Original article

Infections in Cardiac Implantable Electronic Devices: Diagnosis and Management in a Referral Center

Encarnación Gutiérrez Carretero,[a] Eduardo Arana Rueda,[b] José Manuel Lomas Cabezas,[c] Fernando Laviana Martínez,[a] Manuel Villa Gil-Ortega,[d] Jesús Acosta Martínez,[e] Alonso Pedrote Martínez,[b] and Arístides de Alarcón González[f,*]

[a] *Servicio de Cirugía Cardiaca, Hospital Universitario Virgen del Rocío, Sevilla, Spain*
[b] *Unidad de Electrofisiología, Servicio de Cardiología, Hospital Universitario Virgen del Rocío, Sevilla, Spain*
[c] *Infectious Diseases Department, Oxford University Hospitals, NHS Foundation Trust, United Kingdom*
[d] *Unidad de Hemodinámica, Servicio de Cardiología, Hospital Universitario Virgen del Rocío, Sevilla, Spain*
[e] *Servicio de Anestesia y Reanimación, Hospital Universitario Virgen del Rocío, Sevilla, Spain*
[f] *Unidad de Gestión Clínica de Enfermedades Infecciosas, Microbiología y Medicina Preventiva, Hospital Universitario Virgen del Rocío, Grupo de Investigación en Enfermedades Infecciosas, Instituto de Biomedicina de Sevilla, Sevilla, Spain*

A B S T R A C T

Introduction and objectives: Infections in cardiac implantable electronic devices are increasing due to the expansion of the indications of these devices. The management of some aspects is controversial. Here, we report our broad experience.
Methods: Between 1985 and 2015, 325 infections (196 local and 129 systemic) were registered; 28.5% of them were referred from other centers: 229 pacemakers, 69 implantable cardioverter-defibrillators, and 27 patients with cardiac resynchronization therapy. The follow-up was at least 1 year after hospital discharge.
Results: Percutaneous traction (PCT) was the most frequent procedure (n = 280) in local (n = 166) and systemic infections (n = 114), with complete extraction of the system in 82.5% of the patients, clinical success in 89%, and few complications (2 deaths attributable to the technique). Overall mortality was 1% in local infections and 8% in systemic infections. After 212 complete PCT, a new device was placed in 209: of these, a contralateral system was implanted in the same procedure in 152 (73%) and in a second procedure in 57, with no differences in relapses (2 in the 1-stage procedure, and 1 in the 2-stage procedure).
Conclusions: Percutaneous traction in experienced hands has good results with very few complications. It is possible to perform contralateral implantation of the new device on the same day without increasing the risk of relapse.

© 2016 Sociedad Española de Cardiología. Published by Elsevier España, S.L.U. All rights reserved.

Infecciones en dispositivos de estimulación cardiaca: diagnóstico y tratamiento en un centro de referencia

R E S U M E N

Introducción y objetivos: Las infecciones en dispositivos de electroestimulación cardiaca son cada vez más frecuentes debido a las indicaciones cada vez más amplias de estos sistemas. Algunos aspectos sobre su tratamiento son controvertidos y aportamos aquí nuestra amplia experiencia.
Métodos: Se atendieron 325 infecciones (196 locales y 129 sistémicas) durante los años 1985 a 2015, el 28,5% de ellas procedentes de otros centros: 229 marcapasos, 69 desfibriladores automáticos implantables y 27 pacientes con terapia de resincronización cardiaca, con un seguimiento mínimo de 1 año tras el alta hospitalaria.
Resultados: La tracción percutánea (TPC) fue la técnica utilizada más frecuentemente (n = 280), en infecciones tanto locales (n = 166) como sistémicas (n = 114), con una tasas de extracción completa del sistema del 82,5% del total y de curación, del 89%; las complicaciones fueron escasas (2 muertes achacables a la técnica). La mortalidad total fue del 1% en infecciones locales y el 8% en las sistémicas. Tras 212 TPC completas, se reimplantó un nuevo sistema contralateral en 209: en 152 de ellas en el mismo acto (73%) y en 57 en un segundo tiempo; no se apreciaron diferencias en el número de recidivas en el nuevo sistema (2 en 1 tiempo y 1 en 2 tiempos).

Conclusiones: La TPC en manos expertas arroja buenos resultados en términos de eficacia, con escasas complicaciones. Se puede realizar el reimplante de dispositivos en un solo tiempo sin que ello conlleve un mayor riesgo de recidiva.

Abbreviations

CIEDs: cardiac implantable electronic devices
PCT: percutaneous traction

INTRODUCTION

The first permanent pacemaker implantation was performed in 1954, with the first implantable cardioverter defibrillator implantation occurring in 1980. The use of these cardiac implantable electronic devices (CIEDs) has exponentially increased in the last 10 years due to technological advances, expansion of their indications, and improved life expectancy of the recipient population.[1–3] This increment has been accompanied by a largely unforeseen increase in infectious complications affecting the devices.[4] The treatment of these complications is complicated and, despite the existence of specific management guidelines,[5,6] certain aspects related to diagnosis and particularly treatment are still a matter of debate. The aim of this work was to describe our broad experience in the treatment of these infections, primarily by analyzing the success of the various therapeutic approaches used.

