

New Insights into Predictors of Cardiac Implantable Electronic Device Infection

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Infection is an important complication of cardiac implantable electronic device procedures. To further study the factors associated with infection, we retrospectively reviewed the records of 3,205 consecutive patients who had undergone de novo or revision cardiac electronic device implantation at our institution from March 2011 through March 2015. We recorded all infections and specified whether they were related to the characteristics of the patient, device, or procedure. To identify predictors of infection, we performed multivariate analysis.

Device infections were identified in 85 patients (2.7%), at a mean follow-up time of 27 ± 11 months. The main predictors of device infection were use of an implantable cardioverter-defibrillator or a cardiac resynchronization therapy defibrillator device (odds ratio [OR]=16; 95% CI, 4.14–61.85; $P=0.0001$), stage 3 chronic kidney disease (OR=9.41; 95% CI, 1.77–50.04; $P=0.009$), a revision procedure (OR=8.8; 95% CI, 3.37–23.2; $P=0.0001$), or postoperative hematoma (OR=6.9; 95% CI, 1.58–30.2; $P=0.01$). We also identified 2 novel predictors of infection: a low body mass index of $<20 \text{ kg/m}^2$ (OR=1.03; 95% CI, 1.01–1.06; $P=0.005$), and use of povidone-iodine rather than chlorhexidine-alcohol for topical antisepsis (OR=4.4; 95% CI, 2.01–9.4; $P=0.03$).

We conclude that comorbidities, device characteristics, procedure types, and postoperative noninfective complications all increase the risk of device infection after a cardiac implantable electronic device procedure. (*Tex Heart Inst J* 2018;45(3):128-35)

During the past 2 decades, the use of cardiac implantable electronic devices (CIEDs) has substantially increased; these include permanent pacemakers (PMs), implantable cardioverter-defibrillators (ICDs), and cardiac resynchronization therapy (CRT) devices.¹ From 1993 to 2008, a 96% increase in CIED implantation was reported in the United States, and this was accompanied by a 210% increase in the annual incidence of device-related infections during the same period.² These infections are associated with substantial morbidity and mortality rates and financial cost.³⁻⁶ In one European study, the additional healthcare costs for a patient with a CIED infection was more than €7,000 (comparable to \$15,000 in the U.S.).⁷

Several studies on predictors of CIED infections have been limited by small sample sizes, the examination of few variables, and conflicting results.⁸⁻¹³ To determine the predictors of device-related infections, we studied a relatively large population of patients who had undergone CIED implantation.

Patients and Methods

We retrospectively reviewed all recorded cases of CIED infection at our institution from March 2011 through March 2015. All cases were identified by using our hospital's computerized database and our electrophysiology laboratory index. An institutional review committee approved the study protocol, and the patients had given informed consent.

Antibiotic Prophylaxis. We followed American Heart Association recommendations for preoperative antibiotic prophylaxis (1–2 g of cefazolin given intravenously within 1 hr before incision or, in case of cephalosporin allergy, 1 g of vancomycin given intravenously within 2 hr before incision).¹⁴ Whether patients received antibiotics postoperatively was at the treating physician's discretion. The protocol included

intravenous cefazolin or vancomycin, administered for one day after the procedure, and then oral ciprofloxacin (250–500 mg twice/d for 5–7 d).

Risk Factors. Risk factors for CIED infection were divided into 3 categories: 1) patient-related, including age, sex, body mass index (BMI); the lack of antibiotic prophylaxis, antiplatelet or anticoagulant use; and the presence of diabetes mellitus, renal failure, or heart failure; 2) device-related, including the use of a defibrillator device and implantation of ≥ 2 leads; and 3) procedure-related, including procedure duration, the use of a topical antiseptic for skin preparation, the use of a temporary pacemaker before CIED implantation, the presence of a postoperative hematoma, and the need for early reintervention or revision.

Device Infection. Device infection can present as a suture line infection or pocket infection, or as infective endocarditis. A suture line infection was defined as localized inflammation at the pocket incision, without evidence of pocket involvement.⁵ These infections are benign and do not necessitate device removal, so we included only pocket infection and infective endocarditis in our final analysis.

