semiquantitative analysis was performed in all FDG-PET/CT studies by measuring the maximum standardized uptake value (SUVmax) of a volume of interest (VOI) sphere including the totality of the pocket and a VOI sphere placed on the most active part of each segment of the lead (subcutaneous, endovascular and intracardiac).

For reference, blood pool-SUVmean was calculated by setting a 3 cm3 spherical VOI at the descending thoracic aorta as well as liver-SUVmean placing a 5 cm3 spherical VOI in the liver avoiding the inclusion of any abnormal area. SUV ratios were calculated by dividing the SUVmax of the area of interest by the liver SUVmean with the aim of overcoming any bias related to each subject physiological individual fluctuation of 18F-FDG distribution.

Spleen and bone marrow metabolism

Values for SUVmean were obtained from the spleen and bone marrow (BM) to assess indirect signs of infection/inflammation as described in Boursier et al (2). For this purpose, a 5 cm3 spherical VOI was

positioned close to the center of the spleen carefully avoiding the inclusion of any abnormal area secondary to possible lesions (neoplastic, abscesses, ischemic, etc.). Lumbar-column BM SUVmean was obtained by placing a spherical VOI placed on the bodies of the 3rd lumbar vertebra (L3) with a diameter set at the vertebra height. In case of damaged L3 (e.g., crushed vertebra, severe discarthrosis, or spondylitis) VOI was placed in another lumbar vertebra.

Follow-up FDG PET/CT

At least one FDG-PET/CT within the first six months after discharge was performed in all the patients from whom the device could not be removed entirely. Some patients had more than one FDG-PET/CT scheduled every 4–6 months. Data on ABS, duration, and type of infection were also analyzed.

Supplemental figures

Figures S1. S1a ROC curve for bacteremic CIED infections spleen SUVmean cut-off point 1.7 [Sn: 84.2%, Sp: 58.3%]. S1b ROC curve for bacteremic CIED infections BM SUVmean cut-off point of 1.6 [Sn: 79% Sp: 66.7%].

Figure S2. ROC curve for CIED pocket according to the SUVmax/SUVmean poolvascular with a cut-off point of 0.9 [Sn 88.9% Sp 73.6%].

Figure S3. ROC curve for CIED subcutaneous lead according to the SUVmax/SUVmean liver with a cut-off point of 0.6 [Sn 85.7% Sp 71.7%] in S3a. ROC curve for CIED subcutaneous lead according to the SUVmax/SUVmean pool vascular with a cut-off point of 0.6[Sn 82.1% Sp 77.4 %] in S3b.

Figure S4. ROC curve for CIED endovascular lead according to the SUVmax/SUVmean liver with a cut-off point of 1.2 [Sn 50% Sp 94.3%] in S4a. ROC curve for CIED endovascular lead according to the SUVmax/SUVmean poolvascular with a cut-off point 1.1 [Sn 50% Sp 86.8%] in S5b.

Figure S5. ROC curve for CIED intracardiac lead according to the SUVmax/SUVmean liver with a cut-off point of 1.1 [Sn 66.7% Sp 84.9%] in S6a. ROC curve for CIED intracardiac lead according to the SUVmax/SUVmean pool vascular with a cut-off point of 1.1 [Sn 56.7% Sp 83%] in S6b.

Figure S6. Patients without complete device removal flowchart.

Supplemental tables

Table S1. Clinical characteristics, microbiology, and outcomes of patients with CIED infections according to isolated local CIED infection or systemic CIED infection.

	Total	Isolated local infections N=13	Systemic infections N=41	P value
Clinical features				
Fever	29 (53.2%)	0	29 (70.7%)	**<0.01**
Local signs of device infection	47 (87.0%)	13 (100%)	34 (82.9%)	**<0.01**
C Reactive Protein (mg/dL)	1.3 (0.4–3.32)	1.2 (0.9–2.9)	1.3 (0.4–3.32)	0.64
Diagnosis criteria				
Patients with positive cultures	49 (90.7%)	10 (76.9%)	39 (95.1%)	0.14
Positive pocket swab	29 (53.7%)	10 (76.9%)	19 (46.3%)	**0.03**
Positive device culture	18 (33.3%)	3 (23.1%)	15 (36.6%)	0.33
Positive blood culture	18 (33.3%)	0	18 (43.9%)	**<0.01**
Positive lead culture	39 (90.7%)	0	39 (95.1%)	**<0.01**
Device 16-S RNA PCR positive*	4 (7.4%)	1 (7.6%)	3 (7.3%)	0.96
Lead 16-S RNA PCR positive*	5 (9.3%)	0	5 (12.2%)	**0.02**
Patients with negative cultures	5 (9.3%)	3 (23.1%)	2 (4.8%)	0.14
Positive echocardiography	14 (25.9%)	0	14 (34.1%)	**<0.01**
Microbiology				
CoNS [a]	27 (50%)	6 (46.1%)	21 (51.2%)	0.75
• *MRSE*	11 (20.3%)	1 (7.7%)	10 (24.4%)	0.10
• *Other CoNS*	6 (11.1%)	3 (23.0%)	3 (7.3%)	0.19
S. aureus	13 (24%)	2 (15.4%)	11 (26.8%)	0.35
• *MRSA*	1 (1.9%)	0	1 (2.4%)	0.31
GN non-*HACEK*	4 (7.4%)	1 (7.7%)	3 (7.3%)	0.96
Polymicrobial [b]	3 (5.5%)	1 (7.7%)	2 (4.8%)	0.73
Outcome				
Complete device removal	36 (66.7%)	6 (46.2%)	30 (73.2%)	**0.03**
Incomplete device removal	9 (16.7%)	5 (38.5%)	4 (9.8%)	**<0.01**
No device removal	9 (16.7%)	2 (15.3%)	7 (17%)	0.15
CAS	18 (33.3%)	8 (61.5%)	10 (24.4%)	**0.01**
Re-implant	36 (66.6%)	8 (61.5%)	28 (68.3%)	0.54
In-hospital mortality	3 (5.6%)	0	3 (7.3%)	0.07
Relapses	2 (3.7%)	1 (7.7%)	1 (2.4%)	0.50

*16SrRNA-PCR was not performed for all cases, because it was not systematically included in the diagnosis procedure at the time the study protocol was designed.

[a] Other coagulase negative bacteria: *S. schleiferi, C. acnes, C. jeikeium.* [b]Polymicrobial flora includes: *S. aureus, S. epidermidis* and mixed flora

Abbreviations. CAS: chronic antibiotic suppression, CoNs: staphylococcus coagulase negative, MRSE: methicillin-resistant *Staphylococcus epidermidis*, MRSA: methicillin-resistant *Staphylococcus aureus*.

Table S2. Systemic CIED infection characterization according to the EHRA consensus diagnosis criteria [2] considering clinical presentation, microbiological isolation (blood and endovascular/intracardiac lead cultures positivity) and echocardiographic data.

	Systemic infections N=41
SI with positive blood culture (BC)	**18 (43.9%)**
- Positive BC + positive TEE	7/18 (38.9%)
- Positive BC + negative TEE	11/18 (61.1%)
SI with positive lead culture (LC) without positive blood culture	**23 (56.1%)**
- Positive LC + positive TEE	7/23 (30.4%)
- Positive LC + negative TEE*	16/23 (69.6%)

*All these patients presented systemic signs of CIED infection, e.g., persistent fever and local signs of device infection with positive local cultures.

Table S3. Comparison of baseline characteristics and [18F]FDG PET/CT results according to the interval between CIED implant/replacement and [18F]FDG PET/CT (<3 months vs. >3 months).

	< 3 months N=9	**>3 months N=45**	***P* value**
Baseline and matching characteristics			
Age (years, IQR)	72.0 (59.0–79.0)	81.0 (72.0–86.0)	0.12
Female gender	3 (33.3%)	13 (28.9%)	0.80
CIED Type:			
PPM	8 (88.8%)	33 (73.3%)	0.21
ICD	1 (11.1%)	11 (24.4%)	0.28
CRT	0	1 (2.2%)	0.31
Local infection signs	8 (88.9%)	39 (86.7%)	0.85
Echocardiography			
Echo vegetation	2 (22.2%)	12 (26.7%)	0.85
Lead vegetation	2 (22.2%)	12 (26.7%)	0.85
Tricuspid valve vegetation	0	2 (4.4%)	NA
[18]FDG-PET/CT			
Positive [18F]FDG-PET/CT	8 (88.9%)	38 (84.4%)	0.71
Pocket	8 (88.9%)	29 (64.4%)	0.06
Subcutaneous lead	3 (33.3%)	24 (53.3%)	0.26
Endovascular lead	2 (22.2%)	7 (15.6%)	0.66
Intracardiac lead	1 (11.1%)	3 (6.7%)	0.69
Systemic emboli	0	1 (2.2%)	NA
Pulmonary emboli	0	1 (2.4%)	NA
Interval between CAS initiation and [18F]FDG-PET/CT (Days, IQR)	6.0 (0–13.0)	6.5 (0.0–18.5)	0.88
Interval between in-hospital admission and device removal (Days, IQR)	13.0 (11.0 – 14.0)	7.0 (1.0–14.0)	0.42

Abbreviations. CIED: cardiac implantable electronic device; PPM: pacemaker; ICD: implantable cardiac defibrillator; CRT: cardiac resynchronization therapy; NA: not available; CAS: chronic antibiotic suppression.

Table S4. Comparison of spleen and bone marrow SUV_{mean}

	SUV_{mean} spleen	**SUV_{mean} bone marrow lumbar column**
Cases *vs.* controls		
- Cases	1.8 (1.6-2.1)	1.75 (1.5-1.9)
- Controls	1.9 (1.7-2.1)	1.74 (1.39-2)
p-value	0.4	0.9
- Cases/liver SUV_{mean}	0.9 (0.8-0.9)	0.9 (0.7-1)
- Controls/liver SUV_{mean}	0.9 (0.8-0.9)	0.8 (0.7-0.9)
p-value	0.4	0.3
Isolated local (LI) *vs.* systemic infection (SI)		
- Isolated local Infection	1.8 (1.6-1.9)	1.75 (1.6-2)
- Systemic Infection	1.8 (1.7-2.2)	1.6 (1.1-1.9)
p-value	0.5	0.2
- LI/liver SUV_{mean}	0.9 (0.9-1.1)	0.9 (0.8-1)
- SI/liver SUV_{mean}	0.9 (0.7- 0.9)	0.8 (0.7-0.9)
p-value	0.06	0.2

Table S5. Clinical characteristics and outcomes of 18 patients with non-complete device removal on chronic antibiotic suppression therapy (CAS).

Case	Sex/Age	Clinical presentation	Microbiology	TEE	Baseline FDG PET/CT	Surgery*	Reason for non-complete removal	CAS therapy	Follow-up FDG PET/CT (months)	CAS Duration	Outcome treatment (months)
1	Male/93	Pocket + CIED-IE	*MSSA* Negative BC	Negative	Positive pocket and SC lead	Not performed	Comorbidities	Levofloxacin plus TMP-SMX	Negative (4)	Four months	No relapses after 43 months off CAS **Not-related death**
2	Male/60	Pocket + CIED lead infection	*CoNS* Positive BC	Positive: Lead veg.	Positive pocket	Not performed	Medical agreement IE-team	Linezolid	Negative (6)	Eight months	No relapses after 44 months off CAS
3	Male/89	Lead CIED infection	*MSSA* Repeated positive BC	Positive: Lead veg.	Negative	Not performed	Comorbidities	Levofloxacin plus rifampicin	Negative (5)	Six months	No relapses after 38 months off CAS Not-related death
4	Female/75	Pocket +SC CIED infection	*C. acnes* Negative BC	Negative	Positive pocket and SC lead	Only pocket. Abandoned lead	Comorbidities	Linezolid	Negative (2)	Two months	No relapses after 38 months off CAS
5	Female/85	Pocket + lead CIED infection	*MSSA* Negative BC	Positive: lead veg.	Positive pocket- SC lead	Only pocket. Abandoned lead (>4cm)	Comorbidities	Levofloxacin and rifampicin	Negative (3)	Three months	No relapses after 17 months off CAS
6	Female/80	Pocket CIED infection	*MRSA* Negative BC	Negative	Negative	Not performed	-	Linezolid	Negative (1)	One month	No relapses after 36-months off CAS
7	Male/78	EV-Lead CIED infection	*MSSA* Repeated positive BC	Positive: lead veg.	Negative	Not performed	-	Levofloxacin*/ TMP-SMX	Negative (3)	Ongoing	No relapses after 38 months on CAS
8	Male/51	CIED-IE	*MSSA* Repeated positive BC	Positive: lead veg.	Negative	Only pocket. Abandoned lead* (<4cm)	Comorbidities	Levofloxacin	Negative (6)	Ongoing	No relapses after 9 months on CAS **Not-related death**
9	Female/82	Pocket CIED infection	*CoNS* Negative BC	Negative	Positive pocket and SC lead	Only pocket. Abandoned lead (>4cm)	Comorbidities	TMP-SMX	Negative (12)	Ongoing	No relapses after 29 months on CAS