METHODS

Study Population and Period

The present study analyzed consecutive patients with CIED infections treated between 1985 and 2015 in our center. From 1985 to 1998, the patients were referred from the clinic to the infectious disease service. In 1999, a specific intervention program developed by a multidisciplinary team was implemented for these types of infections. When a CIED infection was suspected, the patients (from the hospital itself or transferred from other centers) were evaluated by a team member (A. de Alarcón González) to determine the type of infection and the priority for action. Data were prospectively and systematically collected according to a preestablished protocol.

Microbiological Sample Collection and Echocardiography Results

Two batches of serial blood cultures (baseline and at 30 and 60 minutes) were obtained from all patients at a 12-hour interval. If patients showed local signs of infection, the exudate was sampled for Gram staining and aerobic and anaerobic cultures; if there was no external discharge, sampling was performed using needle aspiration of the generator pocket. During the surgery, samples were obtained from the pocket and the region 4 cm distal to the leads; some of the samples were cultured while the remainder was stored at −20 °C. From 2005, negative cultures were additionally analyzed with genomic sequencing techniques, specifically, 16S rRNA polymerase chain reaction (PCR). If systemic infection was suspected and/or the blood cultures were positive,

cardiac ultrasound was performed (in transesophageal mode from 1999 onward).

Definitions

Infections were classified according to location as:

- Local infection: infections were considered local when patients showed no systemic symptoms (fever, shock, embolisms, or remote infectious complications), blood cultures were negative, and there were signs of infection in the region of the generator pocket, such as pain, erythema, and purulent material.
- Systemic infection: infections were considered systemic when patients showed systemic symptoms and blood cultures were repeatedly positive. Negative blood cultures required the presence of vegetation in the lead or right-sided cardiac structures.

Depending on the time of onset, infections were classified as: *a)* acute: those appearing before 1 month after device implantation or manipulation; *b)* delayed: those appearing between 2 and 12 months after implantation or manipulation; and *c)* late: those appearing after 12 months.

Antibiotic Therapy

Antibiotic therapy was always performed in accordance with the antibiogram of the causative agent isolated in culture. After device removal, oral antibiotic therapy continued for 1 or 2 weeks for local infections. If the device was not removed, the duration varied from patient to patient.

Initial treatment of systemic infections always involved intravenous antibiotics before device removal; except in patients with severe sepsis, the device was not removed until the blood cultures were negative (typically at 1 week). If the removal was complete, the therapy was maintained for 2 further weeks and, after the first week, could be switched to oral therapy. If valves were affected (eg, the tricuspid), the antibiotic therapy was maintained for at least 4 weeks.

Surgical Procedure

The surgical procedures are detailed in the supplementary material.

Replacement of the Implantable Electronic Device

Device replacement was performed in 1 or 2 stages, depending on the type of device, as described in the supplementary material.

Follow-up

Patients of our hospital underwent a specific follow-up for 1 year in a clinic specializing in infectious diseases and then for life in a pacemaker assessment clinic. Patients referred from other

centers underwent a minimum follow-up for 3 months in our hospital; all such patients also underwent follow-up blood cultures for systemic infections and stayed in contact with the referral hospital for 1 year.

Infection relapse was considered to have occurred if, during the 1-year follow-up, the newly implanted device was infected by the same microorganism isolated from the originally extracted system. In contrast, the infection was considered to be a reinfection if a different microorganism was isolated; it was then recorded as a new episode. Persistence of the original signs and symptoms or continued isolation of the same microorganism after a specific therapeutic intervention was defined as treatment failure.

Statistical Analysis

A descriptive analysis with measures of central tendency and dispersion was performed for continuous variables, as well as a frequency distribution for qualitative variables. For the comparison of continuous variables, the Student t test was used (after analysis of normality with the Kolmogorov-Smirnov test); the Mann-Whitney U test was used if the distribution was not normal. For categorical variables, the chi-square test or Fisher exact test was used as appropriate. $P < .05$ was considered statistically significant.

RESULTS

Epidemiological Characteristics

During the study period, 325 infections were recorded in 314 patients, 226 (72%) men and 88 women; 28.5% of the patients had been referred from other centers. The median patient age was 69 [60-76] (range, 14-90) years and 32% had 2 or more concomitant chronic diseases.

The infection was related to a pacemaker in 229 patients (71%), to an implantable cardioverter defibrillator in 91, and to cardiac resynchronization therapy in 27 (22 had received an implantable cardioverter defibrillator). The main characteristics of the patients are summarized in Table 1.

The infections were categorized as local in 196 episodes (60.3%) and systemic in 129 (39.7%). In 160 patients (49%), the infection developed after further manipulation (generator replacement in 80% of these infections). The infections were classified as acute (n = 131 [40.3%]), delayed (n = 100 [30.8%]), and late (n = 94 [28.9%]).