Pocket infection usually presents with redness, swelling, warmth, fluctuation, erosion, or purulent discharge.⁵ In contrast, infective endocarditis presents with fever, chills, malaise, and pulmonary symptoms, and it is diagnosed according to the modified Duke criteria (that is, the presence of an oscillating intracardiac mass on a valve or supporting structure, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation).¹⁵ Infection was confirmed by positive cultures from a pocket swab or tissue sample obtained at the time of device removal, from a lead tip, or from blood.⁵

Operative Terms. The initial CIED implantation was defined as a de novo procedure. Generator replacement, lead revision, and system upgrades were considered to be revision procedures. Significant hematoma was defined as hematoma needing surgical evacuation, resulting in prolonged hospitalization for at least one day, or necessitating interruption of anticoagulation therapy.¹⁶

Evaluation of Kidney Function. We used the Cockcroft–Gault equation¹⁷ to calculate the glomerular filtration rate (GFR), as follows:

$$GFR \text{ (mL/min/1.73 m}^2\text{)} = \frac{[140 - \text{age (yr)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85 \text{ if female.}$$

Stage 3 chronic kidney disease (CKD) (GFR, < 60 mL/min/1.73 m²) has been associated with a significant increase in device infection. Therefore, we used this cut-off to evaluate the role of renal insufficiency on device infection.

Statistical Analysis

Statistical analysis was performed with SPSS version 21.0 (SPSS, an IBM company). Continuous variables were presented as mean \pm SD, and categorical variables were reported as frequencies with percentages. Comparisons between patients with and without infection were performed by using the Student *t* test for continuous variables and the Pearson χ^2 or Fisher exact test for categorical variables. Risk factors for CIED infection were identified by binary logistic regression, using a stepwise approach. A 2-sided *P* value ≤ 0.05 was considered statistically significant.

Results

We enrolled 3,205 consecutive patients who underwent a CIED procedure (Table I). Their mean age was 62 ± 16 years (range, 16–92 yr), and 1,997 (62%) were male. Of the CIEDs implanted, 843 were PMs, and 2,362 were ICDs. Most (76%) of the devices had 2 or more leads. Of the total patients, 2,208 (69%) underwent a de novo procedure, and 997 (31%) underwent revision. The procedures were performed by 4 attending physicians and 6 fellows-in-training.

During a mean follow-up time of 27 ± 11 months, 85 patients (3%) met the criteria for CIED infection

TABLE I. Baseline Characteristics of the Study Population (N=3,205)

Variable	Value
Male	1,997 (62)
Diabetes mellitus	651 (20)
Stage 3 CKD	36 (1)
Device	
Permanent PM	843 (26)
ICD	2,362 (74)
Multiple-lead device	2,434 (76)
Temporary PM	624 (19)
Procedure	
De novo	2,208 (69)
Revision	997 (31)
Generator replacement	738 (23)
Lead revision	160 (5)
Upgrade	99 (3)
Antithrombotic therapy	
Anticoagulant	318 (10)
Antiplatelet	1,543 (48)
Combined	387 (12)
Antibiotic therapy	
Preoperative	3,205 (100)
Postoperative	1,663 (52)

CKD = chronic kidney disease; ICD = implantable cardioverter-defibrillator; PM = pacemaker

Data are presented as number and percentage.

(infection rate, 2.7%); infections were microbiologically confirmed in 96% of these patients. Coagulase-negative staphylococci and *Staphylococcus aureus* were responsible for 80% of the infections; streptococci and gram-negative bacilli caused the remaining 20%. Most infections (n=61, 72%) occurred within the first year after device implantation: there were 11 (13%) in the first month, 33 (39%) in months 2 through 6, and 17 (20%) in months 7 through 12. The mean time from device implantation to infection was similar for de novo and revision procedures (9.4 ± 12 vs 11 ± 9 mo; $P=0.56$). The onset of infection was earlier in patients with ICDs than in those with pacemakers, but this did not reach statistical significance (6 ± 8 vs 9 ± 8 mo; $P=0.19$).

