Reimplantation and Repeat Infection After Cardiac-Implantable Electronic Device Infections
Experience From the MEDIC (Multicenter Electrophysiologic Device Infection Cohort) Database

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Background—Infection is a serious complication of cardiovascular-implantable electronic device implantation and necessitates removal of all hardware for optimal treatment. Strategies for reimplanting hardware after infection vary widely and have not previously been analyzed using a large, multicenter study.

Methods and Results—The MEDIC (Multicenter Electrophysiologic Device Infection Cohort) prospectively enrolled subjects with cardiovascular-implantable electronic device infections at multiple institutions in the United States and abroad between 2009 and 2012. Reimplantation strategies were evaluated overall, and every patient who relapsed within 6 months was individually examined for clinical information that could help explain the negative outcome. Overall, 434 patients with cardiovascular-implantable electronic device infections were prospectively enrolled at participating centers. During the initial course of therapy, complete device removal was done in 381 patients (87.8%), and 220 of them (57.7%) were ultimately reimplanted with new devices. Overall, the median time between removal and reimplantation was 10 days, with an interquartile range of 6 to 19 days. Eleven of the 434 patients had another infection within 6 months, but only 4 of them were managed with cardiovascular-implantable electronic device removal and reimplantation during the initial infection. Thus, the repeat infection rate was low (1.8%) in those who were reimplanted. Patients who retained original hardware had a 11.3% repeat infection rate.

Conclusions—Our study findings confirm that a broad range of reimplant strategies are used in clinical practice. They suggest that it is safe to reimplant cardiac devices after extraction of previously infected hardware and that the risk of a second infection is low, regardless of reimplant timing. (Circ Arrhythm Electrophysiol. 2017;10:e004822. DOI: 10.1161/CIRCEP.116.004822.)

Key Words: cardiovascular infection • device infection • electrophysiology • lead extraction • lead management

Cardiovascular-implantable electronic device (CIED) infections constitute a major burden for patients and providers. They are associated with severe morbidity and mortality, high costs of treatment, and long hospital stays.¹⁻³ There is growing recognition of the impact and incidence of these infections because many large prospective studies have helped characterize them and inform guidelines for their management. A central pillar of effective treatment is complete device removal. Extraction of all hardware is now a class I recommendation in all cases of pocket infection and endocarditis, regardless of whether there is definite evidence of device involvement.⁴

When considering device reimplantation after infections, there is less evidence underpinning management strategies. An ideal reimplant strategy would minimize the number of procedures and the amount of discomfort for the patient.

Received November 6, 2016; accepted February 3, 2017.

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Circ Arrhythm Electrophysiol is available at http://circep.ahajournals.org

DOI: 10.1161/CIRCEP.116.004822
without raising the risk of reinfection. The 2010 Heart Rhythm Society expert consensus on transvenous lead extraction suggests that all patients should have negative blood cultures for at least 72 hours before reimplantation. Operators are encouraged to extend that interval to at least 14 days when there is evidence of valvular vegetations. However, these recommendations carry an evidence level of C, meaning they reflect the consensus opinion of experts, case studies, or standard of care. These are based largely on a single retrospective study of 127 patients. For that reason, approaches vary considerably in clinical practice. CIEDs are reimplanted anywhere from minutes to months after extraction using a wide variety of temporary pacing methods. Data are lacking on the relative merits of these approaches. The aim of this study was to determine the risk of repeat infections after CIED reimplantation by analyzing outcomes from a multicenter prospective registry.

Methods

MEDIC (Multicenter Electrophysiologic Device Infection Cohort) is a prospective registry of CIED infections consisting of patients from 10 institutions in the United States, Spain, and Germany. Subjects were enrolled between January 1, 2009, and December 31, 2012, and followed for a period of 6 months. Information in the registry includes demographic, clinical, laboratory, and outcome data. At each participating site, the institutional review board approved the study protocol, and participants provided valid consent.

Study Protocol

On admission and enrollment, patients in this database had multiple blood and pocket cultures. All patients received a transthoracic echocardiogram to assess for vegetations, and many also received a transesophageal echocardiogram. In the vast majority of cases, percutaneous or surgical device removal was attempted. However, individual decisions regarding device extraction and reimplantation were left to treating physicians. As a result, the timing of these procedures varied considerably. Any extracted hardware was analyzed for bacteriology, and patients received antibiotic therapy in accordance with published guidelines.

