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Use of an Antibacterial Envelope is Associated with Reduced Cardiac Implantable Electronic Device Infections in High-Risk Patients

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Abstract

Introduction—The incidence of cardiac implantable electronic device (CIED) infections has risen rapidly since 2004. A commercially available minocycline and rifampin impregnated antibacterial envelope has been associated with a low CIED infection rate. We performed a retrospective cohort study analyzing CIED infection rates in patients receiving an antibacterial envelope.

Methods—Prospectively applied criteria for use of the antibacterial envelope included 2 of the following: diabetes, renal insufficiency, anticoagulation, chronic corticosteroid use, fever or leukocytosis at the time of implantation, prior CIED infection, 3 leads (cardiac resynchronization therapy or abandoned leads), pacemaker dependence, or early pocket reentry. CIED infection rate was compared to a cohort of patients with matched risk factors and a CIED implanted prior to use of the antibacterial envelope.

Results—A total of 260 antibacterial envelopes were implanted from November 1, 2009 to April 30, 2012. The mean number of CIED infection risk factors was 2.8 ± 1.2 . The control cohort (N = 639) was matched for mean number of CIED infection risk factors (2.8 ± 1.2), though individual risk factors differed. After a minimum of 90 days of follow-up, there was one CIED infection among patients who received an antibacterial envelope (0.4%), compared to 19 (3%) in controls (odds ratio [95% confidence interval] 0.13 [0.02–0.95], $P = 0.04$). This difference persisted after adjustment for covariates (0.09 [0.01–0.73], $P = 0.02$) and propensity score matching (0.11 [0.01–0.85], $P = 0.04$).

Conclusions—In patients prospectively identified at high risk for CIED infection, use of a commercially available antibacterial envelope was associated with a marked reduction in CIED infections when compared to a matched control cohort.

Keywords

CRT; new technology; pacing

Introduction

The number of cardiac implantable electronic devices (CIED) implanted annually in the United States has grown steadily over the past two decades, largely due to expanding indications for implantable cardioverter-defibrillators (ICDs), cardiac resynchronization (CRT) for patients with heart failure, and permanent pacing in our aging population.¹⁻³ The increasing incidence of CIED infections has outpaced the number of new devices implanted.^{4,5} Various patient-specific, procedural, and health care delivery-related risk factors for CIED infections have been proposed.^{2,6-12} In essence, the disproportional increase in CIED infections is likely due to implantation in younger patients with multiple comorbidities, who subsequently require serial device generator changes and lead revisions. Recent research demonstrates the significant cost burden and mortality associated with CIED infections, particularly when associated with bacterial endocarditis.^{1,4,13,14}

Various strategies for avoiding CIED infections have been proposed.² A novel strategy employs the use of the AIGISRx® minocycline and rifampin-eluting antibacterial envelope (TyRX Inc., Monmouth Junction, NJ, USA) at the time of new CIED implantation, generator change, or revision. Utilization of this antibacterial envelope was associated with a low risk of CIED infections in a preclinical study¹⁵ and in the multicenter, retrospective COMMAND study.¹⁶ We report our institutional experience using the AIGISRx® envelope in patients prospectively identified at high risk for CIED infection, and compare the incidence of CIED infections with a matched high-risk control cohort.

Methods

Study Participants

Patients aged ≥ 18 who had an AIGISRx® envelope implanted at Vanderbilt Heart and Vascular Institute (VHVI) based on our institutional guidelines for use (see below) between November 1, 2009 and April 30, 2012 were included in the study. The control population included adult patients with ≥ 2 risk factors for CIED infection who had a device implanted in the 18 months prior to use of the AIGISRx® envelope at our institution. Controls were derived from the Vanderbilt University Medical Center StarPanel Synthetic Derivative, a deidentified, time-shifted, and previously validated clone of the electronic medical record.^{17,18} The study protocol was reviewed by our institution's internal review board and found to be exempt from requiring informed consent.

Definitions

Patients were prospectively selected for AIGISRx® envelope implantation if two of the following previously described risk factors were present: diabetes (history of diabetes or use of glycemic control agents), renal insufficiency (creatinine ≥ 1.5 mg/dL 24 hours prior to implantation), systemic anticoagulation (treatment-dose heparin or warfarin), chronic daily corticosteroid use, fever ≥ 100.5 F or leukocytosis ≥ 11,000 WBC/ μ L 24 hours prior to implantation, prior documented CIED infection, ≥ 3 transvenous leads (3 lead CRT systems or ≥ 1 abandoned leads), pacemaker dependence, or early pocket reentry within 2 weeks of original implantation (Table I). Each individual chart was audited retrospectively and risk factors were tabulated.