Of the 85 patients with infection, 14 (16.5%) had a PM, and 71 (83.5%) had an ICD. Eight (9.5%) had suture line infections, 74 (87%) had pocket infections, and 3 (3.5%) had endocarditis. In comparison of infection type by device type, suture line infections occurred in 3 (27%) patients with PMs and in 5 (7%) with ICDs, and pocket infections occurred in 11 (73%) with PMs and in 63 (89%) with ICDs. The 3 (4%) patients with endocarditis had ICDs: one had a dual chamber ICD, and the other 2 had a cardiac resynchronization therapy defibrillator (CRT-D). Infection occurred after a de novo procedure in 42 (49%) patients, and after a revision procedure in 43 (51%) patients.

Patient-Related Factors. Table II compares the baseline characteristics of patients with and without CIED infection. The patients in the group with infection were more likely to have diabetes mellitus (32% vs 20%;

$P=0.008$), stage 3 CKD (9.4% vs 0.9%; $P=0.0001$), and a low BMI (25 vs 27 kg/m²; $P=0.04$). Of note, more patients with CRT devices had diabetes than did those with other types of CIEDs (34% vs 15%; $P=0.0001$).

All patients received preoperative antibiotic prophylaxis. In both groups, fewer patients received antibiotics postoperatively, but the lack of postoperative therapy was more prevalent in the group with infection ($P=0.0001$). Previous therapy with antiplatelet drugs, anticoagulant drugs, or both was not associated with an increased risk of infection (all $P>0.05$).

Device-Related Factors. The infection rate was higher in patients with ICDs than in those with PMs (3% vs 1.7%; $P=0.04$), as well as in patients with ≥ 2 leads than in those with one lead (3% vs 1.3%; $P=0.004$) (Table III).

Infection was most likely to occur in patients who had a CRT-D device (3.5%). The infection rate was 0.6% in patients with single chamber PMs and 2% in those with ICDs. In patients with dual chamber devices, the infection rate was 2.4% for PMs and 2.8% for ICDs. No infection was detected in patients with CRT pacemaker (CRT-P) devices (Fig. 1).

Procedure-Related Factors. Temporary PM use before permanent device implantation was associated with a higher rate of device infection (4.5% vs 2.2%; $P=0.001$). The type of antiseptic solution used for skin preparation also had a clear effect on the device infection rate; 5.8% of patients receiving topical antiseptics with povidone-iodine had device infection, compared

TABLE II. Patient Characteristics Compared in Terms of Device Infection

Variable	Device Infection (n=85)	No Device Infection (n=3,120)	P Value
Age (yr)	61 ± 17	62 ± 16	0.63
Male	60 (71)	1,937 (62)	0.11
LV function	0.30 ± 0.14	0.29 ± 0.14	0.42
Body mass index (kg/m ²)	25 ± 5	27 ± 5	0.04
Diabetes mellitus	27 (32)	624 (20)	0.008
Stage 3 CKD	8 (9)	28 (0.9)	0.0001
Antithrombotic therapy			
Anticoagulant	6 (7)	312 (10)	0.4
Antiplatelet	43 (50)	1,500 (48)	0.5
Combined	10 (12)	377 (12)	0.75
Antibiotic therapy			
Preoperative	85 (100)	3,120 (100)	1
Postoperative	25 (29)	1,638 (53)	0.0001

CKD = chronic kidney disease; LV = left ventricular

Data are presented as mean ± SD or as number and percentage. $P \leq 0.05$ was considered statistically significant.

TABLE III. Device and Procedural Characteristics Compared in Terms of Device Infection

Variable	Device Infection (n=85)	No Device Infection (n=3,120)	P Value
ICD or CRT-D device	71 (84)	2,291 (73)	0.037
Multiple leads	74 (87)	2,285 (73)	0.004
Procedural time (hr)	1.9 ± 0.6	1.6 ± 0.7	0.001
Topical skin antiseptics			
Povidone-iodine	49 (58)	793 (25)	0.0001
Chlorhexidine-alcohol	36 (42)	2,327 (75)	—
Temporary PM	28 (33)	596 (19)	0.001
Procedure			
De novo	42 (49)	2,166 (69)	0.0001
Revision	43 (51)	954 (31)	—
Postoperative hematoma	9 (11)	53 (1.7)	0.0001

CRT-D = cardiac resynchronization therapy defibrillator; ICD = implantable cardioverter-defibrillator; PM = pacemaker

Data are presented as number and percentage or as mean ± SD. $P \leq 0.05$ was considered statistically significant.