Definitions

Only patients with CIED infections were included in the MEDIC database. Device infection was defined as inflammatory changes at the generator pocket with or without systemic manifestations. Local inflammatory markers included erythema, warmth, purulent drainage, or skin erosion. Systemic manifestations included fever, positive blood cultures, and intracardiac vegetations. Infective endocarditis (IE) was defined by the modified Duke Criteria. A definitive IE diagnosis required ≥2 positive blood cultures and the visibility of a vegetation on valves or device leads in at least 2 echocardiographic planes. IE was also diagnosed in subjects with negative blood cultures if there was evidence of both a vegetation on echocardiography and clinical manifestations of a pocket infection.

Classification of device removal or maintenance was informed by the Heart Rhythm Society 2010 expert consensus on lead extraction. Patients with more than a minimum amount of hardware remaining after attempted removal were classified with those in whom no attempt was made. Patients with residual lead material after extraction were those who achieved clinical success, meaning that remaining material was limited to lead tips or small parts of the lead that are judged to not increase the risk of perforation, embolic events, or other undesired outcomes.

Successful treatment was defined as completion of prescribed antibiotic course in the absence of clinical evidence of an infection as reflected by erythema, warmth, purulence, erosion, tenderness, fever, or positive cultures. After 6 months, patients were classified as having 1 of the 4 outcomes: (1) successful treatment without evidence of repeat infection, (2) chronic antibiotic therapy without evidence of repeat infection, (3) evidence of repeat infection, and (4) mortality.

With CIED infections, relapse refers specifically to a repeated infection with the same organism. In this cohort, bacteriology was assessed during the initial infection, but was not available after

WHAT IS KNOWN

- In the setting of cardiac implantable electronic device infections, a wide range of extraction, temporary pacing, and reimplantation strategies are used in clinical practice.

WHAT THE STUDY ADDS

- In a large, multicenter, prospective study, repeat infection rates were low for patients who had new devices implanted shortly after extraction of infected hardware.
- Patients with device infections who did not have all hardware removed were not likely to remain alive and infection free at 6 months.

Fig. 1. Overview of lead management strategies after initial infection.
discharge or during follow-up. Consequently, we were unable to distinguish true relapses from secondary infections caused by different organisms. The category of repeat infection applies to patients who experienced a second infection and also to those who failed to recover from the original infection.

Statistical Analysis
The statistics used in this study were descriptive. Because of the highly nonrandom application of various reimplantation strategies and, thus, a large number of confounding variables, inferential statistics and hypothesis testing were not performed. Analyses were performed using JMP (SAS Institute Inc, Cary, NC). Categorical variables are presented as percentages. Continuous variables are presented as mean (±standard deviation) or median (interquartile range [IQR]).

Results
Frequency of Reimplantation
Overall, 434 patients presented to participating centers with device infections during the study period. Overall, rates of extraction and reimplantation are summarized in Figure 1. During the course of therapy, device removal was completed in 381 patients (87.8%), although some residual material was left behind in 23 of those cases. In the 53 patients (12.2%) who did not undergo device removal, the physician justifications varied (Figure 2). The most common factor was that the procedure was not felt necessary/not considered, followed by risk considered too high. Among the 381 patients who had their devices removed, 220 (57.7%) were ultimately reimplanted with a new one. Demographics and infection characteristics for each of the above groups are summarized in Table 1. They show high rates of comorbid conditions in all groups, but noticeably lower rates of moderate and severe renal disease in patients who were eventually reimplanted.

Timing of Reimplantation
The timing of reimplantation procedures varied considerably across the study population. A graphical representation can be found in Figure 3. The median time was 10 days, with an IQR of 6 to 19 days. Twenty-three patients were reimplanted on the same day that their original devices were removed, 220 (57.7%) were ultimately reimplanted with a new one. Among the 381 patients who had their devices removed, 220 (57.7%) were ultimately reimplanted with a new one. Demographics and infection characteristics for each of the above groups are summarized in Table 1. They show high rates of comorbid conditions in all groups, but noticeably lower rates of moderate and severe renal disease in patients who were eventually reimplanted.

As suggested by existing guidelines, patients were treated differently when they had confirmed endocarditis. Patients without IE were reimplanted after a median of 8 days (IQR, 5–14), and those with IE, both lead and valvular, were...
reimplanted after a median of 13 days (IQR, 7–22). Positive blood cultures, on their own, did not seem to have as much of an influence on the timing. Even patients without any positive blood cultures had a median of 8 days between extraction and reimplantation (IQR, 4–14). Time to reimplant was also similar for different infective organisms. Median intervals for methicillin-resistant \textit{Staphylococcus aureus}, methicillin-sensitive \textit{S. aureus}, and coagulase-negative \textit{Staphylococcus} were 11.5, 11, and 10 days, respectively.