Etiology and Yield of the Diagnostic Tests

The most frequently isolated microorganisms were coagulase-negative staphylococci (42.8%) and *Staphylococcus aureus* (16.9%). A more detailed description of the microbial etiology can be found in Table 2A and Table 2B.

When there were local symptoms, the culture yield of the generator region was high (75.0%-85.3% of isolations); also high were the culture positivity of the leads in systemic infections (75%) and even in local infections (52.6%). A more detailed summary of these results is shown in Table 3.

An echocardiographic study before device removal was performed in 116 patients (90%) with systemic infection: 45 patients underwent a transthoracic study, 42 underwent a transthoracic and transesophageal study, and 29 proceeded directly to a transesophageal study. Of the 87 transthoracic ultrasound studies, vegetation was visible in 24 (27.5%) vs 63.3% (n = 45) of the 61 transesophageal studies.

Clinical Manifestations

The clinical signs and symptoms are shown in Table 4. Of the patients with systemic infection, 77 (57.7%) had local signs; because these signs were present a long time before the onset of the systemic infection in 32 (25%) patients, they were given standard therapy for local infection (typically with local septic surgery) before the disease progressed to a systemic infection.

Therapeutic Approach

In 102 local infections (55.6%), the therapeutic approach of choice involved various types of percutaneous traction (PCT). Unsatisfactory results were obtained in 75 (73.5%). Local surgery (generator removal with the leads left *in situ*, pocket debridement and cleaning, and placement of a new generator) had a clinical success rate of just 20%, with a median of 2.5 [1-3] (1-12) procedures per patient. The cables were left in place on 9 occasions, even though a system was implanted contralaterally to the infected generator; in all patients, extrusion and discharge were witnessed in the same region months afterward. Isolated antimicrobial therapy was successful on 48.3% of occasions. A comparison of the patients successfully treated with this therapy (n = 15) with those who were not (n = 16) revealed the following: *a*) the patients had a significantly shorter median clinical course:

Table 1
Epidemiological Characteristics of Patients by Type of Infection

Characteristics	Local (n = 196)	Systemic (n = 129)	Total (n = 325)
Diabetes mellitus	60 (33.7)	37 (28.7)	103 (31.7)
Ischemic heart disease	68 (34.7)	39 (30.2)	107 (32.9)
Cardiomyopathy	53 (27)	30 (23.3)	83 (25.5)
COPD	25 (12.8)	19 (14.7)	44 (13.5)
Renal failure on HD	16 (8.2)	11 (8.5)	27 (8.3)
Cerebral vascular disease	20 (5.1)	6 (4.7)	16 (4.9)
PM			
Single-chamber	20 (10.2)	17 (13.2)	37 (11.4)
Dual-chamber	110 (56.1)	82 (63.5)	192 (59)
CRT-PM (without ICD implantation)	3 (1.5)	2 (1.6)	5 (1.5)
ICD	49 (25)	20 (15.5)	69 (21.2)
CRT-ICD	14 (7.1)	8 (6.2)	22 (6.8)

COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; HD, hemodialysis; ICD, implantable cardioverter-defibrillator; PM, pacemaker.
Data are expressed as n (%).

Table 2
Etiology of the Infections

A. According to time of onset				
Microorganism	Acute	Delayed	Late	Total
CNS[a]	48 (36.6)	46 (46)	45 (47.9)	139 (42.8)
Staphylococcus aureus[b]	30 (22.9)	13 (13)	12 (12.8)	55 (16.9)
GNB	16 (12.2)	4 (4)	4 (4.3)	24 (7.3)
Streptococcus	1 (0.8)	1 (1)	4 (4.3)	6 (1.8)
Anaerobic	6 (6.6)	5 (5)	2 (2.1)	13 (4)
Other	2 (1.5)	4 (4)	5 (5.3)	12 (3.6)
Polymicrobial	16 (12.2)	9 (9)	9 (8.5)	33 (10.2)
Unknown	12 (9.2)	18 (18)	13 (13.8)	43 (13.2)
Total	131	100	94	325

B. According to location			
Microorganism	Local	Systemic	Total
CNS[a]	90 (45.9)	49 (38)	139 (42.8)
Staphylococcus aureus[b]	20 (10.2)	35 (27.1)	55 (16.9)
GNB	13 (8.6)	11 (8.5)	24 (7.3)
Streptococcus	1 (0.5)	5 (3.9)	6 (1.8)
Anaerobic[c]	13 (6.6)	0	13 (4)
Other[d]	6 (3.1)	6 (4.5)	12 (3.6)
Polymicrobial[e]	12 (6.1)	22 (16.3)	33 (10.2)
Unknown	41 (20.9)	2 (1.6)	43 (13.2)
Total	196	129	325

CNS, coagulase-negative staphylococci; GNB, Gram-negative bacillus (including enterobacteria and non-fermenting bacilli).
In 11 CNS-related infection episodes, various species were isolated that have been omitted from the "polymicrobial" category.
    [a] 51% of the strains were methicillin-resistant.
    [b] 8% of the strains were methicillin-resistant.
    [c] *Propionibacterum acnes*, 12; *Fusobabcterium nucleatum*, 1.
    [d] *Enterococcus corynebacterium* spp., 5; *E. faecalis*, 3; *Haemophylus influenza*, 1; *Micobacterium* spp., 1; *C. tropicalis*, 1.
    [e] CNS and *S. aureus*, 11; CNS and BGN, 5; CNS and others, 8; *S. aureus* and BGN, 2; *S. aureus* and others, 4; various BGN, 1; *Coxiella burnetii* and *Brucella* spp. 1; *E. cloacae* and *Corynebacterium* spp.