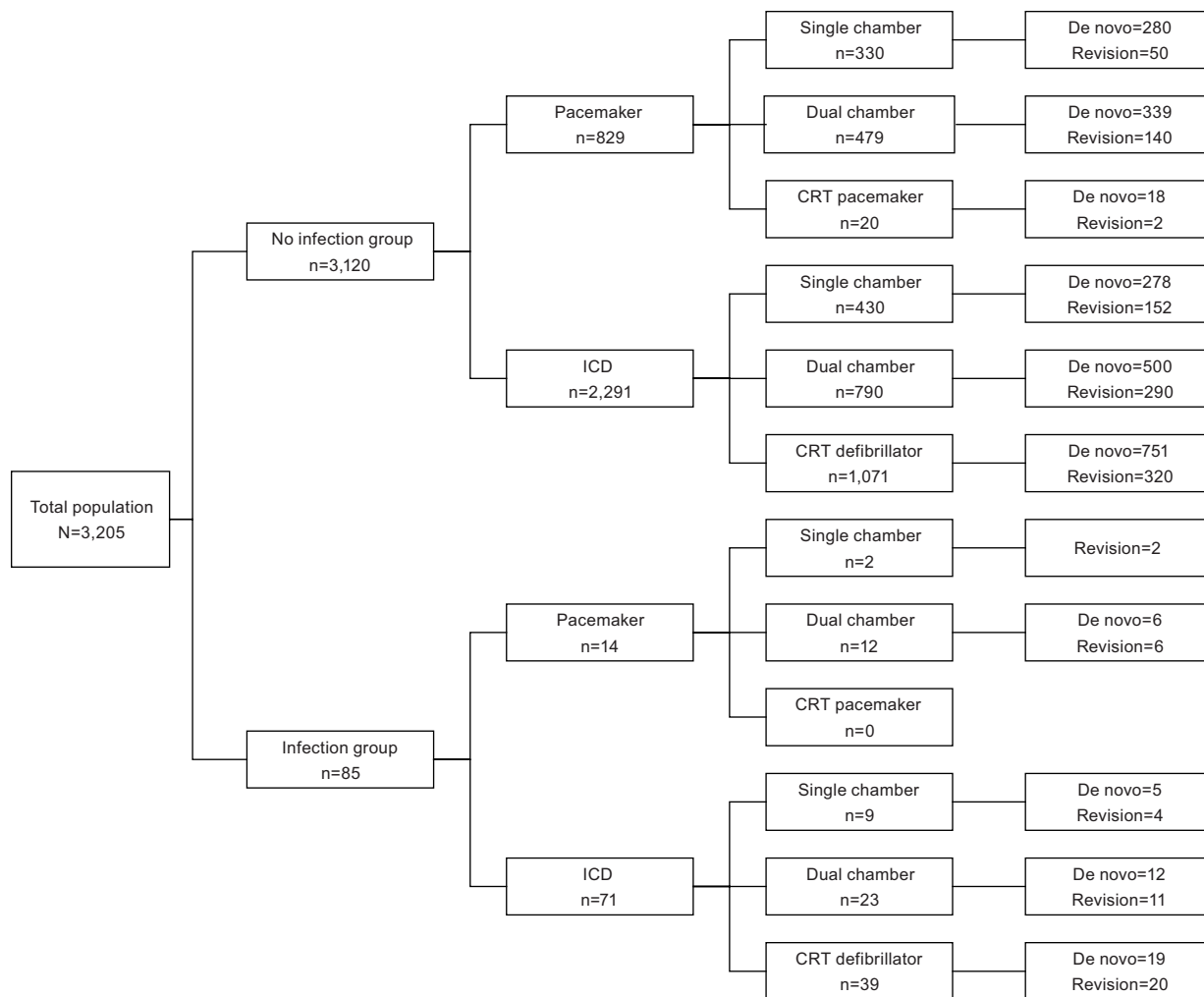


Fig. 1 Chart shows device type and procedure category in patients with and without infection.