Six-Month Outcomes
Table 2 shows the outcomes for patients according to device management strategy. Those patients whose therapy did not include device removal had the worst outcomes. At the end of 6 months, 26.4% patients were deceased, 11.3% had repeat infections, and 28.3% were on chronic antibiotic therapy. Only 34.0% of patients remained infection free without chronic suppression. Patients who were treated with device removal had superior outcomes. Regardless of the reimplantation window, between 70% and 86% of patients remained alive and infection free without the need for chronic antibiotics.

Repeat Infection
Eleven (2.5%) of the 434 patients in the registry experienced a second CIED infection or relapse within 6 months. Table 3 contains detailed information about their initial infections. Similar information was not collected during repeat episodes. Six were treated with antibiotics alone and not device removal initially. The other 5 had complete device removal, with 4 being eventually reimplanted. One patient was described as a repeat infection, despite not being reimplanted because his prosthetic aortic valve became infected during the follow-up period. Of the 4 patients with second infections that were initially treated with extraction and reimplantation (hereafter referred to as patients A–D), a variety of management strategies were used.

Patient A was a 77-year-old male with a 7-year-old biventricular implantable cardioverter-defibrillator. His history was notable for coronary artery disease, myocardial infarction, a vascular graft, mild renal disease, and anticoagulation for a prosthetic heart valve. He was enrolled in the study after presenting with a fever, chills, sepsis, and numerous signs of a pocket infection. During the initial infection, 6 blood cultures were positive for methicillin-sensitive \textit{S. aureus}, but no vegetations were detected. His device was not immediately removed. Instead, he was placed on 28 days of cefazolin. One month after the conclusion of antibiotic therapy, he was readmitted for laser lead extraction and same-day contralateral placement of a new device. The extraction was a procedural success, but bleeding from the pocket site was noted. Five months after placement of the new device, the patient was determined to have a second infection. Information about bacteriology and device management were not collected during the second episode.

Patient B was a 76-year-old male with cerebrovascular disease, dementia, history of malignancy, and severe liver disease who underwent complete device removal 3 days after presenting with fever, chills, sepsis, and pocket inflammation. No vegetations were seen on echocardiography, but 6 blood cultures were positive for methicillin-sensitive \textit{S. aureus}. Laser lead extraction was uncomplicated, and contralateral reimplantation occurred after 5 days of temporary pacing. In all, daptomycin therapy lasted for 28 days. Three months after the conclusion of therapy, the patient was readmitted for another CIED infection, but bacteriology was not defined. He was again managed with complete device removal and antibiotics.

Patient C was a 65-year-old male with a history of malignancy who presented with chills accompanied by pain and swelling around his pacemaker generator. On the day of admission, the CIED, which had been in place for 2 years, was removed.

<table>
<thead>
<tr>
<th>Management Strategy</th>
<th>Therapy Complete—No Sign of CIED Infection</th>
<th>Chronic Suppression—No Sign of CIED Infection</th>
<th>Repeat Infection</th>
<th>Patient Deceased</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original device maintained (n=53)</td>
<td>18 (34.0)</td>
<td>15 (28.3)</td>
<td>6 (11.3)</td>
<td>14 (26.4)</td>
</tr>
<tr>
<td>Device removed, not reimplanted (n=161)</td>
<td>123 (76.4)</td>
<td>7 (4.3)</td>
<td>1 (0.6)</td>
<td>30 (18.6)</td>
</tr>
<tr>
<td>Reimplanted same day (n=23)</td>
<td>16 (69.6)</td>
<td>2 (8.7)</td>
<td>1 (4.3)</td>
<td>4 (17.4)</td>
</tr>
<tr>
<td>Reimplanted in 1–7 days (n=59)</td>
<td>51 (86.4)</td>
<td>2 (3.4)</td>
<td>2 (3.4)</td>
<td>4 (6.8)</td>
</tr>
<tr>
<td>Reimplanted in 8–14 days (n=68)</td>
<td>58 (85.3)</td>
<td>3 (4.4)</td>
<td>0 (0.0)</td>
<td>7 (10.3)</td>
</tr>
<tr>
<td>Reimplanted in 15–21 days (n=28)</td>
<td>23 (82.1)</td>
<td>1 (3.6)</td>
<td>0 (0.0)</td>
<td>4 (14.3)</td>
</tr>
<tr>
<td>Reimplanted after 21 days (n=42)</td>
<td>35 (83.3)</td>
<td>0 (0.0)</td>
<td>1 (2.4)</td>
<td>6 (14.3)</td>
</tr>
</tbody>
</table>