All patients in the intervention and control cohorts received periprocedural antibiotic prophylaxis infused 0–15 minutes prior to skin incision. Outpatients received 1-g intravenous cefazolin, unless penicillin allergic, in which case 1-g intravenous vancomycin was used. Due to the high prevalence of antibiotic resistance at our institution, 1-g vancomycin was used as the first line agent for inpatients.

The control population was derived by conducting a multitiered search of the Vanderbilt University Medical Center Synthetic Derivative database. Patients who had a CIED implanted in the 18 months prior to the institutional use of the AIGISRx® envelope were selected by searching for the following Current Procedural Terminology (CPT) codes: 33206, 33207, 33208, 33212, 33213, 33214, 33215, 33216, 33217, 33218, 33220, 33224, 33225, 33226, 33233, 33234, 33235, 33240, and 33249. The resulting patient records were queried for the presence of diabetes, renal insufficiency, systemic anticoagulation, chronic corticosteroid use, fever, or leukocytosis, as defined earlier. The resulting records were manually reviewed for the remaining risk factors and for the incidence of CIED infection.

CIED infection, the primary study outcome, was defined as a local or systemic infection (e.g., sepsis, bacteremia, or endocarditis) requiring systemic antibiotics and/or explantation of the CIED system. Patients and controls were followed for a minimum of 90 days after the index procedure.

Statistical Analysis

Group comparisons were made using Student's *t*-test for continuous variables or χ^2 test for categorical variables. For the primary outcome, CIED infection at a minimum of 90 days follow-up, univariate logistic regression was used to test the difference in incidence between recipients of the AIGISRx® envelope and controls. Given the large number of risk factors evaluated and to avoid overfitting, individual risk factors were not used in a multivariate logistic regression model. Rather, a propensity score for implantation of the AIGISRx® envelope, without regard for the primary study outcome, was calculated and included in multivariate logistic regression. The variables in the propensity score model included age, sex, diabetes, renal insufficiency, use of anticoagulation, chronic steroid use, 3 leads, pacemaker dependence, fever or leukocytosis at the time of implantation, generator change or device upgrade/revision, early pocket reentry, and previous CIED infection.

To further account for differences in risk factors among cases and controls, propensity score matching was performed, wherein cases and controls were matched based on similarity of propensity scores, and outliers in each treatment group without an available match were excluded from further analysis.^{19,20} Logistic regression was then used to test for the difference in CIED infections in the propensity score-matched cohort. Statistical analysis was performed using SPSS (v20, SPSS Inc., Chicago, IL, USA). Propensity score matching was performed using R (available at www.r-project.org), the plugin R Essentials for SPSS (<http://www.ibm.com/developerworks/spssdevcentral>) and a publicly available custom dialog for SPSS (<http://sourceforge.net/projects/psmspss/files>). Nominal statistical significance was taken as a two-tailed $P = 0.05$.

Results

Baseline Characteristics and Risk Factors

During the study period from November 1, 2009 to April 30, 2012, an antibacterial envelope was implanted in 260 patients. Baseline patient characteristics and CIED infection risk factors are presented in Table II. Mean patient age was 66.7 years and 70% were male. Eighty-eight percent of patients had at least two CIED infection risk factors, with a mean number of risk factors of 2.8 ± 1.2 . The most frequent risk factors included 3 leads in 62.7%, systemic anticoagulation in 59.2%, diabetes in 40.8%, and renal insufficiency in 36.5%. Eighteen percent of patients had fever or leukocytosis within 24 hours of implant.

The control cohort included 639 patients with CIED infection risk factors who underwent a CIED implantation without an antibacterial envelope from August 2007 to February 2009.

Mean age in the control cohort was 67.8 years and 63% were male (Table II). Eighty-six percent of control patients had at least two CIED infection risk factors, with a mean number of risk factors of 2.8 ± 1.2 . The most frequent risk factors were systemic anticoagulation in 67.9%, diabetes in 54.1%, and renal insufficiency in 46.3%. Twenty-eight percent had fever or leukocytosis within 24 hours of implant.