10 [3-15] (2-60) days vs 35.5 [16-187] (11-474) days (*P* < .01), and *b*) the patients less frequently developed skin erosion: 4 occasions (28.6%) vs 11 (64.7%; *P* = .07). In both situations, the prescribed antimicrobial therapy was prolonged—60 [40-90] days—and was always guided by the antibiogram.

In contrast, PCT ultimately achieved clinical success in 96.3% of complete removals (n = 94) and in 86.2% of incomplete removals (n = 20) due to retained intravascular fragments after lead rupture. In 3 cases, the patients developed, months later, a systemic infection that ultimately led to open heart surgery.

The antimicrobial therapy had poor efficacy for systemic infections (an 85.1% failure rate) and a high mortality rate (11.1%). Complete PCT achieved a clinical success rate of 89.3%, whereas incomplete PCT had a failure rate of 60% (n = 12), leading to cardiac surgery in 11 patients and subsequent femoral snare removal in the remainder. Of the 21 patients who underwent

Table 3
Yields of the Various Cultures Performed by Type of Infection

Diagnostic test	Negative	Positive	Total performed
Local infections (n = 196)			
Blood cultures	174 (100)	0	174 (88.7)
Pocket cultures	48 (25)	144 (75)	192 (98)
Lead cultures	45 (47.3)	50 (52.6)	95 (48.3)
Systemic infections (n = 129)			
Blood cultures	14 (10.9)	115 (89.1)	129 (100)
Pocket cultures[*]	12 (14.6)	70 (85.3)	82 (63.5)
Lead cultures	21 (25)	63 (75)	84 (65.1)

Data are expressed as n (%).
    [*] Only 77 patients (57.7% of patients with systemic infections) had local signs: 32 were present before the onset of systemic signs and symptoms, 39 were concomitant, and 7 were present during the clinical course after the first systemic manifestations.

Table 4
Clinical Manifestations

Signs and symptoms	Local	Systemic
Pain	171 (87.2)	76 (58.9)
Erythema	169 (86.2)	70 (54.3)
Skin erosion	162 (82.7)	63 (48.8)
Discharge	154 (78.5)	61 (47.3)
Partial extrusion[a]	49 (25)	12 (9.3)
Complete extrusion[b]	9 (4.5)	3 (2.3)
Fever	12 (6.1)	106 (82.2)
Embolisms	0 (0)	21 (16.3)
Deep vein thrombosis[c]	7 (3.6)	15 (11.6)
Septic shock	0	16 (12.4)
Spondylitis	0	6 (4.6)
Left-sided endocarditis	0	3 (2.3)
Total infections	196	129

Data are expressed as n (%).
    [a] Partial exteriorization of the generator body or the leads alone.
    [b] Complete exteriorization of the generator body.
    [c] Assessed before device removal using computed tomography or venography.

Table 5

Local and Systemic Infection Outcomes by Type of Approach

	Death	Failure	Success	Contralateral relapse	Contralateral reinfection	
Local infections						Total (n = 196)
ATB alone	0	16 (51.6)	15 (48.3)	–	–	31 (15.8)
Local surgery	0	50 (80.6)	12 (19.3)	–	–	62 (31.6)
Generator removal and alternative PM	0	9 (100)	0	0	0	9 (4.5)
Complete PCT[a]	1 (0.7)	0	132 (96.3)	2 (1.4)	2 (1.4)	137 (69.8)
Incomplete PCT[b]	1 (0.7)	3 (10.3)[c]	25 (86.2)	0	0	29 (14.7)
Systemic infections						Total (n = 129)
ATB alone[d]	3 (11.1)	23 (85.1)	1 (3.7)	–	–	27 (20.9)
Complete PCT[e]	4 (4.2)	0	84 (89.3)	1 (1)	5 (5.3)	94 (72.8)
Incomplete PCT[f]	1 (5)	12 (60)	7 (35)	0	0	20 (15.5)
Cardiac surgery[g]	2 (9.5)	0	19 (90.5)	0	0	21 (16.2)

ATB, antibiotic; PCT, percutaneous traction; PM, pacemaker.

Data are expressed as n (%).

[a] 83 PCTs as initial technique and 54 as secondary technique after failure of other approaches (antibiotic treatment alone or in combination with local surgery).

[b] 14 initial and 15 secondary (after failure of other approaches).

[c] These 3 patients later developed a systemic infection.

[d] 15 patients had no local symptoms; 14 of these underwent ultrasound, with vegetation found in 10. Another 12 patients had local symptoms; of the 10 ultrasounds performed, 7 showed vegetation.