Values are mean±SD or n (%). CIED indicates cardiovascular-implantable electronic device.
with manual traction and a locking stylet. All blood cultures were negative, but a pocket swab was positive for coagulase-negative Staphylococcus. After 6 days of temporary pacing, the patient received contralateral placement of a new device. Antimicrobial therapy consisted of 14 days of vancomycin. One month after the conclusion of antimicrobial therapy, the patient was determined to have a repeat CIED infection. Antimicrobial therapy was reinitiated, and the generator pocket was debrided. The device was not replaced in this instance.

Patient D was a 56-year-old female with a history of severe liver disease, diabetes mellitus, and coronary artery bypass who was also on hemodialysis. She did not have a permanent catheter in place for dialysis. At the time of admission, the patient showed fever, chills, and sepsis. Echocardiography revealed a 4-mm lead-associated vegetation. Four separate blood cultures were positive for methicillin-resistant S. aureus. Vancomycin therapy was initiated. On the seventh day in the hospital, her biventricular implantable cardioverter-defibrillator was removed by laser lead extraction. After the procedure, she developed a hematoma that required surgical evacuation. In all, vancomycin therapy lasted for 28 days. On the 34th day after extraction, a new device was implanted in the contralateral chest. Four months after the conclusion of therapy, the patient experienced a repeat infection of unknown bacteriology. She was treated with antibiotics alone.

Discussion

Although the MEDIC database was not designed to directly compare reimplantation strategies, this prospective registry constitutes one of the largest known data sets that can be used to assess management of device reimplantation. The present study features a variety of reimplantation strategies in a diverse patient population that was, in most other respects, treated according to current practice guidelines. Our findings suggest that no particular time frame is especially high or low risk for reimplantation. In this study population, reimplantation soon after extraction was a relatively safe practice overall.

The majority of 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. The frequency of repeat infection in the former group is interesting in light of published guidelines that call for removal of all device components, regardless of the presenting CIED infection syndrome.

Not only were repeat infection rates low in patients who had devices removed, but those rates remained low, regardless of the timing of reimplantation. It is important to note that 4 patients with second infections after hardware removal and reimplantation had numerous risk factors, including hemodialysis, malignancy, pocket hematomas, and S. aureus bacteremia.14,15 Taken together, it is conceivable that an array of risk factors played a larger role in these cases than any decision about reimplantation.

Although it is difficult to generalize from a sample this small, these findings suggest delaying reimplantation after S. aureus bacteremia or hematoma development. On the other hand, 1 patient suffered a relapse despite waiting 34 days for reimplantation. Interestingly, this was the patient receiving hemodialysis. In a patient as complicated as this one, it is important to consider alternatives such as a subcutaneous implantable cardioverter-defibrillator or leadless pacemaker for reimplantation.16

Interestingly, none of the 23 patients who had residual material after extraction had repeat infections in the follow-up period, although 2 were deceased. As noted in the study design, these patients maintained only a minute portion of lead material. In addition, 7 of these patients were kept on chronic suppression.

Table 3. Initial Infection Characteristics and Treatment Strategies in All 11 Patients Who Had Repeat Infections Within 6 Months