10	Female/81	EV-Lead CIED infection	*C. acnes* Positive BC	Negative	Positive EV lead	Not performed	Comorbidities	Amoxicillin	Negative (10)	Ongoing	No relapses after 26 months on CAS
11	Female/85	Pocket-SC lead CIED infection	*S. epidermidis* Negative BC	Negative	Positive pocket- SC lead	Only pocket. Abandoned lead (>4cm)	Comorbidities	TMP-SMX	Positive pocket - SC lead (12)	Ongoing	No relapses after 20 months on CAS
12	Male/56	Pocket-SC lead CIED infection	*C. acnes and K. oxytoca* Negative BC	Negative	Positive pocket- SC lead	Only pocket. Abandoned lead (>4cm)	Comorbidities	Amoxicillin	Positive pocket- SC lead (3)	Ongoing	No relapses after 9 months on CAS
13	Male/77	Pocket + EV-lead CIED infection	*MSSA* Positive BC	Positive: lead veg	Positive EV-lead	Only pocket. Abandoned lead (>4cm)	Comorbidities	Levofloxacin plus rifampicin	Positive EV-lead (1)	Ongoing	No relapses after 30 months on CAS
14	Female/73	EV-Lead CIED infection	*MSSA* Repeated positive BC	Negative	Negative	Not performed	Comorbidities	Levofloxacin	Not performed	Two months	No relapses after 29 months off CAS
15	Female/96	Pocket-SC lead CIED infection	Mixed flora	Negative	Positive pocket and SC lead	Only pocket. Abandoned lead (>4cm)	Comorbidities and patient's refusal	Ciprofloxacin	Not performed	Ongoing	No relapses after 25 months on CAS **Not-related death**
16	Male/85	Pocket-SC lead CIED infection	*CoNS*	Negative	Positive pocket and SC lead	Only pocket. Abandoned lead (>4cm)	Comorbidities	TMP-SMX	Not performed	Ongoing	No relapses after 35 months on CAS
17	Male/82	Pocket CIED infection	*S. epidermidis*	Negative	Negative	Not performed	Comorbidities	Tedizolid	Not performed	Ongoing	No relapses after 28 months on CAS **Not-related death**
18	Male/59	CIED IE	*MRSA* Positive BC	Positive: lead veg	Positive EV lead	Not performed	Comorbidities	Tedizolid	Not performed	Ongoing	No relapses after 6 months on CAS **Not-related death**

Abbreviations: CIED-IE: Cardiac implantable electronic device infective endocarditis BC: blood cultures; CAS: chronic antibiotic suppression; CoNS: coagulase negative staphylococci; SC: subcutaneous lead; EV: endovascular; TMP-SMX: trimethoprim-sulfamethoxazole.
*Surgery: All patients underwent percutaneous manual traction surgery except for Patient 8, who underwent open surgery and whose lead was fragmented during the procedure.
**Levofloxacin was changed to TMP-SMX because of toxicity.

Authorship: All the 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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Study 4

4.4 Prevalence, risk factors and impact of chronic antibiotic suppression in patients with cardiac implantable electronic device infective endocarditis without device removal

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Submitted.

microorganisms

MDPI

Prevalence, risk factors and impact of chronic antibiotic suppression in patients with cardiac implantable electronic device infective endocarditis without device removal

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Abstract: There is limited information on prevalence and outcomes of patients with cardiac implantable electronic device (CIED) infective endocarditis (IE) without device removal. This study aimed to describe the prevalence, clinical characteristics, risk factors and outcomes of patients without device removal and to know the efficacy and safety of chronic antibiotic oral suppression (CAS). We performed a retrospective 40-year study (1981-2021), including 140 consecutive patients with definite CIED-IE. Prevalence of no device removal was 12% (17/140) and was higher in the latter 20 years (4% vs. 14%, p=0.17). There were four relapses (24%), all in patients without device removal. Risk factors for no device removal were older age (OR 95% CI; 1.15[1.05,1.25]) and *S. aureus* etiology (OR 95% CI; 4.35[1.93,20.37]). In-hospital mortality (35.5% vs. 9.8%, p=0.03) and one-year mortality (58.5% vs. 12.2%, p<0.01) were higher in patients without removal. At one-year, CAS was effective in 11/13 (85%) cases, with only two patients (15%) experiencing antibiotic toxicity. The prevalence of no removal in CIED-IE has increased in the last two decades, identifying a subset of older patients with distinctive clinical features and poor outcomes. To avoid relapse, these patients needed CAS, which was effective and safe in most cases in the short-term.

Keywords: Cardiac implantable electronic devices; CIED infective endocarditis; device removal; no device removal; risk factors; chronic antibiotic suppression; [18F] FDG-PET/CT.

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1. Introduction

Cardiac implantable electronic device infective endocarditis (CIED-IE) remains a deadly disease when complete device removal is not performed [1-4]. Recent epidemiological changes in high-income countries due to growing comorbidity and aging populations have led to more complex infections in patients with an increasing surgical risk [1]. Consequently, a significant number of patients cannot undergo complete CIED extraction surgery even if indicated. The proper management strategies, treatment, and follow-up approaches are poorly studied when removal is not performed [4-6]. Chronic oral suppression (CAS) has been proposed to treat this population to avoid relapses [7, 8].

However, there is limited information on the prevalence, risk factors and outcomes of CIED-IE without complete removal.

This retrospective 40-year CIED-IE study aims first to describe the prevalence, clinical characteristics, and outcomes of patients without device removal vs. complete removal; second, to identify risk factors associated with no device removal; and third, to know the efficacy and safety of CAS.

2. Materials and Methods

Design

Observational 40-year retrospective study of prospectively followed CIED-IE at Hospital Clinic de Barcelona (HCB), a referral cardiovascular surgery center for infective endocarditis (IE) and cardiovascular infections. Data were collected during the index hospitalization between 1981 to 2021. All patients had at least one-year follow-up, as previously described [1], by one member of the IE team.

Patient selection and data collection

We included 140 consecutive patients with definite CIED-IE. All patients were discussed at weekly IE team meetings since 1986 [9], and the final diagnosis was accomplished by consensus. The type of oral chronic antibiotic suppression (CAS) and duration were decided by the IE team based on the antibiotic susceptibility pattern of isolated microorganisms.

Inclusion criteria: Only patients with definite CIED-IE using the modified Duke criteria for IE and presented in the IE team meetings were included [10]. All patients, with or without local signs of pocket infection, had vegetations in either valve or lead, and positive blood cultures, and/or positive lead culture and/or 16S rRNA gene amplification and sequencing positive. Due to the aim of this study, we used only the first episode of CIED-IE for each patient.

We divided the cohort into CIED-IE with complete device removal and CIED-IE without removal.

Exclusion criteria: Patients with no definite criteria for IE were excluded.

Definitions

Type of device: Pacemaker (PPM), implantable cardioverter defibrillator (ICD), and cardiac resynchronization therapy (CRT).

Microbiological diagnosis was based on the microorganisms identified in blood cultures or cultures of cardiac device lead and/or by 16S rRNA gene amplification and sequencing (since 2015).

Echocardiographic diagnosis was achieved by transthoracic echocardiography (TTE) between 1981-1990; since January 1991, all cases have undergone transesophageal echocardiography (TEE). Any mass seen on a lead in echocardiography in the context of bacteremia was assumed to be vegetation.

18F-fluorodeoxyglucose positron emission tomography/computed tomography: ([18F] FDG-PET/CT) was included in our center in 2014 [1]. We recorded all [18] FDG-PET/CT data from CIED-IE patients in whom it was performed during the hospitalization phase and during the follow-up in patients whose devices could not be completely removed. Whole-body [18F] FDG-PET/CT studies were acquired 60 minutes after [18F] FDG injection (4.0 MBq/kg) in a hybrid scanner (Biograph mCT 64S; Siemens) with myocardial uptake suppression protocol consisting of a fasting period of 12 hours and intravenous administration of 50 IU/kg of unfractionated heparin 15 minutes before [18F] FDG injection. Diabetic patients were managed as indicated by EANM/SNMMI guidelines for [18F] FDG use in inflammation and infection. Positivity criteria were the presence of any focal or heterogeneous uptake related to the CIED areas identified in both attenuation-corrected and uncorrected images.

Chronic oral suppression (CAS): We evaluated *efficacy* according to the presence of relapse or not, and *safety* in terms of the need to change the antimicrobial therapy due to an adverse event of type 3 or 4. We recorded the antibiotic administered, the duration of treatment, and antimicrobial susceptibilities of the causative isolates. *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 or more days after the end of the antibiotic treatment.

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

Study variables

1) Host factors for removal vs. no removal: age, comorbidities, Charlson comorbidity index (CCI), diabetes, and chronic renal failure.

2) Device-dependent factors for removal vs. no removal: device type, number and age of leads, pocket infection, vegetations location and size, and valve involvement.

3) Etiology of CIED-IE: microorganisms identified by culture or molecular biology.

4) Transferal from other centers.

5) Surgical management of CIED-IE: indication, type of device removal (manual traction/open surgery), and cause of incomplete or no device removal (host-related, device-dependent factors, and/or technical factors).

6) Chronic oral suppression (CAS) in patients with incomplete or without device removal: type of oral antibiotics, duration, and safety.

Statistical analysis

We compared clinical characteristics and outcome in CIED-IE patients with and without complete device removal. The primary endpoint was incomplete or no device removal. Secondary endpoints were in-hospital and one-year mortality, relapse, CAS efficacy, and safety in patients with incomplete or no device removal. Data are presented as median (interquartile ranges) for continuous variables and as frequencies (percentages) for categorical variables. As appropriate, continuous variables were compared using Student's t-test or the Mann–Whitney U-test, and categorical variables using the Chi-squared or Fischer tests. Univariate and multivariate analysis of risk factors of no device removal were calculated. Variables found to have a simple association with non-removal ($p<0.10$) were considered for the final models. For all tests, statistical significance was determined at the $p=0.05$ level. All analyses were performed using Stata statistical package v.14 (Stata Corporation LLC).

3. Results

A total of 140 consecutive cases of CIED-IE were diagnosed: 25 CIED-IE in the first period (1981-2000) and 115 in the second (2001-2021). Complete CIED removal was performed in 123 patients (88%), and 17 (12%) patients did not undergo complete device removal. The complete removal distribution between periods was 96% (24/25) in the first period vs. 86.1% (99/115) in the second ($p=0.17$).

3.1. ***Clinical characteristics and outcomes of patients with/without device removal.***

A comparison between CIED-IE with and without complete CIED removal is shown in **table 1.** Patients without complete CIED removal were older (75 years [71-82] vs. 69 years [58-75], $p<0.01$), had more comorbidities (CCI 5 vs. 4, $p<0.01$), less tricuspid involvement (5.9% vs. 24.4%, $p<0.01$), a higher prevalence of *Staphylococcus aureus* (58.8% vs. 30.1%, $p=0.02$) and a lower prevalence of coagulase-negative staphylococci (CoNS) (23.5% vs. 47.2% $p=0.03$). Patients who underwent complete CIED removal had no relapses, whereas four (23.5%) of 17 cases without complete device removal relapsed.

Figure 1 shows the overall cohort distribution depicting removal, relapses, chronic oral suppression (CAS), and survival. In-hospital mortality (35.5% vs. 9.8%, p=0.03) and one-year mortality (58.5% vs. 12.2%, p<0.01) were both significantly higher in patients without removal.

3.2. Predictors factors for no device removal

Risk factors for no device removal are represented in **table 2**: age (OR 95% CI; 1.15[1.05,1.25]) and *S. aureus* CIED-IE etiology (OR 95% CI; 4.35[1.93,20.37]), but neither Charlson comorbidity index nor device-related factors, e.g., type and age of the device and the number of leads, were independently associated with no device removal.

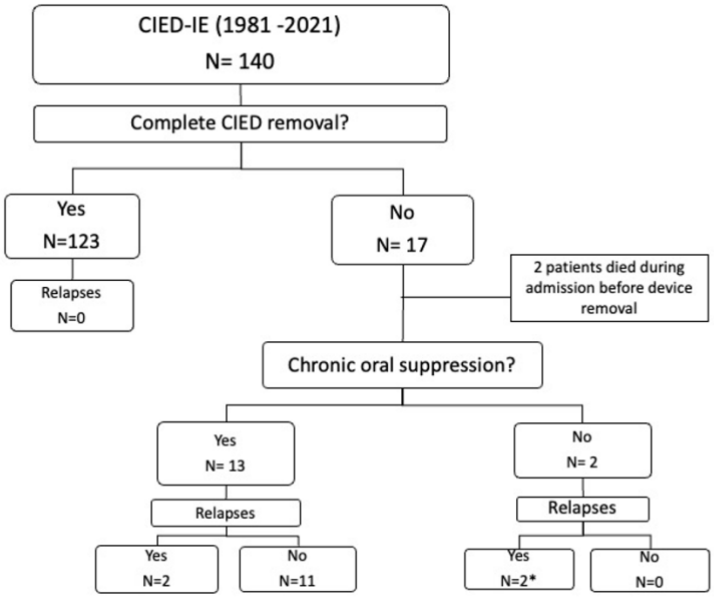

Figure 1. Flowchart of patients with and without CIED removal, patients on chronic oral antibiotic suppression, and relapses. *One patient died due to CIED-IE relapse without CAS. The other underwent complete device removal due to relapse and died from post-operative complications receiving CAS.

Table 1. Comparison of CIED-IE with and without device removal.