CRT = cardiac resynchronization therapy; ICD = implantable cardioverter-defibrillator

to 1.5% of those receiving antiseptics with chlorhexidine-alcohol ($P=0.0001$). The operator had no effect on the rate of infection ($P=0.8$).

The mean procedural duration was longer in the group with infection than in the group without infection (1.9 ± 0.6 vs 1.6 ± 0.7 hr; $P=0.001$), and the risk of infection was higher after revision than after de novo procedures (4.3% vs 1.9%; $P=0.0001$). Of note, patients with CRT devices underwent significantly longer procedures than did those with non-CRT devices (mean, 2 ± 0.6 vs 1.65 ± 0.7 hr; $P=0.001$), and they underwent more revision procedures (61% vs 36%; $P=0.001$). The infection rate in patients with postoperative hematoma was also higher than in those without hematoma (14.5% vs 2.4%; $P=0.0001$) (Table III). All hematomas resolved without intervention.

Multivariate Analysis

All variables with P values <0.1 on univariate analysis were evaluated in a stepwise multivariate binary logistic

regression model. A BMI <20 kg/m² was associated with infection (sensitivity, 87%; specificity, 83%); therefore, we used 20 kg/m² as the BMI cutoff in the regression analysis. A procedural time >2 hours (sensitivity, 90%; specificity, 95%) was also a predictor of device infection. On final analysis, the following variables were found to be independent predictors of CIED infection (Table IV): low BMI (odds ratio [OR]=1.035; 95% CI, 1.01–1.06; $P=0.005$), diabetes mellitus (OR=2.29; 95% CI, 1.04–5.09; $P=0.04$), stage 3 CKD (OR=9.41; 95% CI, 1.77–50.04; $P=0.009$), temporary PM use before permanent device implantation (OR=5.7; 95% CI, 1.38–23.3; $P=0.0001$), postoperative hematoma (OR=6.9; 95% CI, 1.58–30.2; $P=0.01$), a revision procedure (OR=8.8; 95% CI, 3.37–23.2; $P=0.0001$), povidone-iodine rather than chlorhexidine-alcohol antiseptics (OR=4.4; 95% CI, 2.01–9.4; $P=0.03$), a procedural time >2 hr (OR=2.6; 95% CI, 1.5–4.8; $P=0.0001$), and implantation of an ICD or CRT-D (OR=16; 95% CI, 4.14–61.85; $P=0.0001$). Other fac-

TABLE IV. Multivariate Analysis of Infection Predictors

Variable	Odds Ratio (95% CI)	P Value
ICD or CRT-D device	16 (4.14–61.85)	0.0001
Stage 3 CKD	9.41 (1.77–50.04)	0.009
Revision procedure	8.8 (3.37–23.2)	0.0001
Postoperative hematoma	6.9 (1.58–30.2)	0.01
Temporary PM	5.7 (1.38–23.3)	0.0001
Povidone-iodine	4.4 (2.01–9.4)	0.03
Procedure >2 hr	2.6 (1.5–4.8)	0.0001
Diabetes mellitus	2.29 (1.04–5.09)	0.04
BMI <20 kg/m ²	1.03 (1.01–1.06)	0.005

BMI = body mass index; CKD = chronic kidney disease; CRT-D = cardiac resynchronization therapy defibrillator; ICD = implantable cardioverter-defibrillator; PM = pacemaker
P ≤ 0.05 was considered statistically significant.

tors significant in univariate analysis, including multiple leads and postoperative antibiotic prophylaxis, were not independent predictors in the multivariate model.

Discussion

Several important findings emerged from our study. First, our investigation clearly showed that low BMI increases the risk of device infection (to our knowledge, no other studies have confirmed this). Second, skin preparation with chlorhexidine-alcohol was more protective than that with povidone-iodine. Third, ICD or CRT-D implantation was the strongest predictor of CIED infection; PM procedures resulted in fewer cases of device infection. Fourth, patients treated with a temporary PM before undergoing a permanent CIED procedure were more than 5 times as likely to develop a device infection than those who were not. Fifth, non-infective postoperative complications, such as hematoma, and revision procedures were associated with an increased risk of device infection.