<table>
<thead>
<tr>
<th>Initial Infection Data</th>
<th>Patients Who Would Later Become Reinfected (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Organism</strong></td>
<td></td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>5 (45.5)</td>
</tr>
<tr>
<td>CoNS</td>
<td>3 (27.3)</td>
</tr>
<tr>
<td>BHS-Gp B</td>
<td>1 (9.1)</td>
</tr>
<tr>
<td>Polymicrobial</td>
<td>1 (9.1)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (9.1)</td>
</tr>
<tr>
<td><strong>Infection type</strong></td>
<td></td>
</tr>
<tr>
<td>IE</td>
<td>5 (45.5)</td>
</tr>
<tr>
<td>Non-IE bacteremia</td>
<td>3 (27.3)</td>
</tr>
<tr>
<td>Pocket infection</td>
<td>3 (27.3)</td>
</tr>
<tr>
<td><strong>Vegetations</strong></td>
<td></td>
</tr>
<tr>
<td>Lead vegetation</td>
<td>4 (36.4)</td>
</tr>
<tr>
<td>Valvular vegetation</td>
<td>1 (9.1)</td>
</tr>
<tr>
<td>No vegetation</td>
<td>6 (54.5)</td>
</tr>
<tr>
<td><strong>Device management</strong></td>
<td></td>
</tr>
<tr>
<td>Not removed</td>
<td>6 (54.5)</td>
</tr>
<tr>
<td>Removed only</td>
<td>1 (9.1)</td>
</tr>
<tr>
<td>Removed and reimplanted</td>
<td>4 (36.4)</td>
</tr>
<tr>
<td>Residual material left during extraction</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td><strong>Antibiotic therapy</strong></td>
<td></td>
</tr>
<tr>
<td>Vancomycin alone</td>
<td>3 (27.3)</td>
</tr>
<tr>
<td>Daptomycin alone</td>
<td>1 (9.1)</td>
</tr>
<tr>
<td>Cefazolin alone</td>
<td>1 (9.1)</td>
</tr>
<tr>
<td>Penicillin+Rifampin</td>
<td>2 (18.2)</td>
</tr>
<tr>
<td>Penicillin+vancomycin</td>
<td>2 (18.2)</td>
</tr>
<tr>
<td>Vancomycin+aminoglycoside</td>
<td>2 (18.2)</td>
</tr>
<tr>
<td><strong>Duration of antibiotics</strong></td>
<td></td>
</tr>
<tr>
<td>6 wk</td>
<td>6 (54.5)</td>
</tr>
<tr>
<td>4 wk</td>
<td>3 (27.3)</td>
</tr>
<tr>
<td>2 wk</td>
<td>2 (18.2)</td>
</tr>
</tbody>
</table>

Values are mean±SD or n (%). BHS-GpB indicates beta-hemolytic group B streptococcus; CoNS, coagulase-negative Staphylococcus; and IE, infective endocarditis.
Prior to reimplant, all patients should be thoroughly evaluated to reassess their need for a CIED. Reasons for not reimplanting devices include improved ejection fraction, recovery of sinus function, and improvement of symptomatic bradycardia. We do not have patient-level data regarding these evaluations, but the reimplant rate in this study is similar to the rate reported in previous studies.5

Study Limitations
The 6-month follow-up period is a recognized limitation of this study as previous investigations have demonstrated that many CIED infections occur more than a year after surgical manipulation.17 Therefore, it is possible that more CIED infections occurred in this cohort after the recorded 6-month follow-up period. Second, we do not have detailed information about repeat infections, so we are unable to discern whether they were caused by the same organism (relapse) or different organisms (reinfection). Finally, all participating institutions were tertiary referral centers. As a result, there is an inherent referral bias in the study population.

Conclusions
Our study findings confirm that a broad range of reimplant strategies are used in clinical practice in patients with CIED infections. Those findings suggest that it is safe to reimplant cardiac devices after extraction of previously infected hardware and that the risk of a second infection is low, regardless of the timing of reimplantation.

Acknowledgments
We thank the study group: The MEDIC Investigators.

Sources of Funding
This study was funded, in part, by a grant from the American Heart Association (Daniel Z. Uslan, MD, Primary Investigator). Data from the Hospital Clinic of Barcelona, Spain, were supported, in part, by a grant from the Ministerio de Sanidad y Consumo, the Instituto de Salud Carlos III, and the Spanish Network for the Research in Infectious Diseases (REIPI RD06/0008), Madrid, Spain.

Disclosures
Dr Prutkin has research grants from Boston Scientific and St Jude Medical (all <US$ 1000); Dr Greenspon has consulting honoraria from Spectranetics, St Jude Medical, Medtronic; Dr Carrillo has received consulting honoraria from Boston Scientific, St Jude Medical, and Biotronik; Dr Miro has received grant from the Ministerio de Sanidad y Consumo, the Instituto de Salud Carlos III, and the Spanish Network for the Research in Infectious Diseases (REIPI RD06/0008), Madrid, Spain.

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Circ Arrhythm Electrophysiol. 2017;10:
doi: 10.1161/CIRCEP.116.004822

Circulation: Arrhythmia and Electrophysiology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3149. Online ISSN: 1941-3084

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