Variable	No device removal* (N=17)	Device removal (N=123)	P
Age, years (median, IQR)	75 (71 - 82)	69 (58 - 75)	< 0.01
Male gender	13 (76.5%)	105 (85.4%)	0.41
Fever	10 (58.8%)	86 (69.9%)	0.38
Concomitant pocket infection	5 (29.4%)	51 (41.5%)	0.31
Interval implant/exchange - diagnosis <60 days	1402 (476 -3076)	1123 (233 - 3138)	0.89
Study period:			
1981-2000	1/25 (4%)	24/25 (96%)	0.04
2001-2020	16/115 (13.9%)	99/115 (86.1%)	0.85
Place of acquisition:			
Community	8 (47.1%)	74 (60.2%)	0.31
Nosocomial	4 (23.5%)	15 (12.2%)	0.29
HCA-infections	5 (29.4%)	34 (27.6%)	0.88
Transferred from other hospital	5 (29.4%)	45 (36.6%)	0.55
Type of cardiac device:			
PPM	15 (88.2%)	99 (80.5%)	0.37

ICD	2 (11.8%)	22 (17.9%)	0.48
CRT	0	2 (1.6%)	0.16
Type of CIED-IE:			
Early (< one-year)	3 (17.6%)	36 (29.3%)	0.25
Late (> one-year)	14 (82.4%)	87 (70.7%)	0.25
CIED-IE only	13 (76.5%)	78 (63.4%)	0.24
CIED-IE + Valve infection	4 (23.4%)	45 (36.6%)	0.24
Charlson comorbidity index (Median IQR)	5 (5-7)	4 (3 - 5)	<0.01
Diabetes mellitus	6 (35.3%)	41 (33.3%)	0.87
Chronic kidney disease (CKD)	4 (23.5%)	15 (12.2%)	0.29
Coronary heart disease	38 (30.9%)	5 (33.3%)	0.85
Previous heart failure	5 (29.4%)	39 (31.7%)	0.84
Echocardiography			
Vegetation on device	17 (100%)	123 (100%)	NA
Tricuspid valve vegetation	1 (5.9%)	30 (24.4%)	<0.01
Valve vegetation size, Median (IQR)	8.5 (8.0 – 20.0)	10.0 (7.0 – 9.0)	0.09
[18F] FDG-PET/CT	6 (35.3%)	25 (20.3%)	0.22
Positive [18F] FDG-PET/CT result	4/6 (66.7%)	22/25 (88%)	0.30
Microbiology			
Positive blood cultures or lead/valve culture	17 (100%)	123 (100%)	NA
16S-rRNA PCR	4 (23.5%)	28 (22.8%)	0.94
Positive 16S-rRNA PCR result	2/4 (50%)	17/28 (60.7%)	0.70
S. aureus	10 (58.8%)	37 (30.1%)	0.02
MRSA	3 (17.6%)	10 (8.1%)	0.32
Coagulase-negative Staphylococci	4 (23.5%)	58 (47.2%)	0.03
MR-Cons	1 (5.9%)	10 (8.1%)	0.32
Enterococcus sp.	1 (5.9%)	6 (4.9%)	0.86
Gram negative bacilli	1 (5.9%)	9 (7.3%)	0.82
Polymicrobial	0	7 (5.7%)	<0.01
Others	1 (5.9%)	6 (4.8%)	0.08
Complications	14 (82.4%)	61 (49.6%)	<0.01
Pulmonary embolism	3 (17.6%)	9 (7.3%)	0.28
Heart failure	9 (52.9%)	26 (21.1%)	0.01
Sepsis/shock	5 (29.4%)	10 (8.1%)	0.06
Persistent bacteremia	2 (1.6%)	1 (6.7%)	0.44
Type of removal:			
Traction	4* (23.5%)	96 (78%)	<0.01
Open surgery	0	27 (21.9%)	NA
Reimplant	4 (23.5%)	83 (67.5%)	<0.01
Interval complete removal- entire system reimplantation (days, median, IQR)	-	15.0 (10-22)	NA
CAS in patients without removal of cardiac device system	13 (76.5%)	0	<0.01
CAS toxicity	2/13 (15.4%)	NA	NA
In-hospital Mortality**	6 (35.3%)	12 (9.8%)	0.03
One-year follow-up**			
One-year removal surgery	5 (29.4%)	4 (3.3%)	0.02
Mortality	10 (58.8%)	15 (12.2%)	<0.01
Relapses	4 (23.5%)	0	<0.01

* Removal was rejected in 13 patients, but 4 underwent incomplete device removal due to comorbidities, age, lead age, and high risk of sternal sternotomy.

** Causes for in-hospital and one-year mortality are exposed in **supplementary table S1**.

Abbreviations: HCA: healthcare-associated, PPM: pacemaker; ICD: implantable cardiac defibrillator; CRT: cardiac resynchronization therapy; [18F] FDG-PET/CT: 18F-fluorodeoxyglucose positron emission tomography/computed tomography; 16S-rRNA-PCR: 16S Ribosomal RNA Gene-Targeted amplification and Sequencing. Cons: Coagulase-negative Staphylococcus; MR: methicillin-resistant; GVS: viridian's group streptococci. CAS: Chronic antibiotic suppression. NA: not applicable.

3.3. *Chronic antibiotic suppression in patients with non-device removal.*

From the overall cohort, 17 patients did not undergo complete device removal (**Figure 1**). Two patients died before device removal. The reasons (multiple in some patients) for incomplete or no device removal in the remaining 15 cases were host-related in 13/15 (86.7%) cases, device-dependent in 5/15 (33.3%) cases and technical factors in 11/15 (73.3%) cases. Four (26.6%) out of 15 underwent incomplete removal with only pocket or partial lead extraction due to a high risk for cardiac surgery. Two patients (13.3%) did not receive CAS and died due to relapses (caused by *S. lugdunensis* and *S. aureus*), and 13 patients (86.7%) received CAS.

The main characteristics of these 13 patients are summarized in **supplementary table S1**. Whereas late CIED-IE was the most prevalent clinical presentation (73.3%), early CIED-IE only presented in four cases (26.7%%). Most cases had more than two leads (69.2%). Seven (53.5%) CIED-IE episodes were due to *S. aureus*, three (26.7%) CoNS, and *Cutibacterium acnes*, *Enterococcus faecalis* and *Escherichia coli* in one case each (6.6%). All patients without complete removal underwent CAS, except two who died during admission and two who rejected treatment. Antibiotic-schemas were levofloxacin combined with rifampicin (6 cases) and cotrimoxazole (4 cases) in staphylococcal CIED-IE, and amoxicillin (2 cases) in enterococcal CIED-IE. For *E. coli* CIED-IE, CAS was ciprofloxacin Diagnostic [18F] FDG-PET/CT scans were performed in five patients and were positive in 4/5 (80%). A follow-up PET/CT scan within the first year was performed in two (2/4: 50%) of them. In both cases, scans turned positive to negative after four and twelve months of CAS, respectively, and CAS was stopped with no relapses during follow-up.

Table 2. Univariate and multivariate analysis for predictors of no device removal.

	Univariate			Multivariate		
	OR	**CI 95%**	**p**	**OR**	**CI 95%**	**p**
2001-2020 vs. 1981-2000	0.58	(0.12, 2.71)	0.12	-	-	-
Age	1.12	(1.05, 1.21)	<0.01	1.15	(1.05, 1.25)	<0.01
Male gender	0.74	(0.19, 2.87)	0.66	-	-	-
Charlson index	1.18	(0.99, 1.41)	0.05	1.15	(0.97, 1.39)	0.11
Diabetes mellitus	1.09	(0.38, 3.16)	0.87	-	-	-
Chronic renal failure	2.21	(0.64, 7.69)	0.21	-	-	-
Late vs. early CIED-IE	1.93	(0.52, 7.12)	0.32	-	-	-
PPM vs ICD+CRT	1.82	(0.39, 8.49)	0.45	-	-	-
Transferred from another hospital	0.72	(0.24, 2.18)	0.56	-	-	-
> 2 leads vs <= 2 leads	0.57	(0.07, 4.66)	0.60	-	-	-
Concomitant pocket infection	0.55	(0.17, 1.81)	0.33	-	-	-
Concomitant tricuspid vegetation	0.19	(0.02, 1.52)	0.12	0.23	(0.03, 2.03)	0.20
CoNS CIED-IE	0.34	(0.11, 1.12)	0.08	0.60	(0.11, 3.15)	0.54
S. aureus CIED-IE	3.32	(1.17, 9.39)	0.02	4.35	(1.93, 20.37)	<0.01

* Abbreviations: PPM pacemaker, ICD implantable cardioverter-defibrillator, CRT cardiac resynchronization therapy. CoNs*: Coagulase-negative Staphylococci.*

4. Discussion

This is the largest cohort study of CIED-IE patients followed over forty years, focused on the prevalence and risk factors of no device removal, and the efficacy and safety of CAS. Although it is widely accepted that removal is mandatory to cure CIED-IE, limited information prevails regarding the clinical profile of patients or the management strategies when removal cannot be performed [5, 6]. Due to epidemiological changes in CIED-IE, with elderly and comorbid patients requiring high-risk removal procedures, the proportion of cases without device removal is expected to increase [1,5]. In our cohort, the overall prevalence of no removal in patients with CIED-IE was 12%, and higher in the latter 20 years of the study period (4% vs. 14%, p=0.17). Patients without device removal showed different clinical and microbiological profiles with more age, comorbidities, less tricuspid involvement, more *S. aureus* infections and higher one-year mortality rates (58.5% vs. 12.2%, p<0.01).

Only one previous study analyzed the reasons for no removal in CIED infections. *Peacok et al*. describe a CIED infection cohort with a 52.2% prevalence of CIED-IE. They reported Staphylococcal infections and high-risk procedures due to excessive medical comorbidities as the main reasons for incomplete removal. However, they did not analyze predictors of non-removal [7]. We analyzed host and device-dependent factors and identified increasing age and *S. aureus* etiology as risk factors independently associated with incomplete removal. Due to all patients with CIED-IE had many comorbidities, we hypothesized that CCI would not be an independent predictor for no removal. In our cohort, *Staphylococcus aureus* infections indicated more complicated CIED-IE with more frequent transfers from other centers, chronic renal failure, hemodialysis, and septic emboli (data not shown).

CAS therapy is the only strategy available if complete removal is not performed or leads are abandoned in place to prevent relapses. Only two studies reported their results on CAS in patients with incomplete removal in CIED infections. *Peacok et al*. recounted a 29% prevalence of CAS in their cohort, with 22% relapses and 30% in-hospital mortality [7]. *Tan et al*., with 660 CIED infections (88% systemic), described a 7% prevalence under CAS. They observed 18% relapses, and 25% in-hospital and 44% one-year mortality [8]. In our experience, CAS was effective in 85% of cases at one-year. Only two patients (15%) changed the CAS due to toxicity. [18F] FDG-PET/CT has shown its applicability in CIED-IE diagnosis [11], but in our cohort it is proposed also in the follow-up.

Among its strengths, our analysis is the first CIED-IE cohort in the literature to study risk factors for no removal and to characterize clinical, microbiological and outcome profiles comparing complete and no complete device removal. We also describe temporal trends of no removal during a 40-year period of CIED-IE episodes and results for CAS efficacy and safety. Finally, we propose strategies for follow-up, including the potential utility of [18F] FDG-PET/CT in guiding stopping CAS in selected cases whose PET/CT turn negative. On the other hand, our study has some limitations, particularly its retrospective design over a very long period when new technical surgeries, microbiological and imaging diagnosis improvements emerged. However, the homogenous diagnostic and therapeutic management of the IE team has allowed us to mitigate this. Second, since no device removal accounted for a small proportion of patients, some variables could not be identified as independent risk factors. Third, the CAS therapy cohort only included 13 patients, with [18] FDG-PET/CT follow-up data in just five.

In conclusion, the prevalence of no removal in CIED-IE patients was 12%, and more frequently observed in the latter 20 years. Patients without device removal have distinctive clinical and microbiological features and outcomes. Old age and *S. aureus* etiology were associated with no device removal. CAS proved effective in 85% of cases,

with only two patients (15%) requiring CAS modifications due to toxicity. Further studies are needed with larger patient numbers to better evaluate the growing population of CIED-IE patients without complete device removal.

Supplementary Materials: Supplementary files are referred among the manuscript.

Author Contributions: All the authors contributed to the conception and design, acquisition of data, drafting of the article, critical revision, and final approval of the manuscript. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: Suggested Data Availability Statements are available in section "MDPI Research Data Policies" at https://www.mdpi.com/ethics.

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Ethical considerations and Patient Consent Statement: The Institutional Review Board (IRB) 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.

Appendix A

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Table S1. Clinical characteristics, outcomes, and follow-up of 13 patients without device removal on chronic oral suppression.