[e] 58 initial and 36 secondary.

[f] 13 initial and 7 secondary.

[g] 11 after PCT failure in our center and 10 after simple traction attempts in other centers.

cardiac surgery in our center, 11 required it for PCT failure; the remainder had been referred from other centers that had tried simple manual traction. The results of the various approaches are detailed in Table 5.

Percutaneous traction was performed for a total of 280 episodes (166 local infections and 114 systemic infections); complete removal was achieved in 231 patients (82.5%) and a cure was achieved in 246 (89%). The success rate of this technique was related to the age of the implanted CIED (Table 6), with no influence of other factors such as the number of leads, implantation side, and type of device.

In the entire series, there were 12 deaths: 2 patients (1%) with local infection and 10 (7.7%) with systemic infection. Only 2 of these deaths were related to the PCT technique (superior vena cava tear: 1 in a patient with local infection and 1 with systemic infection). In another 7 episodes, the cause was the sepsis itself: 3 of these patients were undergoing antimicrobial therapy, 2 underwent PCT (1 with incomplete removal and 1 with complete removal), and 2 underwent cardiac surgery. Another 2 patients died several days after PCT completion from unrelated causes (stroke, 1 of them with local infection) and, finally, another patient with dilated cardiomyopathy who underwent resynchronization therapy but did not have system replacement died months afterward due to heart failure.

The various PCT-related complications are described in Table 7.

Device Replacement

Device replacement after its removal was not performed in 13 patients (4%) in this series.

In 9 patients with local infections who underwent PCT with complete device removal, a contralateral implantation was first performed and the generator alone was removed; in our center, the remaining leads were removed because the patients continued to show signs of infection. Of the 128 remaining patients, the replacement was performed in the same surgical session in 96 (75%) and in 2 stages in 32, with no significant differences in contralateral infection frequency.

In the 4 patients with systemic infection who underwent PCT, the removal was performed after placement of a contralateral system. Of the 81 remaining replacements, the replacement was performed at the same time as the removal in 56 (69%) and at a later stage in 25. There was 1 infection by the same microorganism and another by a different bacterium (3.5%) in 1-stage procedures, whereas there were 4 infections (16%) by a different microorganism in 2-stage procedures (*P* = .04).

The differences between the 2 procedures are shown in Table 8.

Follow-up

Of the 304 surviving patients, 13 (4.3%) did not complete the minimum follow-up (3 months). The others were followed up for

Table 6

Percutaneous Traction Results by Time From Implantation

Time from implantation	Complete removal	Incomplete removal	All percutaneous tractions
≤ 1 y	97 (97)	3 (3)	100 (35.7)
2-5 y	52 (86.6)	8 (13.4)	60 (21.4)
6-10 y	55 (74.3)	19 (25.7)	74 (26.4)
11-15 y	18 (72)	7 (28)	25 (8.9)
> 15 y	9 (42.8)	12 (57.2)	21 (7.5)
Total	231 (82.5)	49 (17.5)	280 (100)

Data are expressed as n (%).

Table 7
Percutaneous Traction Complications

	n (%)	Treatment	Result
Nonembolic complications[a]			
Venous tears	3 (1)	Surgery in 3[b]	2 deaths
Cardiac tamponade	4 (1.4)	Conservative[c]	Recovery
Deep vein thrombosis[c]	7 (2.5)	Anticoagulation[d]	Recovery
Embolic complications			
Vegetation size (diameter)[e]		Before PCT	After PCT
< 1 cm	13 (24.5)	4 (30.7)	1 (7.69)
1.0-1.9 cm	32 (60.3)	4 (12.5)	1 (3.1)
2.0-2.9 cm	7 (13.2)	5 (71.4)	2 (28.5)
≥ 3 cm	1 (1.8)	0	1 (100)

PCT, percutaneous traction.
In the 59 episodes (45% of all systemic infections) with vegetation, the vegetation was localized to the leads (n = 45), the leads and the right valves (n = 8), and the valves alone (n = 8). The vegetation diameter was measured in 57 episodes and was < 1 cm in 13 patients, 1.0-1.9 cm in 34, 2.0-2.9 cm in 9, and ≥ 3 cm in 1.
  [a] Of a total of 280 percutaneous tractions.
  [b] The repair could be performed in only 1 case using partial replacement of the superior vena cava with a Contegra conduit.
  [c] Contribution of volume. Surgery or pericardial drainage was not performed.
  [d] For 6 months, with partial reopening in 4 at 1 year.
  [e] The 53 patients who underwent PCT are described in this table.

at least 1 year—median 36 [9.5-70.5] (6-309) months—, although 12 patients had not reached this time point by study closure. There were 31 deaths (10%) due to causes unrelated to device problems.