In this large single-center experience with PM, ICD, and CRT procedures, the infection rate was 2.7% at 2.25 years (annual incidence, 1.2%). The device infection rate was 1.7% in patients with PMs and 3% in those with ICDs, and patients with CRT-D devices had the highest infection rate (3.5% at 2.25 yr; annual incidence, 1.55%). Single chamber PM procedures were complicated by infection in only 0.6% of patients during the same follow-up time. No patients with CRT-P devices had infections. Only 3.5% of patients with CIED infections presented with infective endocarditis. The overall infection rate observed in our series is comparable to that reported in other studies.^{18–23} The low

incidence of endocarditis in our series may be explained by the administration of postoperative antibiotics in 29% of the patients.

Romeyer-Bouchard and colleagues¹⁸ reported an infection rate of 4.3% at 2.6 years (annual incidence, 1.7%) for patients who had received CRT devices. Similarly, a 1-year infection rate of 1.77% was reported in the Prospective Evaluation of Pacemaker Lead Endocarditis (PEOPLE) registry of patients with CRT devices.¹⁹ No CRT-P infections were reported in the Complication Rates associated with Pacemaker or Implantable Cardioverter-Defibrillator Generator REPLACEMENTS and Upgrade Procedures (REPLACE) registry²⁰; this finding, which was similar to ours, may be explained by the very small number of patients with CRT-P devices in both studies. Mounsey and colleagues²¹ reported an infection rate of 2.7% at a mean follow-up time of 19 months in patients with permanent PMs or ICDs, and Cengiz and associates²² reported a rate of 2.45% at a mean follow-up time of 35 months. Mittal and colleagues²³ reported an infection rate of 2.9% within the first 6 months in patients with ICD or CRT-D devices.

Among the patient-related risk factors for CIED infection, diabetes mellitus, renal failure, and low BMI were associated with a higher risk of infection. Although there are conflicting reports, a recent meta-analysis has identified diabetes as a risk factor for infection,²⁴ and our investigation supports this finding; the risk of infection in diabetic patients was twice that in nondiabetic patients, which may be related to the immunosuppressive effect of longstanding hyperglycemia. Therefore, blood glucose control should be an integral part of patient preparation programs, especially before elective CIED procedures. Before a procedure, a glycosylated hemoglobin level of <7% is recommended, and the morning after the procedure, the target blood glucose level is <180 mg/dL.²⁵

In our study population, moderate-to-severe renal dysfunction (GFR, <60 mL/min/1.73 m²) significantly increased the risk of infection after a CIED procedure (*P*=0.009), and similar results have been documented in previous studies.^{8,26} The heightened risk of infection is related to uremia-induced immunodeficiency, bacteremia due to repeated intravenous access, associated comorbidities, and elevated risks of bleeding and pocket hematoma.

A low BMI, which is associated with a thin subcutaneous fat layer, may predispose patients to skin erosion and secondary pocket infections. In addition, the higher incidence of post-CIED hematoma in patients with a low BMI may explain the association between low BMI and infection.²⁷

Among the device-related factors, implantation of an ICD or CRT-D was the strongest predictor of CIED infection (OR=16; 95% CI, 4.14–61.85; *P*=0.0001). The higher infection rate associated with ICDs, espe-

cially CRT-Ds, is most likely related to longer procedural times, the presence of multiple leads, the higher incidence of early reintervention for left ventricular lead complications, and the higher incidence of associated comorbidities. A larger generator size may also predispose the patient to skin necrosis and subsequent pocket infection. Nery and colleagues²⁸ monitored 2,417 patients who underwent CIED procedures and identified CRT device and generator replacement as independent predictors of infection. Similarly, Margey and associates¹¹ reported implantation of a biventricular device as an independent predictor of infection in a study of 3,105 patients (OR=7.57; 95% CI, 2.4–23.7; $P=0.0001$), and Palmisano and colleagues' retrospective analysis of 2,671 patients²⁹ showed that CRT device implantation was an independent predictor of infection (OR=28.54; 95% CI, 3.49–233.07; $P=0.002$) during a median follow-up time of 27 months.