Case	Sex/ Age	Clinical presentation and presenting symptoms	TEE	Microorganisms	Incomplete removal or no device removal	Time since implant/number of leads	Reason for no removal	CAS: Schema	CAS Duration (months)	CAS Toxicity	Baseline [18F] FDG-PET/CT	Follow-up [18F] FDG-PET/CT	Relapses	Outcome/follow-up
1	M/71	Late ICD-IE	Lead vegetation	MSSA. Positive blood cultures.	No removal	9 years/3 leads	Comorbidities	Levofloxacin plus rifampicin	Two weeks	No	Negative	Not performed	No	One-year mortality. Unrelated death
2	M/81	Late ICD-IE and pocket infection.	Lead vegetation	E. coli. Positive blood cultures. Pocket and lead positive cultures.	Pocket and right auricle lead extraction, right ventricle lead retained.	12 years/2 leads	Comorbidities	Ciprofloxacin	18 months	Clostridium difficile infection.	Not performed.	Not performed.	No	Alive. 18 months of follow-up
3	M/82	Late PVE-IE and PCM-IE	Lead and aortic valve vegetations	MSSA. Positive blood cultures	No removal	3 years/2 leads	Comorbidities and patient fragility. High risk procedure	Levofloxacin plus rifampicin	16 months	No	Positive endovascular and valve	Not performed	No	Alive. 16 months of follow-up
4	M/75	Late PCM-IE and pocket infection.	Lead vegetation	MSSA. Positive blood and pocket cultures.	Pocket extraction and retained leads.	2 years/2 leads	Comorbidities Patient refusal.	Cotrimoxazole	37 months	No	Not performed.	Not performed.	No	Unrelated death during follow-up. 37 months follow-up
5*	M/65*	Early PCM-IE	Lead and tricuspid vegetation	MSSA. Positive blood cultures.	No removal	15 days/1 lead	Comorbidities	Levofloxacin plus rifampicin	Unknown	No	Not performed.	Not performed.	Yes	One-year mortality. Related death
6	M/69	Late PCM-IE	Lead vegetation	MSSE Positive blood cultures.	No removal	2 years/2 leads	Hemorrhagic stroke	Rifampicin	One month	Rash	Not performed.	Not performed.	Yes	One-year mortality. Related death.
7	M/74	Early Mitral native valve IE and PCM-IE	Lead and mitral valve vegetations	MRSE. Positive blood cultures.	No removal	2 months/2 leads	Comorbidities and fragility. Futility	Cotrimoxazole	Two months	No	Not performed.	Not performed.	Yes	In hospital mortality. Related death
8	M/79	Late PCM-IE	Lead vegetation	MRSA. Positive blood cultures.	No removal	2 years/1 lead	Comorbidities and fragility. Futility	Cotrimoxazole	108 months	No	Not performed.	Not performed.	No	Unrelated death during the follow-up. 108 months follow-up
9	M/78	Late PCM-IE and pocket infection	Lead vegetation.	MSSA. Positive blood cultures.	No removal	6 years/2 leads	Comorbidities	Levofloxacin. Toxicity. Changed to Cefuroxime	41 months	No	Not performed.	Not performed.	No	Alive. 41 months follow-up
10	M/93	Late PCM-IE and pocket infection	Lead vegetation	MSSA. Positive blood culture and pocket swab.	Pocket extraction and retained leads.	9 years/1 lead	Comorbidities and fragility. Futility	Levofloxacin plus cotrimoxazole	4 months	No	Positive pocket and lead CIED-IE	Negative: after 4 months CAS	No	Alive. 17 months follow-up
11	F/79	Late PCM-IE and pocket infection	Lead vegetation	Propionibacterium acnes. Pocket and lead positive culture.	Pocket and right auricle lead extraction, right ventricle lead retained.	4 years/1 lead	Comorbidities and fragility.	Amoxicillin	12 months	No	Positive EV lead	Negative: after 12 months CAS	No	Alive. 26 months follow-up
12	F/86	Late PCM-IE	Lead vegetation	MSSE. Positive blood cultures.	No removal	13 years/2 leads	Comorbidities and fragility. Futility	Cotrimoxazole	4 months	No	Not performed.	Not performed.	No	One-year mortality. Unrelated death
13	M/75	Early Native aortic valve IE and PCM-IE	Aortic and lead vegetation	E. faecalis. Positive blood cultures.	No removal	six months/2 leads	Active acute leukemia.	Amoxicillin	44 months	No	Positive aortic valve and EV lead.	Not performed.	No	Unrelated death during follow-up. 44 months follow-up

* This patient voluntarily stopped treatment and systematically refused medical attention. He was admitted two months after the first admission with a relapse of PCM-IE, and finally, died due to staphylococcal sepsis and complications related to advanced alcoholic cirrhosis.

Study 5

4.5 Effectiveness of Daptomycin plus Ceftaroline in the treatment of methicillin-resistant and vancomycin resistant *Staphylococcus epidermidis* Experimental Endocarditis

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Manuscript in preparation.

Title: Effectiveness of daptomycin plus ceftaroline in the treatment of methicillin-resistant and vancomycin resistant *Staphylococcus epidermidis* Experimental Endocarditis.

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Short running title: Daptomycin plus ceftaroline in the treatment of MRSE/VRSE experimental endocarditis

2. Material and methods

2.1 *Bacterial isolates*

For *in vitro* studies, five MRSE (MRSE-125, MRSE-158, MRSE-317, MRSE-337, MRSE-375) and one VRSE strain (NRS-6) isolates were selected. Except for the NRS-6 collection strain, the rest of them had been isolated from blood cultures of patients diagnosed with IE at our institution. The NRS-6 has been acquired from the NRSA collection. MRSE-375 and NRS-6 were selected for the *in vivo* studies. The isolates were stored at -80º C in skim milk.

2.2 *Antimicrobial agents*

For *in vitro* studies daptomycin and ceftaroline powder were purchased from Sigma (St Louis, MO). Drugs were prepared according to the manufacturers' recommendations. For the *in vivo* studies pharmaceutical forms of daptomycin and ceftaroline were provided by our local Pharmacy department.

2.3 *Susceptibility Testing*

MICs and MBCs were determined using the broth microdilution method according to standard recommendations [27]. For daptomycin, broth was supplemented with Ca2+ to 50 mg/L according to the manufacturer's recommendations. All the assays were performed in duplicated.

2.4 *Synergy studies*

Time-kill methodology was used to test the activity of combined antibiotics according to previously described criteria [28]. Two different initial inoculums were tested: a standard inoculum (SI) of 10^5colony forming units (CFU)/mL, and a higher inoculum (HI) equal to 10^8CFU/mL, that mimics the density of CFU in mature infected vegetation. For synergy testing, concentration equal to 1x MIC was chosen for CTL and DAP. *Synergy activity* between the two antibiotic was defined as a 2-$\log_{10}$ decrease in the number of cfu/ml between the test tube with the combination and the test tube with the most active agent alone after 24 hours: the number of surviving organisms in the presence of the combination had to be 2-$\log_{10}$ cfu/ml below the starting inoculum. *Bactericidal activity* was defined as at least a 3-$\log_{10}$ reduction in cfu/ml at 24h in comparison with the initial inoculum. All experiments were performed in duplicate.

2.5 *Study animals*

In accordance with articles 34 and 38 of Royal Decree 53/2013, of 1 February and the EU Directive 2010/63/EU, which establishes the basic rules applicable to the protection of animals used in experimentation and other scientific purposes, including teaching, the Animal Experimentation Ethics Committee of the University of Barcelona approved all animal experimentation in this study (CEEA register number 182/21).

New Zealand white rabbits (body weight, 2.5 kg) provided by San Bernardo farm (Pamplona, Spain) were used. Half of the animals were females and half were males. The animals were randomly assigned into the different treatment groups in such a way that the ratio of males to females was maintained in all groups of the study. In any case, no sex differences have been reported in the treatment process of infective endocarditis.

Housing took place in the animal facilities of the University of Barcelona, School of Medicine, which is equipped with high-efficiency particulate air filter in an automatic air exchange system, as well as circadian light cycle. They were nourished ad libitum.

2.5.1 *Human pharmacokinetics (PK) simulation studies*

The *in vivo* experimental pharmacokinetics of daptomycin and ceftaroline has already been described [29,30]. Antibiotics were administered using a computer-controlled infusion pump system designed to reproduce human serum pharmacokinetics in rabbits after an intravenous infusion. Animal infusion rates were chosen to simulate the human pharmacokinetic profile. Ceftaroline (600g/8h iv) and daptomycin (6 mg/kg iv once daily) regimens were administered, following the recommendations of the AHA and ESC guidelines [12,13].

2.5.2. *Endocarditis model*

The experimental aortic valve IE model was induced according to the method described by Garrison and Freedman [31]. Briefly, after the animals were placed under anaesthesia for surgery a catheter was inserted through the right carotid artery into the left ventricle. The catheter used for antibiotic administration was placed into the inferior vena cava through the jugular vein. The infusion pump delivered 2 ml/h of 0.9% saline solution until the beginning of antimicrobial administration. Forty-eight hours later, each animal was inoculated via the marginal ear vein with either the MRSE-375 or NRS6 strain (1 mL of 1 x 10^9 CFU/ cfu/ml). Treatment was initiated

forty-eight hours after microorganism inoculation, before initiation of the antimicrobial therapy, one milliliter of blood was obtained to confirm bacteremia. Antibiotic treatments were started, and animals were treated for two days using a computer-controlled pump. After completion of the treatment, six additional half-lives of the antibiotics were left to elapse, allowing the elimination of residual antibiotic concentrations within the cardiac vegetations. After this, the animals were euthanized using an intravenous bolus of pentobarbital. Aortic valve vegetations, portions of the spleen and left kidney were aseptically obtained, weighed and homogenized in 2 ml of saline. Quantitative and qualitative cultures were then performed.

2.5.2.1.*Treatment group*

The infected rabbits were randomly assigned into the different treatment arms simulating human pharmacokinetics. They were treated with CTL (600 mg/8h iv) or DAP (6 mg/kg/d). Each group included 10 animals.

2.5.2.2. *Analysis of endocardial vegetations, spleen and left kidney*

The cfu counts recovered from tissues were expressed as the number of $\log_{10}$ cfu per gram of tissue ($\log_{10}$ cfu/g tissue). The result was assigned a value of zero and the vegetation, spleen or left kidney were considered sterile if there was no growth from the initial quantitative and qualitative cultures and from the homogenates cultured for a week. The result was assigned a value of 2 $\log_{10}$ cfu/g tissue if there was no growth on the quantitative plates and growth in the qualitative culture and from the homogenates cultured for a week. All the isolates recovered from the tissues were stored, and tested for daptomycin MIC, to detect the possible emergence of daptomycin-resistant isolates after treatment.

2.6. *Statistical analysis*

The results were expressed as the median and the interquartile range (IQR) of the number of $\log_{10}$ cfu/g tissue. The Mann Whitney non-parametric test was used to compare the $\log_{10}$ CFU-tissue values among the different treatment groups. The Fisher exact test was used to compare the rate of sterilized vegetation and analyze whether there were differences between treatment groups.

3. Results

3.1 Susceptibility testing

The minimum inhibitory concentration (MIC) and the minimum bactericidal concentration (MBC) of cloxacillin, ceftaroline, daptomycin and vancomycin of the six strains used in the *in vitro* studies are summarized in **table 1**. All strains were resistant to cloxacillin, and susceptible to ceftaroline and daptomycin, except NRS-6, which was resistant to vancomycin and daptomycin and susceptible to ceftaroline. All results were expressed according to the Clinical and Laboratory Standards Institute (CLSI standard) and EUCAST standard MIC breakpoints [25].

3.2. *In vitro* time-kill curve *studies*

The results of the time-kill curves synergy studies for ceftaroline plus daptomycin combinations are displayed in **Figure 1**; all individual data are recorded in **Table S1** Two different initial inoculums were tested: a standard inoculum (SI) of 10^5 cfu/ml and a higher inoculum (HI), to mimic the density of cfu in mature infected vegetation, equal to 10^8 cfu/ml.

After 24 hours of incubation, the combination of ceftaroline plus daptomycin (**Figure 1.A** and **Table S1**), at SI showed a synergistic and bactericidal activity that was observed in all MRSE strains. At HI, the combination retains the synergistic activity for four strains, and bactericidal effect was observed in three of them including the VRSE strain (**Figure 1.B** and **Table S1**).

3.3. *Human PK simulation studies*

The mean maximum (C_{max}) ant trough concentrations (C_{min}) achieved were: daptomycin 86/15 mg/l for a single dose of 6 mg/Kg/day The mean maximum (C_{max}) and trough (C_{min}) concentrations achieved were 28 mg/L and 3 mg/L.

3.4. *Treatment of experimental endocarditis*

In vivo studies results to compare the efficacy of drugs in monotherapy or in combination in the experimental model against the two strains studied are shown in **Figure 2 and Tables S2 and S3**. **Table S2 and Table S3** show the results of the treatment of experimental endocarditis (with the

143 median and the interquartile range) caused by MRSE-375 and NRS-6 (VRSE strain) respectively.
144 In both cases, all control (untreated) rabbits had infected aortic valve vegetations, spleen and
145 kidney, with a median bacterial titer of 8 log_{10} cfu/g veg; 2.3 log_{10} cfu/g and 2 log_{10} cfu/g, and 7.6
146 log_{10} cfu/g veg; 2 log_{10} cfu/g and 2 log_{10} cfu/g respectively.
147 Ceftaroline at monotherapy showed similar activity in vegetation and spleen for the two strains
148 (MRSE-375 and NRS-6) with sterile rates of 0/10 (0%) and 1/10 (10%); 0/10 (0%) and 1/10
149 (10%) respectively. Ceftaroline monotherapy showed to be active to sterilize kidney 10/10
150 (100%) in MRSE-375 and to a much lesser extent [4/10 (40%)] in NRS-6 (Figure 2).
151 Regading daptomycin activity in monotherapy, 2/10 (20%) and 0/10 (0%) of the vegetation were
152 sterilized, respectively. Daptomycin monotherapy was partially active in renal involvement
153 MRSE-375 7/10 (70%) and NRS-6 5/10 (50%), but more active in splenic involvement than
154 ceftaroline [MRSE-375 8/10 (80%) and NRS-6 3/10 (30%) $p<0.05$ all comparisons]. Data shown
155 at supplementary tables S2 and S3.
156 Daptomycin monotherapy did not lead to significant regrowth with emergence of resistant
157 derivatives.
158 For the MRSE-375 strain, the combination of daptomycin plus ceftaroline was synergistic and
159 bactericidal, showing significant better activity than monotherapies in reducing bacterial load in
160 the vegetations (p=0.001 in both cases). (the sterilization rate of vegetations, spleen and kidney
161 (p=0.63, p=0.0007 *vs* CTL, and p = 0.09 *vs* DAP respectively). In NRS-6 (VRSE) strain, the
162 combinations of daptomycin plus ceftaroline were synergistic and bactericidal, had a better
163 activity than monotherapies in reducing the bacterial load in the vegetations (p=0.004 and p=0.02
164 respectively) , and in the sterilization rate of kidney (p=0.011 and p=0.032 *vs* CTL and DAP
165 respectively)
166 The development of daptomycin-resistant subpopulations was not observed in any case.

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Figure legends:

Figure 1. Results of the *in vitro* study: time-kill curve for MRSE and VRSE strains. The strains were incubated with ceftaroline (CFT) plus daptomycin (DAP) at concentration of 1 × MIC for all antibiotics. **(A)** Standard inoculum equal to 10^5 CFU/mL **(B)** High inoculum equal to 10^8 CFU/mL. Values are means ± standard deviation from two independent experiments. The dashed line indicates the 3 $\log_{10}$ decreased *vs*. the initial inoculum (bactericidal activity).