Table 8
Characteristics of the Patients Who Underwent Percutaneous Traction and Replacement in 1 or 2 Stages

	1 stage	2 stages	P
Local infections			
Patients, n	96	32	
Type of device			
PM	82 (85.5)	7 (21.8)	< .01
CRT-ICD	14 (14.5)	25 (78.2)	
Hospital stay	8 [6-17]	8 [5-23]	NS
Duration of ATB therapy	21 [17-28]	21 [21-28]	NS
Replacement interval (d)	0	6 [4-9]	
Number of relapses	1 (1)[a]	1 (3)[b]	NS
Number of reinfections	2 (2)[c]	0	NS
Systemic infections			
Patients, n	56	25	
Type of device			
PM	52 (92.8)	9 (36)	< .01
CRT-ICD	4 (7.2)	16 (64)	
Hospital stay	22 [16-32]	32 [10-53]	< .05
Duration of ATB therapy	29 [28-45]	32 [21-43]	NS
Replacement interval (d)	0	10.5 [5-21]	
Number of relapses	1 (1.8)[d]	0	NS
Number of reinfections	1 (1.8)[e]	4 (16)[f]	< .05

ATB, antibiotic; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; PCT, percutaneous traction; PM, pacemaker.
Data are expressed as n (%) or median [interquartile range].
  [a] *S. haemolyticus.*
  [b] *S. epidermidis.*
  [c] Initial isolations: *S. epidermidis* and *P. acnes;* final isolations: *C. striatum* and *S. epidermidis*, respectively.
  [d] *P. aeruginosa.*
  [e] Initial isolation: *S. aureus*; final isolation: *P. aeruginosa.*
  [f] Initial isolations: *S. aureus, S. aureus,* methicillin-sensitive *S. epidermidis, S. aureus;* final isolations: *S. agalactiae,* methicillin-resistant *S. epidermidis,* methicillin-resistant *S. epidermidis,* and *P. aeruginosa,* respectively.

DISCUSSION

There are few reports on CIED infections in Spain,[7–9] although the general consensus is clear on the need to completely remove these devices when they are infected.[5,6] However, this attitude is not shared by all members of our community, and a surprisingly high number of local surgeries are performed (even several in the same patient), even though the clinical success rate with this procedure is less than 20%. Therefore, it is not particularly surprising that up to 25% of systemic infections recorded in this series were due to a local infection that was treated with an inadequate approach. The reasons for this poor management could be a lack of recognition of the infection and an inadequate preparation for complete device removal. However, when correctly performed, culture sampling provides highly pertinent information; in this regard, data on the efficacy of antimicrobial therapy for local infections are particularly interesting when culture sampling is performed in favorable circumstances.

The best treatment for any local infection is complete device removal, but 50% of infections develop after a manipulation (typically, generator replacement)[10,11] of a device with years-old leads. In this situation, unless a team trained in device removal is available, appropriate and early antimicrobial therapy can resolve the problem in certain selected patients. In contrast, in systemic infections, the aim should always be complete removal because, in our experience, isolated antimicrobial therapy leads to failure or death in 96% of events. In the literature, there are examples of cures with antimicrobial therapy alone but only 1 study endorses this protocol-based alternative in patients without symptoms at the generator or visible vegetation in the transesophageal ultrasound.[12] In our series, only 4 patients fulfilling this condition were exclusively treated with antimicrobials but all showed infection relapse; consequently, our center abandoned this approach, which has even been linked to higher mortality.[13] Thus, PCT performed by experienced operators is the technique of choice and we do not believe that its rejection is justified even in patients with vegetation > 2 cm due to embolism risk, as recommended in some reports.[14,15] In this study, 3 patients with vegetation > 2 cm who underwent PCT had symptoms of pulmonary embolism after device removal but recovered quickly. This finding is in line with that of other authors who, without denying the higher number of embolizations with a higher vegetation diameter, failed to observe

that the diameter influenced the final outcome or the duration of hospital stay of the patients.[16]

Cardiac surgery should be considered a secondary option due to its high mortality rate (10% in this series), which is not surprising given the age and comorbidities of most of these patients.[17] Neither is PCT free from major, potentially fatal, complications (2 patients in this study). Even when performed by experienced operators and under optimal safety conditions,[18] there is a need for the support of cardiac surgeons well-acquainted with the technique to immediately act if major complications develop. The success of PCT largely depends on operator experience and lead age.[19] In local infections, even an incomplete removal can achieve a cure.[20] However, notably, on 3 occasions in this series, an incomplete extraction for a local infection led to a systemic infection months later. In fact, the classification of local and systemic infections based on blood culture positivity and/or detection of lead vegetation seems reasonable but the lead culture was positive in 50% of the patients with infections categorized as "local" in this series. One possible explanation for this finding is that upon PCT removal of the lead, it passes through the infected area at the generator pocket.[21] However, up to 72% of the intravascular portion of leads extracted via the femoral route from patients with infection categorized as strictly local have positive cultures.[22] Thus, the difference between local and systemic infection is sometimes unclear and should always prompt the removal of all material, regardless of infection type.