In our evaluation of procedure-related factors, the presence of a transvenous temporary PM at the time of permanent device implantation increased the risk of device infection by more than 5-fold. This finding agrees with those in previous studies.^{30–32} Use of temporary PMs may increase the risk of bacteremia and of a secondary CIED infection. In addition, these devices are usually implanted in an urgent situation, which prevents appropriate antibiotic administration. Therefore, a temporary PM should be implanted only when there are no viable alternatives, and it should be removed as soon as possible to reduce the risk of infection.

The current study also shows that preoperative skin cleansing with chlorhexidine-alcohol is more protective against CIED infection than is povidone-iodine. Previous investigators^{33,34} have reported this result in clean-contaminated surgeries—such as colorectal, biliary, and gynecologic operations—and in intravascular catheter procedures. However, 2 other studies^{35,36} revealed no advantages of one antibiotic over the other in preventing CIED infection. Our investigation is, to our knowledge, the first to show that topical antisepsis with povidone-iodine is an independent predictor of infection in patients undergoing CIED procedures.

Revision procedures, including generator replacements, lead revisions, and system upgrades, were associated with an 8.8-fold greater risk of infection. The risk was especially high in patients who needed early reintervention for lead malfunctions or who underwent system upgrades. It has been suggested that this risk is related to bacterial contamination of the avascular capsule that forms around the generator, which may hinder the diffusion of systemic antibiotics and inflammatory cells to the device pocket site.^{37–39} This finding is particularly relevant in regard to generator or lead advisories and recall notices. Before a device is replaced, the benefits and risks of device and accessory replacement—including the risk of death due to device failure, the rate of device

failure, and the risk of procedure-related death—should be carefully considered.⁴⁰

Our study, as did that of Romeyer-Bouchard and colleagues,¹⁸ showed that procedure duration is an independent predictor of infection, which is especially relevant in patients who are candidates for CRT device implantation. Improvements in left ventricular lead design, delivery systems, and over-the-wire technology may substantially shorten procedure time and decrease the likelihood of infection.

Investigators have frequently correlated postoperative hematoma with CIED infection.¹⁶ We confirmed this finding in our study: the risk of infection increased nearly 7-fold in patients who had a substantial hematoma. Similarly, in the BRUISE CONTROL INFECTION study (Bridge or Continue Coumadin for Device Surgery Randomized Controlled Trial Extended Follow-Up for Infection), Essebag and colleagues¹⁶ found that hematoma increased the risk of infection 7.7-fold by mechanisms including tissue necrosis due to compressive effects of a blood clot in the suture line, breaches in wound healing, contamination caused by wound tension from a hematoma, and the presence of a fertile environment for microorganism colonization. Consequently, to reduce the risk of hematoma in patients undergoing CIED procedures, bleeding sites should be meticulously cauterized to ensure adequate hemostasis; antiplatelet and anticoagulation therapy should be interrupted before the procedure when feasible; and pressure dressings should be applied for the first 12 to 24 hours after the procedure.

Study Limitations

The limitations of our study are those of a retrospective analysis, including selection bias and missing data. To reduce selection bias, we used a standardized definition of device infection, a similar implantation strategy, and the same anticoagulation and antibiotic protocols. Our study was also limited because it included patients from a single center. However, the infection rate and pattern among our patients were like those seen in large patient registries, such as PEOPLE and REPLACE.

Conclusion

We identified several predictors of device infection in a relatively large series of patients who underwent CIED procedures and found that most infections are related to the device characteristics, the procedure type, and the postoperative noninfective complications. Taking appropriate interventional measures for modifiable factors may dramatically reduce device-related infection; these measures include optimizing blood sugar level and renal function before a procedure, preoperative skin cleansing with chlorhexidine-alcohol, shortening the procedure time, avoiding unnecessary temporary PM implanta-

tions, appropriately fixing leads, and establishing blood hemostasis during the procedure.

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