Figure 2. **Results of the *in vivo* study: Treatment of experimental endocarditis caused by strains MRSE-375 and VRSE-NRS-6.** Densities of MRSE/VRSE in aortic vegetations, spleen and left-kidney in the IE model due to 10^5-CFU/mL challenges of study strains. The number of rabbits with sterile tissues/total number of rabbits (%) is shown for each treatment group under the abscissae. Each dot represents one animal. Horizontal black bars indicate mean and interquartile MRSE/VRSE densities. CFU: colony forming units.

Table 1. *S. epidermidis* strains tested and corresponding MIC/MBC ratios for vancomycin, cloxacillin, Ceftaroline and daptomycin.

	MIC/MBC (mg/L)			
Strains	**Vancomycin**	**Cloxacillin**	**Daptomycin**	**Ceftaroline**
MRSE-125	1/2	256/512	0.5/1	0.5/2
MRSE-158	2/2	64/256	0.5/1	0.5/0.5
MRSE-317	1/2	256/>512	0.5/2	1/1
MRSE-337	1/1	32/128	0.25/0.5	0.5/2
MRSE-375*	2/4	256/512	1/1	0.5/0.5
NRS-6*	8/16	8/32	2/2	0.5/0.5

* *In vivo* study strains.

Figure 1A

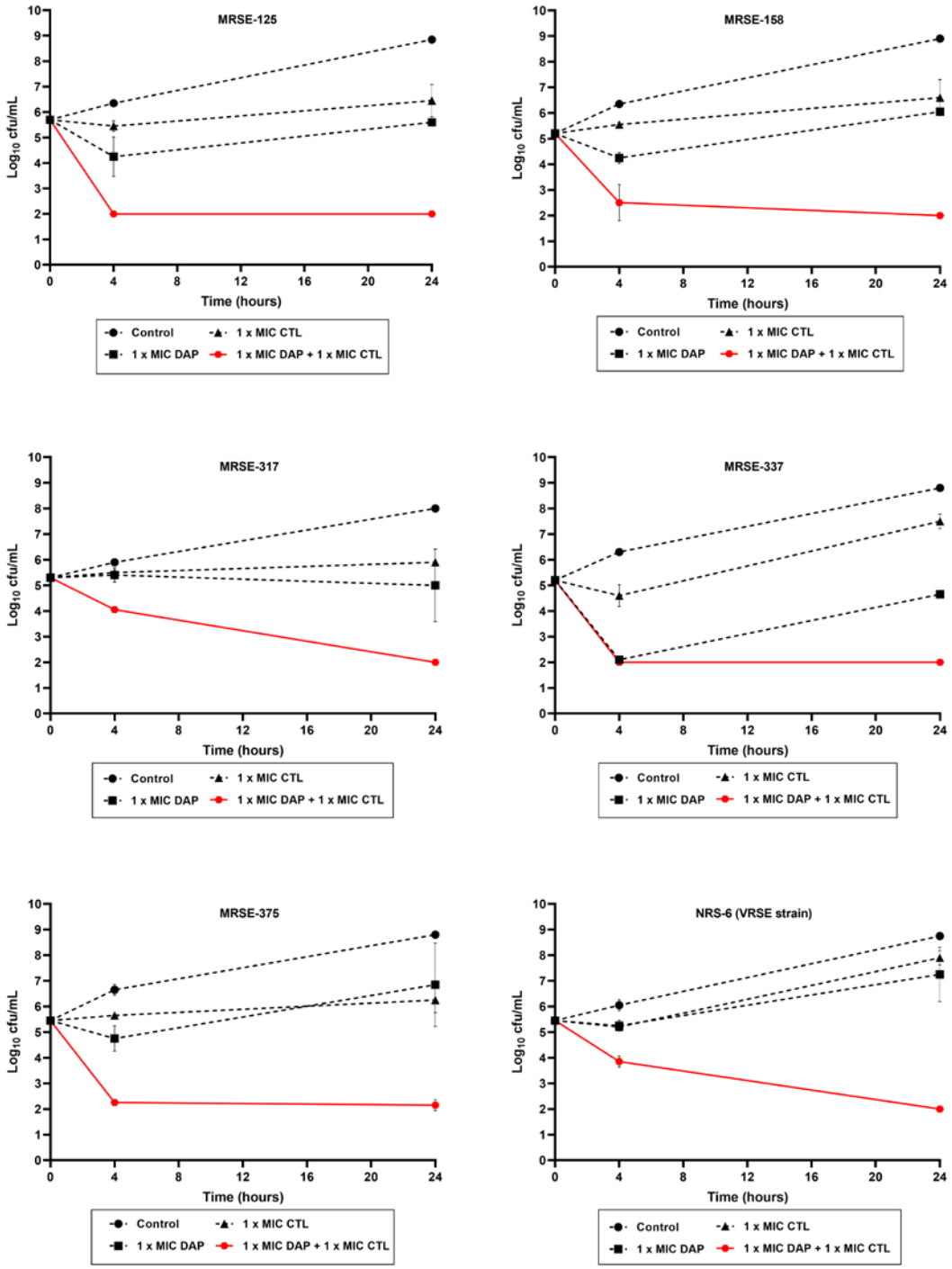

MRSE-125
MRSE-158
MRSE-317
MRSE-337
MRSE-375
NRS-6 (VRSE strain)
Log10 cfu/mL
Time (hours)
Control
1 x MIC CTL
1 x MIC DAP
1 x MIC DAP + 1 x MIC CTL

Figure 1B

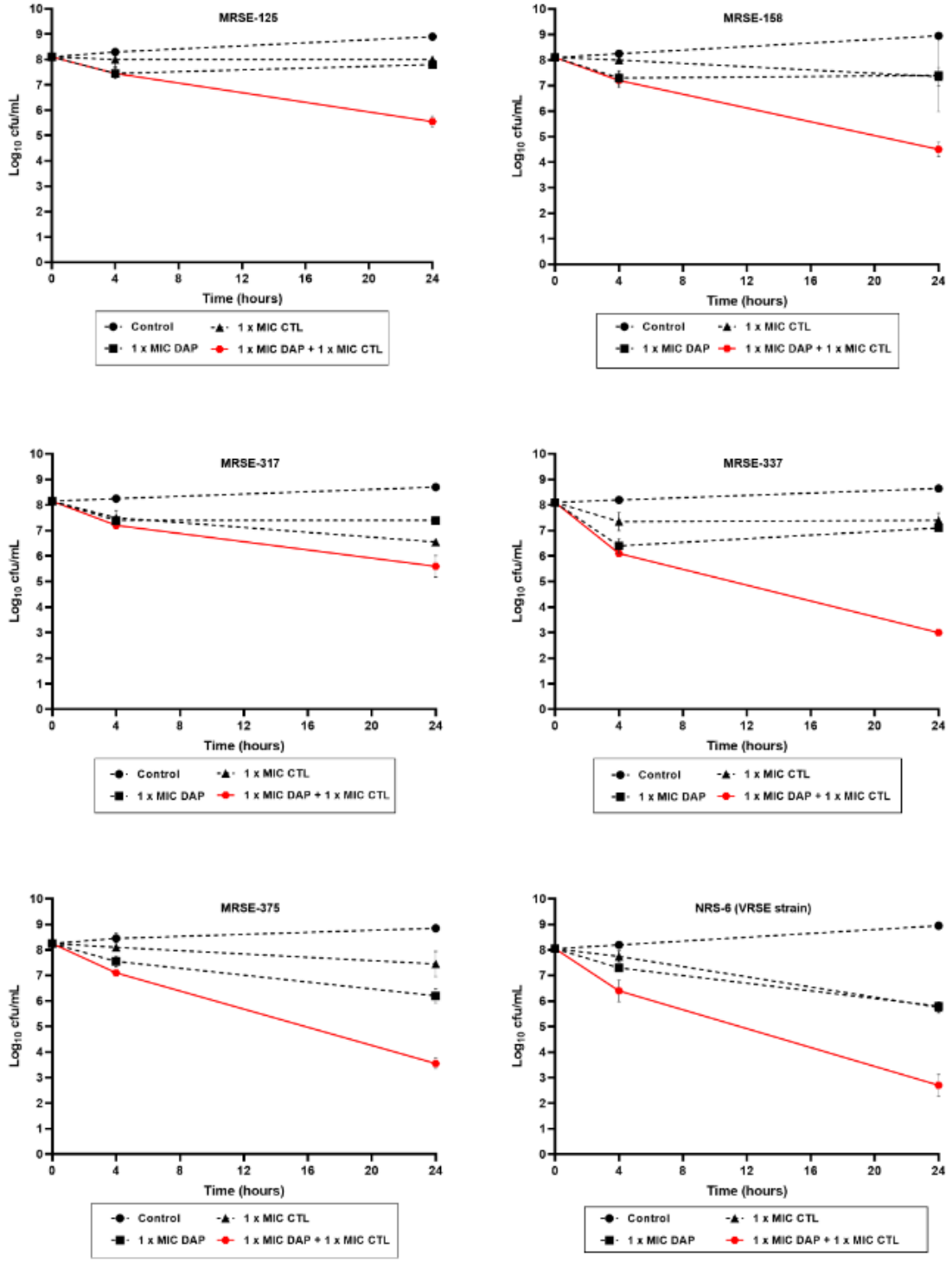
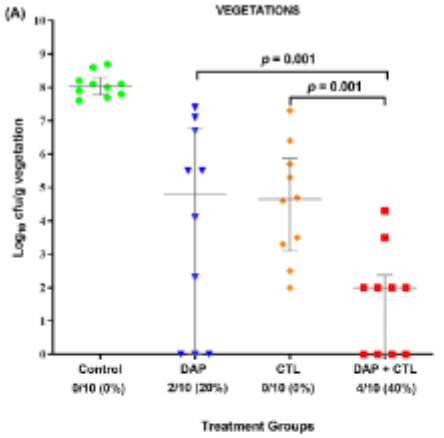
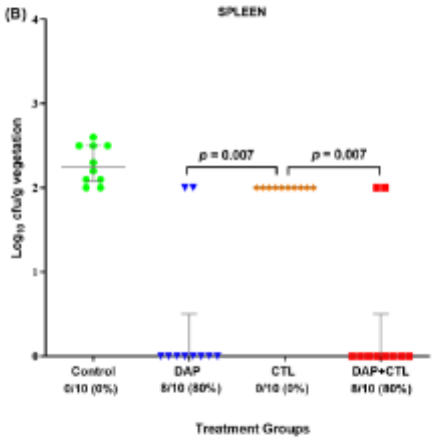

MRSE-125
MRSE-158
MRSE-317
MRSE-337
MRSE-375
NRS-6 (VRSE strain)
Log10 cfu/mL
Time (hours)
Control
1 x MIC CTL
1 x MIC DAP
1 x MIC DAP + 1 x MIC CTL

Figure 2A


(A)
VEGETATIONS
p = 0.001
p = 0.001
Log10 cfu/g vegetation
Control
0/10 (0%)
DAP
2/10 (20%)
CTL
0/10 (0%)
DAP + CTL
4/10 (40%)
Treatment Groups


(B)
SPLEEN
p = 0.007
p = 0.007
Log10 cfu/g vegetation
Control
0/10 (0%)
DAP
8/10 (80%)
CTL
0/10 (0%)
DAP+CTL
8/10 (80%)
Treatment Groups

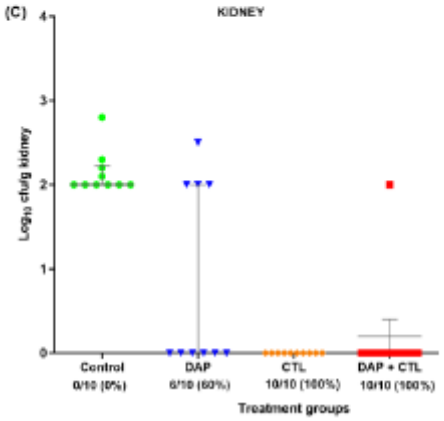
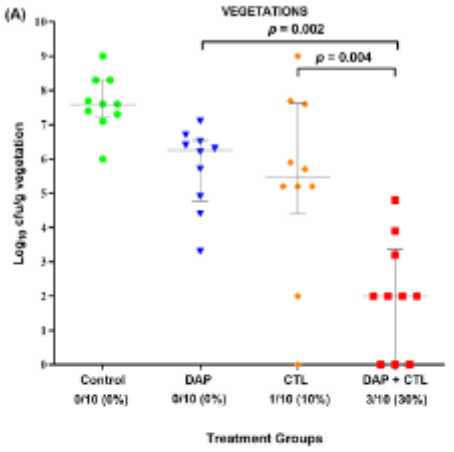
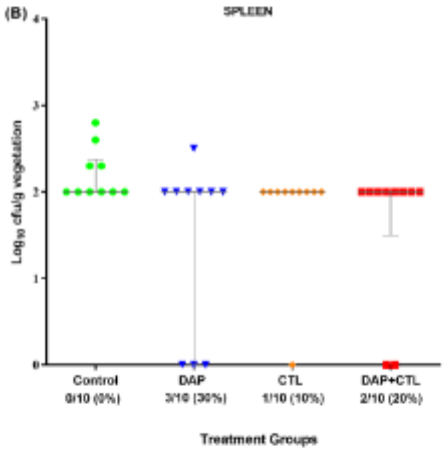
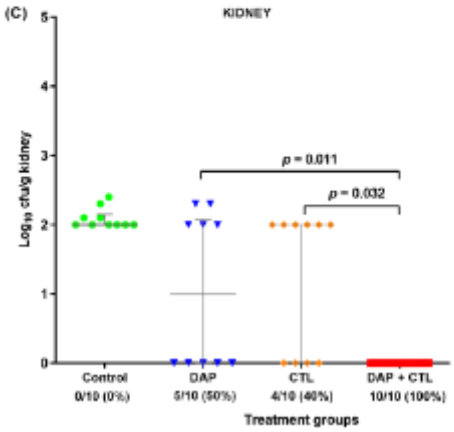

(C)
KIDNEY
Log10 cfu/g kidney
Control
0/10 (0%)
DAP
6/10 (60%)
CTL
10/10 (100%)
DAP + CTL
10/10 (100%)
Treatment groups

Figure 2B


(A)
VEGETATIONS
p = 0.002
p = 0.004
Log10 cfu/g vegetation
Control
0/10 (0%)
DAP
0/10 (0%)
CTL
1/10 (10%)
DAP + CTL
3/10 (30%)
Treatment Groups


(B)
SPLEEN
Log10 cfu/g vegetation
Control
0/10 (0%)
DAP
3/10 (30%)
CTL
1/10 (10%)
DAP+CTL
2/10 (20%)
Treatment Groups


(C)
KIDNEY
p = 0.011
p = 0.032
Log10 cfu/g kidney
Control
0/10 (0%)
DAP
5/10 (50%)
CTL
4/10 (40%)
DAP + CTL
10/10 (100%)
Treatment groups

Supplementary material

Table S1. *In vitro* time-kill synergy studies. MRSE Daptomycin and Ceftaroline single and combined time-kill curves.