Our study found interesting results regarding the frequent performance of implantation replacement in a single stage. This approach reduced the length of hospital stay and optimized operating room use. In a survey performed in Europe, most centers implanted devices in a second stage with an interval ranging from 48 hours to 2 weeks depending on the infection type[23]; in this period, temporary pacemakers were inserted via jugular, femoral, or epicardial access. In fact, the clinical practice guidelines recommend device removal with a temporary pacing system and implantation of the new definitive system if the blood cultures are negative at 72 hours.[5,6] However, the value of this "expert recommendation" for local infections has recently been questioned, with Mountantonakis et al.[24] showing that replacement in a 1-stage intervention is not associated with a higher incidence of reinfections. In systemic infections, the reluctance to perform the replacement at the same time as the removal is even greater because it is assumed that replacement in the same intervention could contaminate the new system with the old. However, antimicrobial therapy strongly affects the adhesion of microorganisms to abiotic materials, even at suboptimal concentrations, as shown in *in vitro* studies[25] and experimental models.[26] Thus, there is no convincing reason to believe that there is a higher risk of infection of the new device in a patient receiving appropriate antimicrobial therapy and with negative blood cultures who undergoes complete removal of the infected material. This has been shown in other implants[27] and, in fact, in our series, there was no association between 1-stage replacement and a higher reinfection rate. In fact, when these procedures were split into 2 stages, there was a higher rate of infection of the new device by microorganisms resistant to the administered therapy. Long-term antimicrobial therapy might favor greater skin colonization by species naturally insensitive to the antibiotic. Other authors[21,28] also believe that the time to replacement should be reduced when blood cultures are negative.

Limitations

Our work has some limitations: *a)* this study was performed in a referral center and there may have been an excessive number of local septic surgery failures because most patients referred to us had already undergone this failed approach, which means that the data fail to reflect its real efficacy; however, the analysis was repeated with patients from our center alone (data not shown) and the results were identical; *b)* because a marked percentage of patients were referred from other centers, the positive results of the microbiological studies shown here might be even lower than the actual figures, given that in many cases the cultures were not correctly obtained in the original hospital and the patients were already undergoing antimicrobial therapy, greatly complicating the identification of the causative agent; similarly, because a transesophageal echocardiographic study was not performed in all patients with systemic infections, the number of vegetations might actually be higher than that reported here; however, we do not believe that this would markedly affect the fundamental crux of the study, which is analysis of the various therapeutic approaches; and *c)* replacement in 1 or 2 stages was not random, with a greater number of defibrillator and resynchronization implants in the 2-stage replacement group; due to their greater size and the increased implantation difficulty, the surgical procedure is longer and favors a greater number of infections. However, this does not invalidate the conclusion that the 1-stage replacement is equally as safe and avoids the inconvenience of the "bridge interval" in pacemaker-dependent patients (bedridden and long-term hospitalized).

CONCLUSIONS

Although CIED infections are an emerging problem, they are sometimes poorly recognized and treated in Spain. However, PCT in experienced hands can achieve satisfactory results and largely avoid the need for cardiac surgery. One-stage replacement does not appear to be inferior to 2-stage replacement.

CONFLICTS OF INTEREST

None declared.

WHAT IS KNOWN ABOUT THE TOPIC?

– Although CIED infections are an emerging problem, they are not always adequately diagnosed.
– Despite the existence of guidelines and recommendations on their treatment, there are serious doubts about some aspects of the indicated treatment (duration, administration route, efficacy of percutaneous removal) and the time of replacement.

WHAT DOES THIS STUDY ADD?

– Few studies have been published on the topic in Spain.
– Our work comprises an extensive series collected from a single center and with a uniform methodology.
– The article details the microbial etiology and the yield of the diagnostic techniques, analyzes the distinct efficacies of the diverse therapeutic procedures available, and addresses the problem of device replacement.
– Our results robustly support the use of PCT and 1-stage device replacement.

ACKNOWLEDGMENTS

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.rec.2016.09.031.