Strains tested		CONTROL Δ Change (x hours) in log_{10}cfu/ml		DAP Δ Change (x hours) in log_{10}cfu/ml		CFT Δ Change (x hours) in log_{10} cfu/ml		DAP+CFT Δ Change (x hours) in log_{10} cfu/ml	
Baseline (0 hours) Log_{10} CFU/mL		4h	24h	4h	24h	4h	24h	4h	24h
Standard inoculum (10^5cfu/ml)									
MRSE-125	5.7	+0.6	+ 3.2	- 0.9	-0.2	- 0.1	+1.2	-3.7	-3.7
MRSE-158	5.1	+1.2	+3.8	- 1	+0.9	+0.5	+1	-2.1	-3.1
MRSE-317	5.2	+0.6	+2.7	+0	-1.2	+0.3	+0.6	-0.5	-3.2
MRSE-337	5.2	+1.1	+3.5	-3.2	-0.6	-0.9	+2.1	-3.2	-3.2
MRSE-375*	5.5	+1.3	+3.2	-0.4	+2.5	+0.2	+0.4	-3.2	-3.2
NRS-6*	5.4	+0.8	+3.3	-0.3	+2.6	-0.3	+2.6	-1.4	-3.4
High inoculum (10^8cfu/ml)									
MRSE-125	8.1	+0.1	+0.9	-0.8	-0.2	+0.1	+0	-0.6	- 2.4
MRSE-158	8.1	+0.2	+0.7	-0.3	-1	-0.2	-1.8	-0.5	-2.4
MRSE-317	8.2	+0.1	+0.6	-0.6	-0.6	-0.4	-1.6	-0.9	-2.8
MRSE-337	8.1	+0.1	+0.6	-1.5	-1	-0.5	-0.9	-2	-5
MRSE-375*	8.3	+0.3	+0.5	-0.9	-1.9	-0.3	-1.2	-1.1	-4.6
NRS-6*	8.1	-2	+1	-0.6	-2.2	-0.4	-2.4	-1.3	-5

* *In vivo* study strains

Table S2. Treatment of experimental endocarditis caused by MRSE-375 strains.

3A) Vegetations

Treatment group	Rabbits with sterile veg. /total rabbits (%)	Log_{10}cfu/g vegetation [median (IQR)]
Control (non-treated) *	0/10 (0%)	8 (7.8 – 8.3)
Ceftaroline (Simulating 600mg/8h)	0/10 (0%) [a]	4.7 (3.5 – 5.7) [c]
Daptomycin (Simulating 6 mg/kg/once daily)	2/10 (20%) [b]	5.3 (2.8 – 6.5) [d]
Daptomycin + Ceftaroline (Simulating 6 mg/kg/once + 600 mg/8h)	4/10 (40%) [a,b]	2 (0 – 2) [c,d]

[a]P=0.628, [b]P=0.087; [c]P=0.001; [d]P=0.00; cfu: colony-forming unit; IQR, interquartile range. *The control animals were sacrificed 24h after the infection was started.

3B) Spleen

Treatment group	Rabbits with sterile spleen/ # total rabbits (%)	Log_{10}cfu/g spleen [median (IQR)]
Control (non-treated) *	0/10 (0%)	2.3 (2 - 3)
Ceftaroline (simulating 600 mg/8h)	0/10 (0%) [a,b]	2 (2 - 2) [c,d]
Daptomycin (simulating 6 mg/kg/once daily)	8/10 (80%) [a]	0 (0 – 0) [c]
Daptomycin + Ceftaroline (Simulating 6 mg/kg/once + 600 mg/8h)	8/10 (80%) [b]	0 (0 – 0) [d]

[a,b]P = 0.0007; [c,d]P = 0.003, cfu: colony-forming unit; IQR, interquartile range. *The control animals were sacrificed 24h after the infection was started.

3C) Kidney

Treatment group	Rabbits with sterile kidney/ total rabbits (%)	Log_{10}cfu/g kidney [median (IQR)]
Control (non-treated) *	0/10 (0%)	2 (2 – 2)
Ceftaroline (simulating 600 mg/8h)	10/10 (100%) [a]	0 (0 – 0) [c]
Daptomycin (simulating 6 mg/kg/once daily)	6/10 (60%) [a,b]	0 (0 – 2) [c,d]
Daptomycin + Ceftaroline (Simulating 6 mg/kg/once + 600 mg/8h)	10/10 (100%) [b]	0 (0 – 0) [d]

[a,b]P = 0.09; [c,d]P = 0.14; cfu: colony-forming unit; IQR, interquartile range. *The control animals were sacrificed 24h after the infection was started.

Table S3. Treatment of experimental endocarditis caused by VRSE (NRS-6) strains.

3A) Vegetations

Treatment group	**Rabbits with sterile veg. /total rabbits (%)**	**Log_{10}cfu/g vegetation [median (IQR)]**
Control (non-treated) *	0/10 (0%)	7.6 (7.2 – 8.3)
Ceftaroline (simulating 600mg/8h)	1/10 (10%)	5.5 (5.2 – 7.6) [b]
Daptomycin (simulating 6 mg/kg/once daily)	0/10 (0%) [a]	6.3 (5.2 – 6.6) [c]
Daptomycin + Ceftaroline (simulating 6 mg/kg/once + 600 mg/8h)	3/10 (30%) [a]	2 (1 – 3.5) [b,c]

[a]*P* = 0.21; [b]*P* =0.002 [c]*P* =0.004; cfu: colony-forming unit; IQR, interquartile range. *The control animals were sacrificed 24h after the infection was started.

3B) Spleen

Treatment group	**Rabbits with sterile spleen/ total rabbits (%)**	**Log_{10}cfu/g spleen [median (IQR)]**
Control (non-treated) *	0/10 (0%)	2 (2 – 2.3)
Ceftaroline (simulating 600 mg/8h)	1/10 (10%)	2 (2 – 2)
Daptomycin (Simulating 6 mg/kg/once daily)	3/10 (30%)	2 (1 – 2)
Daptomycin + Ceftaroline (simulating 6 mg/kg/once + 600 mg/8h)	2/10 (20%)	2 (2 – 2)

cfu: colony-forming unit; IQR, interquartile range. *The control animals were sacrificed 24h after the infection was started.

3C) Kidney

Treatment group	**# Rabbits with sterile kidney/ # total rabbits (%)**	**Log_{10}cfu/g kidney [median (IQR)]**
Control (non-treated) *	0/10 (0%)	2 (2 – 2.1)
Ceftaroline (simulating 600 mg/8h)	4/10 (40%) [a]	2 (0 – 2) [c]
Daptomycin (simulating 6 mg/kg/once daily)	5/10 (50%) [b]	1 (0 – 2) [d]
Daptomycin + Ceftaroline (Simulating 6 mg/kg/once + 600 mg/8h)	10/10 (100%) [a,b]	0 (0 – 0) [c,d]

[a,] *p*=0.011, [b] *p*=0.032, [c,] *p*=0.025, [d,] *p*=0.06 ; cfu: colony-forming unit; IQR, interquartile range. *The control animals were sacrificed 24h after the infection was started.

5. Discussion

The investigation presented in this thesis is focused on some of the current challenges and last epidemiological variations facing the management of CIED infections, with a particular interest in CIED-IE due to its greater risk, complex diagnosis and treatment, and higher mortality rate.

As presented throughout this work, the epidemiology of IE has shown a trend towards an older population with a higher comorbidity index, an increased complexity of cases, and, therefore, a shift in the microbiological causes, favoring staphylococcal etiology [11]. One of the objectives of this thesis was to underline the overall improvement in outcomes in Europe over time, despite this increased complexity of cases (i.e., higher rates of comorbidities e.g., hemodialysis or diabetes mellitus). When comparing the European regions over the two periods (2000-2006 vs. 2008-2012), we found that mortality was consistently lower for a given Charlson score in the second period. The reasons for this late overall better prognosis are not entirely understood, although it may reflect several factors: more early surgery, better management of IE complications (e.g., heart failure and central nervous system emboli), the utilization of more effective, better tolerated, and active antimicrobial agents, and the multidisciplinary approach of IE-teams. In fact, although recommended treatment regimens have remained almost unchanged for the past decades [48], antimicrobial management of IE in referral centers frequently differ from the recommendations [132].

Regarding geographical trends among regions, during the early period (2000-2006), prognosis was slightly better in NCE countries, and was associated with higher rates of cardiac surgery. We did not identify any relevant major microbiological differences between regions or periods, apart from a significant increase in the proportion of enterococcal IE. This may be related to the progressive aging of patients with IE [133] and the increasing prevalence of colorectal pathology in the general population [134,135]. *S aureus* and CoNS IE, on the rise during in recent decades, have remained stable during the two periods of our study.

Moreover, we have demonstrated a reduction in mortality rates, translating into a modest but positive trend in the field of IE. Setting our data in the context of present-day Europe (Euro-Endo registry, 2016-2018), in hospital-mortality in our study was 20.1% for the first period and 17.8% for the second, compared to 17% in the Euro-Endo registry [14]. Finally, we showed a significantly higher prevalence in SE compared with NCE countries (9.9% vs. 5.5%) in the proportion of CIED IE, and a significantly more CIED-IE episodes in the latter period (8.9% vs. 7.3%).

Gathering all the previous information into its broader context, we focused our second study in the epidemiological, clinical and outcome evolution of CIED infective endocarditis over a 40-year period. We reported the largest CIED-IE historical cohort of patients managed by the same IE team in a referral center. In this aforementioned study, we described the fundamental changes in the epidemiology for IE: an increase in median age of patients, more comorbidities, and new types of CIED. We also reported new diagnostic techniques and greater antimicrobial resistance in isolated pathogens. Despite all 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), nor did one-year mortality (24% during 1981–2000 vs 15% during 2001–2020; and 12.5% during 2001–2010 vs 17.4% during 2011–2020). However, the proportion of patients with unremovable CIED-IE has notably augmented over time (4% vs 12.4%) in the context of the increase of comorbid conditions, age, and devices complexity. The cause of the higher number of infections, despite a decrease in overall device-related complications, is not clear [115,137]. One possibility might be the accumulative numbers of ICDs and CRTs, whose longevity is lower than PPMs, requiring more complex procedures and battery exchanges, which are strongly associated with risk of infection [50]. Essentially, our analysis revealed a 4.5-fold increase in ICD/CRT-IE compared with PPM-IE when analyzed the cases from the two different periods. In the second period, the demographic and clinical characteristics of PPM-IE compared to those of ICD/CRT-IE were entirely different. Patients who received ICD/CRT were significantly younger, predominantly male, and had higher rates of ischemic cardiomyopathy,

diabetes, and HF. Greenspon et al. showed the nonvariation of the four significant comorbidities (i.e., renal failure, respiratory failure, HF, and diabetes) over almost the two last decades. Nevertheless, there was a substantial increase in infection rate, mostly in ICDs (i.e., ICDs represented 35% of all devices) [50].

In addition, the incorporation of [18F] FDG-PET/CT and molecular biology in our cohort had a significant impact in the second period, with an overall sensitivity and specificity of 82.8% and 52.7%, respectively; and the [18F] FDG-PET/CT diagnostic yield has been thoroughly assessed in the third study of this thesis. Regarding etiology, we showed a predominance of staphylococcal infections as the main cause of CIED-IE, as previously has been reported in literature [115,137–140]. Interestingly, we identified an increase of E*nterococcus spp.* infections in the second period, probably due to the aging of the population and the growth in comorbidities. In the MEDIC Study, Oh et al. [28] conducted a descriptive analysis of 433 CIED infections and reported 4.8% of enterococcal infections. Whereas they showed no significant increase in enterococcal CIED infections over time, we did find a significant increase to 5.3% in the second period of our study. Additionally, both studies consistently reported the profile of an emerging old population (median age, 70 years) with multiple underlying comorbidities (median CCI score, 6) and late onset infections. Finally, in our cohort, CoNS were the primary cause of CIED-IE, and the methicillin resistance was expanding.

The medical and surgical approach did not change between the two periods, thus removing the entire device is mandatory [141-143]. In the second period, the population was older and presented more frequent comorbidities, the proportion of non-removed 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 chronic oral antibiotic suppression therapy to manage CIED-IE when device removal is not feasible [80, 119].

Since CIED-IE has low in-hospital mortality rates when compared to left-sided IE, we have calculated variables associated with one-year survival. In this analysis, the CCI and septic shock has been shown as independent prognostic factors for one-year mortality, whereas transfer from community centers was protective and more frequent in the second period. This finding may be explained by the tendency to transfer patients with better prognoses and fewer comorbidities for device removal [12,13]. Complete device removal is the most important protective factor. Despite aging and greater case complexity, survival rates have unchanged over the years. This may be explained by improvements in diagnosis and medical and surgical management. Indeed, higher accuracy in diagnosis has been observed since the implementation of molecular techniques (e.g., 16S rRNA PCR), and imaging diagnosis test ([18F] FDG-PET/CT) [12, 144-145].

As mentioned above, introducing [18F] FDG-PET/CT has improved the diagnosis of CIED infections and infective endocarditis. We performed a four-CIED topographical [18F] FDG-PET/CT accuracy evaluation and analyzed both its capacity to differentiate local and systemic CIED infections, and its potential utility during follow-up when complete device removal has not been achieved. For this study, we included our overall CIED infection cohort from 2014 to 2021, aiming to better characterize this clinical entity.

Our analysis revealed an overall sensitivity [18F] FDG-PET/CT for CIED infections of 85%: 79% for pocket infections and 57% for subcutaneous lead infections. On the contrary, as has been reported in previous studies [71,72], our results show low sensitivity on endovascular (22%) and intracardiac leads (10%). [18F] FDG-PET/CT specificity was 100% for all segments except intracardiac lead. Moreover, the [18F] FDG-PET/CT CIED pocket localization was the most frequent area of positive uptake, followed by the subcutaneous lead, explaining the most frequent pathogen mechanism of CIED infection in our cohort. The seven remaining cases (17%) presenting systemic CIED infection without local infection could be explained by the suggestion of Sohail et al., consisting in that CIED lead infection may originate from a distant source of infection [146].

Regarding the false negative rate, several studies have suggested that antibiotic therapy longer than seven days before [18F] FDG-PET/CT acquisition can reduce its diagnostic performance [72,146,147]. However, no significant differences were found in our cohort regarding the period between antibiotic initiation and [18F] FDG-PET/CT performance. The absence of false positive results in our cohort can be partially explained by the longer period elapsed from device implantation to [18F] FDG-PET/CT acquisition in controls, median time of 6.1 (0.05–24.31) year. In the study of Jerónimo et al., the median time between device implantation and [18F] FDG-PET/CT was 2.3 (0.6–6.4) years [72]. Their study, as well as other published works [68] state that false positive results are caused by post-operative inflammatory activity.

It is commonly accepted that TEE is initially performed on patients with suspected systemic CIED infection, whereas [18] FDG-PET/TC should be the election technique to confirm local infections due to the lower [18F] FDG-PET/CT sensitivity for endovascular and intracardiac lead infections. Accordingly, in our cohort, TEE showed higher accuracy in diagnosing intracardiac lead infections. However, it is worth noticing that [18F] FDG-PET/CT performed better in subcutaneous and endovascular lead infections in systemic CIED infection cases with bacteremia. Negative TEE results do not rule out systemic CIED infections [72] and Pizzi et al. have demonstrated an increased sensitivity of [18F] FDG-PET/CT in combination with TEE [148]. Likewise, our data showed that [18F] FDG-PET/CT used in combination with TEE significantly increased the definite diagnosis rate of infection from 30.4% to 56.1% due to the detection of endovascular lead [18] FDG uptake. Furthermore, [18F] FDG-PET/CT has the additional value of being able to detect septic embolisms [75,150–151] as occurred in two of our systemic CIED infection cases.

On the contrary, our study could not confirm the hypothesis that an increased in the metabolic rate of the spleen and bone marrow could be used as an indirect sign of infection [152], as spleen SUV_{mean} and bone marrow SUV_{mean} were similar in cases and controls and in between local and systemic CIED infections. However, these findings could be hampered by the fact that most

control cases were oncologic patients in which spleen and/or bone marrow uptake could be increased due to a neoplastic pathology, chemotherapy, or other hematological alterations. Nonetheless, we found significant differences in spleen and bone marrow metabolism between patients with systemic CIED infection and confirmed bacteremia compared to those with local CIED infection. These results may be explained by the expected hyper-activation of the phagocytic mononuclear system in cases of bacteremia, which could be helpful in distinguishing bacteremic-lead infections from isolated local infections.

Regarding, the utility of [18F] FDG-PET/CT in follow-up when complete device removal could not be achieved, we studied six cases in which [18F] FDG-PET/CT, in combination with clinical evolution, laboratory, and microbiological findings, usefully guided physicians in discontinuing CAS in the absence of relapse for more than two years of follow-up.

We stated that complete device removal in CIED infections is mandatory to cure infection [10,25,46,115,141]; nonetheless, in recent decades a higher number of patients could not undergo complete CIED removal, even if indicated. This might be explained due to the growth in comorbidities, age, and complexity of infections. Therefore, in order to prevent relapses, CAS has been proposed as the only strategy available when complete removal is not performed or leads are abandoned in place [80]. In our CIED infections cohort, patients with non-complete device removal received undefined CAS, in most cases lifelong, bearing a high burden for patients resulting in side-effects, multidrug-resistant infections, and a high cost for the health system. To date there is no tool to guide clinicians on when to stop CAS. Although the number of cases was limited, the third study in this thesis supported the idea that further prospective research could validate [18F] FDG-PET/CT as a reliable tool for stopping CAS safely during the follow-up in the setting of incomplete device removal.

Later the abovementioned, we thoroughly analyzed the prevalence, clinical characteristics, and risk factors of non-removal CIED-IE patients and the efficacy and safety of CAS. We have

presented the largest cohort study of CIED-IE patients, followed for over forty years. We limited our study to the 40-years-CIED-IE cohort to ensure a long-time perspective and follow-up. In our cohort, the overall prevalence of non-removal in patients with CIED-IE was 12% and seemed to be higher in the latest 20 years of the study period (4% vs. 14%). Patients without device removal showed different clinical and microbiological profiles with significantly older age, number of comorbidities, less tricuspid involvement, higher number of *S. aureus* infections and higher one-year mortality rates. To the best of our knowledge, only one previous study investigated the reasons for non-removal in CIED infections. Peacok et al. described a CIED infection cohort with a 52.2% prevalence of CIED-IE, and staphylococcal infections and high-risk procedures due to excessive medical comorbidities were the main reasons for incomplete removal. Though, they did not analyze predictors for device non-removal [119]. In our analysis, we identified older age and *S. aureus* etiology as risk factors independently associated with incomplete removal. Since most CIED-IE patients presented many comorbidities, we hypothesized that CCI would not be an independent predictor for non-removal. In our cohort, *S. aureus* infections indicated more complicated CIED-IE with increased number in transfers from other centers, chronic renal failure, hemodialysis, and septic emboli.

In our experience, CAS was effective in 85% of cases at one-year. Two patients (15%) changed the CAS due to toxicity. Only two studies reported their results on CAS in patients with incomplete removal in CIED infections. Peacok et al. described a 29% prevalence of CAS in their cohort, with 22% relapses and 30% in-hospital mortality [119]. Furthermore, Tan et al., with 660 CIED infections (88% systemic), described a 7% prevalence under CAS. They observed 18% relapses, and 25% in-hospital and 44% one-year mortality [80].

Finally, antimicrobial treatment of CIED infections is complex and requires a multidisciplinary approach [153]. Despite recent advances in antimicrobial therapy, the clinical practice consensus, and guidelines of antimicrobial therapy for CIED infections have not changed significantly [10,25,46,48,53,58]. This might be explained due to the limited availability of high-quality

clinical trial data and the slow incorporation of new treatment approaches, leading to potential under-treatment of infections and suboptimal patient outcomes. Therefore, there is a need to re-evaluate the existing guidelines and include new evidence-based approaches to improve patient outcomes. In this sense, daptomycin and ceftaroline are new anti-staphylococcal antibiotics that have been lesser studied against MRSE or VRSE. As we have previously discussed, the prevalence of MRSE in CIED infections has increased remarkably in the last decade. There are also no studies that have evaluated the efficacy of the combination of both antibiotics against MRSE and VRSE. In our *in vitro* studies, the activity (MIC/MBC) of daptomycin and ceftaroline against MRSE strains was excellent, being 2-4 times more active than vancomycin. On the other hand, daptomycin was non-susceptible (MIC of 2 mg/l) against the VRSE strain with a vancomycin MIC of 8 mg/L while ceftaroline remained active. Time-killing curves performed at standard and high inocula showed that the combination of daptomycin plus ceftaroline was synergistic and bactericidal against most MRSE and VRSE strains, even when the VRSE strain was daptomycin non-susceptible. Furthermore, it is important to note that resistance to daptomycin did not develop. Meanwhile, we decided to test whether the combination of daptomycin and ceftaroline was effective in the endocarditis model experienced by MRSE and VRSE.

The experimental endocarditis animal models provide a fundamental tool for evaluating the safety and the efficacy of new antimicrobial agents. They are a crucial step in developing and optimizing new antimicrobial approaches. Using these models, we can more accurately predict the potential clinical success of antimicrobials before they are tested in human clinical trials [85,86,154,155]. In this regard, we selected one of the five MRSE strains and VRSE strain tested *in vitro,* and we compared the efficacy of the combination of daptomycin plus ceftaroline with their monotherapies against MRSE/VRSE experimental endocarditis. We demonstrated that combinations of daptomycin, at a low dose (6 mg/kg/day), plus ceftaroline were significantly more active than any monotherapy in the MRSE and VRSE experimental endocarditis when comparing their capacity to reduce the density of bacteria within the valve vegetations. In contrast

to vancomycin, which usually remains confined to the periphery of vegetations, daptomycin has shown to penetrate homogeneously into the core of these complex structures [82,84]. In our study, daptomycin monotherapy was able to clear MRSE from infected tissues, without selecting resistant mutants in any of the organs analyzed: spleen, kidney, and valve vegetations. Whereas experimental endocarditis due to MRSE and VRSE is characterized by the presence of vegetations with very high density of bacteria, extracardiac spread seems to be limited with lower concentrations in the spleen and kidney; in contrast, what is observed in *S. aureus* experimental model is a metastatic and systemic disease with high inoculum in all tissues [82,157–158]. Previous *in vitro* and *in vivo* studies had shown potent synergism of daptomycin and both with semi-synthetic penicillin or other beta lactams, e.g., cloxacillin or ceftaroline, against MRSA and MSSA [93]. This synergism has been attributed to the ability of certain beta lactams to increase the anti-staphylococcal activity of various components of the innate immune host response and the reduction of positive electric charge of surface of the microorganisms, thus enabling daptomycin to reach its target more effectively [156–160]. These results suggest the potential usefulness of the combination of daptomycin plus ceftaroline in MRSE and VRSE endocarditis in clinical settings. In the light of our results, we consider that it is time to reappraise the antibiotic treatment of CoNS endovascular infections.

Strengths and limitations of this thesis

The five individual studies making up this thesis have some strengths and limitations that should be acknowledged.

The multicenter nature and the inclusion of well-defined large cohort of IE episodes are important strengths of the first study. They allow a reliable analysis and provides adequate statistical power. Additionally, no previous large studies of this type have been performed in Europe, since the Euro-Endo registry cannot be used to compare two periods of time. Furthermore, we have performed a sub-analysis with centers participating in both periods, in order to avoid the bias of different prognosis being related to a center's experience, and main results did not change.

However, this article has some limitations. Firstly, the UN geoscheme for Europe is a statistical and not a meaningful health care classification, and the categorization of Southern versus Northern-Central is arbitrary. Unfortunately, we were unable to analyze the situation of IE in Eastern Europe, where access to care may be more limited, where intravenous drug use has notably risen recently, and where HIV and IE related to intravenous drug use is becoming a major concern [163]. As a multicenter study, there may be differences in practices even within the same country, and the retrospective nature of the study and the missing data existing for some variables may also affect the results of the analyses. There is a bias of IE selection cases, since mostly large University Tertiary Centers with cardiac surgery provided data to ICE, and the microbiology, predisposing conditions, and outcome of IE in smaller centers in the same countries or regions could differ considerably.

Studies 2 and 4 focused on the CIED-IE cohort are the largest historical cohort over 40-years 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. We also described temporal trends in epidemiology, clinical, microbiology, and outcomes over 40 years. We first compared complete and incomplete device removal CIED-IE profiles over a long-follow up and predictive factors for non-complete device removal analysis. Finally, we have proposed some preliminary strategies including the potential utility of [18F] FDG-PET/CT in guiding the stopping of CAS in selected cases whose PET/CT turns negative.

On the other hand, this study has some limitations, particularly its retrospective design over a very long period when new technical surgeries and microbiological and imaging diagnosis improvements emerged. However, the IE team's homogenous diagnostic and therapeutic management has allowed us to account for the impact of these changes. 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 characterization of episodes managed at community noncardiac surgery centers still need to be improved. 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 rendering the study more broadly applicable. Fourth, since non-device removal accounted for a small proportion of patients, some variables could not be identified as independent risk factors. Finally, the CAS therapy cohort only included 13 patients, with [18] FDG-PET/CT follow-up data in just five.

The key findings of the study on the diagnostic yield of [18F] FDG-PET/CT are the high sensitivity and specificity of [18F] FDG-PET/CT for identifying local CIED infection and its unique role in the assessment of the subcutaneous and endovascular lead infections where other diagnostic techniques are preluded. This work is the first to compare spleen and bone marrow metabolism and their potential utility in stratifying CIED infections, showing a potential role to detect bacteremic cases. Also, our cohort is the largest published case-control series and the only study evaluating [18F] FDG-PET/CT in the management of CAS therapy when complete device removal could not be achieved. That notwithstanding, this study holds limitations, mostly its retrospective nature. It was impossible to evaluate intracardiac leads in the [18F] FDG PET/CTs of control subjects, as they did not undergo a myocardial inhibition protocol, so the specificity analysis for the intracardiac lead was excluded. Second, comparisons between bone marrow and spleen uptake are based on small subgroups of patients with limited statistical power. Third, the control group had devices implanted for longer time compared to cases, so it was not possible to assess the accuracy of [18F] FDG-PET/CT on recently implanted CIEDs. Finally, the number of cases in which CAS therapy was stopped based on negative [18F] FDG-PET/CT was small, and these preliminary results need to be confirmed in further studies with a larger set of patients.