REFERENCES

1. Birnie D, Williams K, Guo A, et al. Reasons for escalating pacemaker implants. *Am J Cardiol.* 2006;98:93–97.
2. Goldberger Z, Lampert R. Implantable cardioverter-defibrillators: expanding indications and technologies. *JAMA.* 2006;295:809–818.
3. Zhan C, Baine WB, Sedrakyan A, et al. Cardiac device implantation in the United States from 1997 through 2004: a population-based analysis. *J Gen Intern Med.* 2008;23(Suppl 1):13–19.
4. Voigt A, Shalaby A, Saba S. Continued rise in rates of cardiovascular implantable electronic device infections in the United States: temporal trends and causative insights. *Pacing Clin Electrophysiol.* 2010;33:414–419.
5. Baddour LM, Epstein AE, Erickson CC, et al. Update on cardiovascular implantable electronic device infections and their management: a scientific statement from the American Heart Association. *Circulation.* 2010;121:458–477.
6. Sandoe JA, Barlow G, Chambers JB, et al. Guidelines for the diagnosis, prevention and management of implantable cardiac electronic device infection. Guidelines for the diagnosis, prevention and management of implantable cardiac electronic device infection. Report of a joint Working Party project on behalf of the British Society for Antimicrobial Chemotherapy (BSAC, host organization), British Heart Rhythm Society (BHRS), British Cardiovascular Society (BCS), British Heart Valve Society (BHVS) and British Society for Echocardiography (BSE). *J Antimicrob Chemother.* 2015;70:325–359.
7. Mosquera VX, Pérez-Álvarez L, Ricoy-Martínez E, et al. Experiencia inicial con la extracción de electrodos de marcapasos y desfibrilador asistida con láser excimer. *Rev Esp Cardiol.* 2011;64:824–827.
8. Centella T, Oliva E, García-Andrade I, et al. Extracción de electrodos de marcapasos y desfibrilador mediante técnicas percutáneas. *Rev Esp Cardiol.* 2007;60:607–615.
9. Del Río A, Anguera I, Miró JM, et al. Hospital Clínic Endocarditis Study Group.-Surgical treatment of pacemaker and defibrillator lead endocarditis: the impact of electrode lead extraction on outcome. *Chest.* 2003;124:1451–1459.
10. Nery PB, Fernandes R, Nair GM, et al. Device-related infection among patients with pacemakers and implantable defibrillators: incidence, risk factors, and consequences. *J Cardiovasc Electrophysiol.* 2010;21:786–790.
11. Sohail MR, Uslan DZ, Khan AH, et al. Risk factor analysis of permanent pacemaker infection. *Clin Infect Dis.* 2007;45:166–173.
12. Dumont E, Camus C, Victor F, et al. Suspected pacemaker or defibrillator transvenous lead infection. Prospective assessment of a TEE-guided therapeutic strategy. *Eur Heart J.* 2003;24:1779–1787.
13. Le KY, Sohail MR, Friedman PA, et al. Mayo Cardiovascular Infections Study Group. Impact of timing of device removal on mortality in patients with cardiovascular implantable electronic device infections. *Heart Rhythm.* 2011;8:1678–1688.
14. Grammes JA, Schulze CM, Al-Bataineh M, et al. Percutaneous pacemaker and implantable cardioverter-defibrillator lead extraction in 100 patients with intra-cardiac vegetations defined by transesophageal echocardiogram. *J Am Coll Cardiol.* 2010;55:886–894.
15. Smith MC, Love CJ. Extraction of transvenous pacing and ICD leads. *Pacing Clin Electrophysiol.* 2008;31:736–752.
16. Meier-Ewert HK, Gray ME, John RM. Endocardial pacemaker or defibrillator leads with infected vegetations: a single-center experience and consequences of transvenous extraction. *Am Heart J.* 2003;146:339–344.
17. Rusanov A, Spotnitz HM. A 15-year experience with permanent pacemaker and defibrillator lead and patch extractions. *Ann Thorac Surg.* 2010;89:44–50.
18. Wilkoff BL, Love CJ, Byrd CL, et al. Heart Rhythm Society; American Heart Association.Transvenous lead extraction: Heart Rhythm Society expert consensus on facilities, training, indications, and patient management: this document was endorsed by the American Heart Association (AHA). *Heart Rhythm.* 2009;6:1085–1104.
19. Arujuna A, Williams S, Whittaker J, et al. Trends, indications and outcomes of cardiac implantable device system extraction: a single UK centre experience over the last decade. *Int J Clin Pract.* 2012;66:218–225.
20. Margey R, McCann H, Blake G, et al. Contemporary management of and outcomes from cardiac device related infections. *Europace.* 2010;12:64–70.
21. Sohail MR, Uslan DZ, Khan AH, et al. Management and outcome of permanent pacemaker and implantable cardioverter-defibrillator infections. *J Am Coll Cardiol.* 2007;49:1851–1859.
22. Klug D, Wallet F, Lacroix D, et al. Local symptoms at the site of pacemaker implantation indicate latent systemic infection. *Heart.* 2004;90:882–886.
23. Bongiorni MG, Blomström-Lundqvist C, Kennergren C, et al. Scientific Initiative Committee, European Heart Rhythm Association.Current practice in transvenous lead extraction: a European Heart Rhythm Association EP Network Survey. *Europace.* 2012;14:783–786.
24. Mountantonakis SE, Tschabrunn CM, Deyell MW, et al. Same-day contralateral implantation of a permanent device after lead extraction for isolated pocket infection. *Europace.* 2014;16:252–257.
25. Proctor RA. The staphylococcal fibronectin receptor: evidence for its importance in invasive infections. *Rev Infect Dis.* 1987;9(Suppl 4):335–340.
26. Tshefu K, Zimmerli W, Waldvogel FA. Short-term administration of rifampin in the prevention or eradication of infection due to foreign bodies. *Rev Infect Dis.* 1983;5(Suppl 3):474–480.
27. Balagué C, Pérez J, Rinaudo M, et al. Inhibition of the adhesion to catheters of uropathogenic Escherichia coli by sub-inhibitory concentrations of cefotaxime. *Eur J Obstet Gynecol Reprod Biol.* 2011;155:150–156.
28. Chua JD, Wilkoff BL, Lee I, et al. Diagnosis and management of infections involving implantable electrophysiologic cardiac devices. *Ann Intern Med.* 2000;133:604–608.