The fifth study of this thesis is the first to evaluate the *in vivo* activity of daptomycin and ceftaroline alone or in combination to treat the experimental endocarditis caused by MRSE and VRSE (vancomycin MIC of 8 mg/L). The main findings describe how the combination of daptomycin plus ceftaroline showed potent, rapid, and synergistic bactericidal activity *in vitro* and *in vivo* against MRSE compared with monotherapies, potentially impacting clinical practice,

and deserving to be explored in clinical trials. Moreover, the combination of daptomycin plus ceftaroline was highly active against VRSE experimental endocarditis despite the VRSE strain showed daptomycin non-susceptibility (MIC of 2 mg/l). The main limitations are derived from *in-vitro* and *in-vivo* study design. We studied *in vivo* only one MRSE and one other VRSE strain in the animal model of experimental endocarditis and a strain-specific effect cannot therefore be ruled out. However, for MRSE, we were able to perform time-killing curves in five MRSE strains, and all the results were concordant, showing a synergistic and bactericidal effect in most cases at both standard and high inocula . Second, combined therapies using high doses of daptomycin (10 mg/kg) were not evaluated, although the synergistic effect would probably be maintained. Moreover, animal models are often used as surrogates for human infection, but it is important to note that the pathogenesis of MRSE/VRSE-induced infective endocarditis differs in humans and the catheter is left in place. However, the experimental endocarditis model is an ideal model and most antibiotic combinations that were effective in the animal model later showed efficacy in humans thorough clinical trials (e.g., the combination of ampicillin plus ceftriaxone for *Enterococcus faecalis* endocarditis or the combination of daptomycin plus fosfomycin for methicillin resistant bacteremia/endocarditis. Therefore, the combination of daptomycin plus ceftaroline should be further explored in clinical trials in humans for treating MRSE or VRSE infective endocarditis.

To summarized, we believe this doctoral thesis could contribute significant knowledge to the field of CIED infections in general and CIED-IE, in particular. Through a comprehensive review of the literature, innovative research methodologies, and the analysis of a large patient cohort, it has identified several key risk factors for CIED infections and has provided important insights into the pathogenesis, diagnosis, and treatment. Furthermore, its multidisciplinary approach, incorporating knowledge from infectious disease, cardiology, epidemiology, microbiology, nuclear medicine, and cardiac surgery, has helped to offer a more comprehensive understanding of this complex disease. As these studies have demonstrated, CIED infections continue to pose a significant challenge to healthcare providers and patients alike. However, the insights gained from

these studies offer hope for the development of more effective preventive, diagnostic, and treatment strategies, which could significantly improve patient outcomes and reduce the burden of these infections on healthcare systems. Considering these findings, it is recommended that healthcare providers adopt a more proactive approach to the prevention, diagnosis, and treatment of CIED infections, incorporating the latest research into their clinical practices. In conclusion, the knowledge gained from this study could help to guide future research and clinical practice, ultimately leading to improved patient outcomes and a better understanding of these major foreign-body cardiovascular infectious diseases.

Future perspective of research

The incidence of CIED infections has been increasing, and upcoming studies might help to postulate a more comprehensive understanding, potentially paving the way for new lines of research that improve the prevention, diagnosis, management, and treatment of these infections.

One future perspective for research would be to develop new preventive strategies to reduce the incidence of CIED infections along the lines of the WRAP-it study, discussed in this thesis. In this regard, the University of Kiel has conducted an observational prospective case-control study focused on preventing CIED infection. The intervention group was compared with a retrospective historical cohort to evaluate the effect of intraoperative topical application of an antiseptic, Taurolidine solution, on CIEDs during any invasive procedure from 2020 to 2022. The primary outcome was all-cause mortality during the in-hospital observation and the 36 months follow-up and the presence of adverse events, but data remain unpublished [ClinicalTrials.gov Identifier: NCT05576194]. Another important study based on prophylaxis to prevent CIED infection was conducted by the Italian group at the University of Ferrata. The PRACTICE study is a single center, cohort study. Using the Sharif score, patients were stratified in two groups: low infective risk (score <3) and high infective risk (score ≥3). Patients in the "low risk" group were treated with only two doses of antibiotics, both intravenous: the first one hour before skin incision and

the second after eight hours. Patients in the "high risk" group were treated with intravenous prophylaxis for two full days (first one hour before skin incision and then every eight hours), followed by another seven days of oral prophylaxis, for a total of nine days. Primary outcome was clinical diagnosis of systemic or local infection involving subcutaneous CIED pocket or intravenous/intracardiac CIED lead or sepsis; data not reported [ClinicalTrials.gov Identifier: NCT04736979]. Further research could investigate the additional risk factors for CIED infections, particularly in populations with a higher risk of incomplete device removal. In this regard, a multicentric approach will provide more patients and a better understanding.

On the other hand, advances in imaging and molecular biology diagnostic techniques could be used to improve the accuracy of diagnosing CIED infections, allowing for earlier intervention and improved patient outcomes. Along this line, a German group managed the prospective DIRT study, which identified procalcitonin (PCT) as the most promising of 14 biomarkers in aiding the diagnosis of pocket infections [ClinicalTrials.gov Identifier: NCT05007158].

Moreover, developing a standardized multidisciplinary cardiovascular infection team and protocols for preventing, diagnosing, and treating CIED infections could be an area of future research, as this could improve the consistency and quality of care for patients with these devices. Based on this idea, Duke University is conducting a Quality Initiative (QI) demonstration project to develop a model to increase guideline-driven care for patients with CIED infection. This program seeks to improve early identification and diagnosis, appropriate treatment, and faster time to treatment of CIED infections [ClinicalTrials.gov Identifier: NCT05471973].

Finally, exploring the complex interplay between bacterial biofilms and the host immune response promises to shed light on the mechanisms underlying CIED infections and to help identify new targets for intervention. The insights gained from this possible research could shed light on the use of alternative options to prevent and treat CIED infections, e.g., immunomodulatory therapies or the use of probiotics, lysins and phages.

6. Conclusions

1. We performed one of the largest studies of infective endocarditis in Europe, including more than 4,000 episodes from 13 European countries, analyzing clinical outcomes over time (2000-2006 vs. 2008-2012) and in different European regions (Southern vs. Northern-Central Europe).

2. The study showed an increase in the complexity of the infective endocarditis profile (including CIED-IE) over time in both European regions and a significant rise in the proportion of patients benefitting from surgical treatment, which was greater than 50%. In-hospital and six-month mortality rates were similar between both regions and significantly decreased in recent years, mainly in Southern countries.

3. Despite the increase in patients' comorbidities and the more complex endocarditis profile, modestly decreasing in-hospital and six-month mortality rates may represent a significant improvement in the overall diagnosis, treatment, and prognosis with potential public health implications for the management of infective endocarditis in Europe.

4. We analyzed a unique cohort of 140 consecutive cardiac implantable electronic device infective endocarditis episodes spanning 40 years. During this period, the prevalence of cardiac implantable electronic device infective endocarditis increased fourfold, and the clinical picture changed. As life expectancy has improved, patient age, the number of comorbidities and the need for more complex devices (especially implantable cardiac defibrillators) has increased. Patients with cardiac implantable electronic device infective endocarditis had more healthcare associated infections, were more often transferred from other centers and more likely presented infections due to resistant staphylococci and enterococci.

5. Despite this worse clinical scenario and the decrease of device removal in recent years, one-year survival has significantly improved in the first two decades of the 21st Century. Mortality was associated with the severity of comorbid conditions and sepsis and improved both in transferred patients and in those with complete device removal.

6. We have confirmed that the diagnostic performance of [18F] FDG-PET/CT is very high in local cardiac implantable electronic device infections but that the sensitivity decreased in the other infected lead segments. However, [18F] FDG-PET/CT and transesophageal echocardiography are complementary–as [18F] FDG-PET/CT is the only technique available for assessing subcutaneous and endovascular lead infection, and transesophageal echocardiography is very useful for intracardiac lead endocarditis–increasing by one-third when they are combined the definite diagnosis of systemic lead infections.

7. Spleen and bone marrow hypermetabolism may help to distinguish between bacteremic-lead infections and isolated local cardiac implantable electronic device infections, but it is not specific for systemic device infections.

8. We have shown for the first time that the disappearance of [18F] FDG-PET/CT uptake during the follow-up could have a potential role in safely stopping chronic oral antibiotic suppression therapy when complete device removal is not performed. These preliminary results could be the basis for prospective studies to confirm its utility in managing these infections.

9. Due to increases in age, comorbidities and device complexity in recent years, the proportion of patients without device removal has increased from 4% to 14% over these 40 years. Therefore, in the last decade in one out of seven cases with cardiac implantable electronic device infective endocarditis, the device could not be removed.

10. Patients without device removal clearly have different clinical and microbiological features, and elderly and the *Staphylococcus aureus* etiology are the predictors of not removing a device.

11. Chronic oral antibiotic suppression was an effective and safe measure in most cases, preventing relapses and increasing the survival of cardiac implantable electronic device infective endocarditis patients without device removal.

12. The *in vitro* activity (MIC/MBC) of daptomycin and ceftaroline against methicillin-resistant *Staphylococcus epidermidis* strains was excellent: 2-4 times more active than vancomycin. On the other hand, daptomycin was non-susceptible against the vancomycin resistant *Staphylococcus epidermidis* strain with a vancomycin MIC of 8 mg/L while ceftaroline remained active.

13. Time-killing curves performed at standard and high inocula showed that the combination of daptomycin plus ceftaroline was synergistic and bactericidal against most methicillin-resistant *Staphylococcus epidermidis* and vancomycin resistant *Staphylococcus epidermidis* strains, even when the vancomycin resistant *Staphylococcus epidermidis* strain was daptomycin non-susceptible.

14. The synergistic *in vitro* results were confirmed *in vivo* in the animal model of methicillin-resistant *Staphylococcus epidermidis* and vancomycin resistant *Staphylococcus epidermidis* experimental endocarditis in rabbits, showing that the combination of daptomycin plus ceftaroline had a rapid, potent, and synergistic bactericidal activity, decreasing by around 6 log10/ml the density of bacteria within the valve vegetations against both microorganisms. In addition, daptomycin non-susceptibility was not identified in the monotherapy arm in neither valve vegetations nor peripheral tissues.

15. These good preclinical results support the potential usefulness of the combination of daptomycin plus ceftaroline for the treatment of methicillin-resistant *Staphylococcus epidermidis* and vancomycin resistant *Staphylococcus epidermidis* bloodstream infections (including infective endocarditis) in clinical settings. Therefore, it is time to update the antibiotic treatment of *Staphylococcus epidermidis* endovascular infections.

7. References

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8. Annexes

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STATEMENT OF THE DOCTORAL CANDIDATE AND DIRECTOR/S OF ORIGINALITY AND GOOD PRACTICES OF THE THESIS

Dr. José María Miró Meda, Professor of Medicine of the University of Barcelona, and Infectious Diseases Senior Consultant of the Hospital Clínic de Barcelona with ID 36925504Q, and **Dr. José María Tolosana Viu**, Assistant Professor of Medicine of the University of Barcelona and Cardiology Consultant of the Hospital Clínic de Barcelona with ID 18038104D,

DECLARE THAT

The doctoral thesis entitled **EPIDEMIOLOGICAL AND CLINICAL CHANGES, ROLE OF [18F] FDG PET/CT IN THE DIAGNOSIS AND MANAGEMENT AND NEW ANTIBIOTIC TREATMENTS OF CARDIAC IMPLANTABLE ELECTRONIC DEVICE INFECTIONS**, is original, containing own results and information, without plagiarism from other thesis, publications, or research from other authors. They also confirm that ethical codes and good practices have been followed for its preparation. They declare that they consent that the thesis may be submitted to procedures to verify its originality.

Signed on the day 17th March 2023

Dr. José M. Miró Meda	**Dr. José M. Tolosana Viu**	**Marta Hernández-Meneses**
Thesis supervisor	Thesis supervisor	Doctoral student

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AUTORIZATION FOR THE PRESENTATION OF THE THESIS

Dr. José María Miró Meda, Professor of Medicine of the University of Barcelona and Infectious Diseases Senior Consultant of the Hospital Clínic de Barcelona, and **Dr. José María Tolosana Viu**, Assistant Professor of Medicine of the University of Barcelona and Cardiology Consultant of the Hospital Clínic de Barcelona, certify that the doctoral thesis entitled:

"EPIDEMIOLOGICAL AND CLINICAL CHANGES, ROLE OF [18F] FDG PET/CT IN THE DIAGNOSIS AND MANAGEMENT AND NEW ANTIBIOTIC TREATMENTS OF CARDIAC IMPLANTABLE ELECTRONIC DEVICE INFECTIONS"

presented by **Marta Hernández-Meneses**, has been carried out under their supervision at the Faculty of Medicine of the University of Barcelona, and under their supervision and direction, and it fulfils all the requirements for preparation and defense before the Assessment Tribunal.

Barcelona, 17th March 2023

Dr. José M. Miró Meda
Thesis supervisor

Dr. José M. Tolosana Viu
Thesis supervisor

DECLARATION OF AUTHORSHIP OF THE THESIS

The doctoral candidate Mrs. Marta Hernández Meneses, with Identity card 4472155F

DECLARE THAT

Is the author of the doctoral thesis entitled "**EPIDEMIOLOGICAL AND CLINICAL CHANGES, ROLE OF [18F] FDG PET/CT IN THE DIAGNOSIS AND MANAGEMENT AND NEW ANTIBIOTIC TREATMENTS OF CARDIAC IMPLANTABLE ELECTRONIC DEVICE INFECTIONS**"

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