Univariate Analysis

The mean follow-up periods were 18.7 ± 7.7 months (range 3.3–32.8 months) for cases and 42.4 ± 5.2 months for controls. The primary study outcome, CIED infection after a minimum of 90 days follow-up, occurred in one patient (0.4%) who received an antibacterial envelope compared to 19 (3%) controls (Table III, odds ratio [OR; 95% confidence interval] 0.13 [0.02–0.95], $P = 0.044$). The patient who received an antibacterial envelope and suffered a CIED infection was a 77-year-old male with a history of atrial fibrillation, chronic anticoagulation, heart failure, and left bundle branch block. He had previously undergone relocation of his left-sided CRT device to the right chest to facilitate local radiation therapy for lung cancer. Forty-five days later, he presented with poor wound healing, necessitating relocation of his system to the left chest. Two months later, he developed skin erosion necessitating pocket revision. An antibacterial envelope was utilized during this procedure. He presented 1 week postoperatively with fevers, pneumonia, purulent discharge from his incision, and blood cultures positive for *Pseudomonas aeruginosa*. He was treated with systemic antibiotics and explantation of his CIED. He later underwent implantation of a new CRT system, utilizing a new antibacterial envelope, and has been followed for over 9 months with no further evidence of infection.

In the control cohort, mean time from CIED implantation until diagnosis of infection was 5.1 ± 4.1 months. Thirteen (68%) patients presented with systemic symptoms and/or signs of infection, while six (32%) presented with symptoms and/or signs localized to the device pocket. Microbiology results for patients with CIED infections are presented in Table IV. The most commonly isolated pathogens were coagulase-negative *Staphylococcus* (CoNS) isolated from three patients, *Enterococcus faecalis* in three, methicillin-resistant *Staphylococcus aureus* (MRSA) in two, and methicillin-sensitive *Staphylococcus aureus* in two. Six patients had negative cultures. Thirteen patients were treated with complete system removal in addition to parenteral antibiotics, while six were treated with antibiotics alone. During the follow-up period, four of the 19 (21%) controls with CIED infections died. Upon individual chart review of the controls that died, CIED infection was a cause of, or major contributing factor to, mortality in three of four patients.

Multivariate Analysis

Given the large number of CIED infection risk factors evaluated, and the small number of infections, particularly in AIGISRx® cases, individual risk factors were not included in a multivariate model in order to avoid overfitting. Rather, a propensity score was calculated for the variable of having had an antibacterial envelope implanted. After adjustment for the resulting propensity score with multivariate logistic regression, the difference in the primary outcome, CIED infection at >90 days, remained statistically significant (OR 0.09 [0.01–0.73], $P = 0.024$).

Propensity Score Matching

To further account for significant differences in individual CIED infection risk factors among cases and controls, propensity matching was used. This resulted in a cohort with 209 cases and 209 controls that were well matched in terms of demographics and individual CIED infection risk factors (Table V). In univariate logistic regression, there was a

statistically significant difference in CIED infections in AIGISRx® cases versus controls (1 vs 9, 0.5% vs 4.3%, OR 0.11 [0.01–0.85], $P = 0.035$, Table III).

Discussion

As the indications for and use of CIEDs have expanded over the past two decades, CIED infections have emerged as important, costly, morbid, and yet potentially preventable complications of device implantation. In our current study of patients who were prospectively selected for use of the AIGISRx® antibacterial envelope during CIED implantation based on the presence of previously identified CIED infection risk factors, we found a marked and statistically significant decrease in CIED infections at a minimum of 90 days follow-up when compared to a high-risk control population. Among 260 patients who received the antibacterial envelope, one patient (0.4%) had a documented infection, compared to 19 of 639 (3%) in the control population (OR 0.13 [0.02–0.95], $P = 0.04$). This difference persisted after adjustment for potential confounders (OR 0.09 [0.01–0.73], $P = 0.02$) and after propensity matching (OR 0.11 [0.01–0.85], $P = 0.04$).

The incidence of CIED infection among controls in our study is in keeping with contemporary studies. Lekkerkerker et al. reported an incidence of CIED infection of 2.2% in 3,410 patients in the Leiden device registry.⁹ de Bie et al. reported a 3-year incidence of infection of 2.6% in their study of ICD and CRT device recipients.¹⁴ A recent large analysis by Greenspon et al. of CIED infection trends from 1993 until 2008 showed that the overall incidence of infection was 1.61%.⁴ Notably, the annual incidence of infection increased significantly from 2004 (1.53%) to 2008 (2.41%), an increase that coincided with higher rates of diabetes and renal failure among device recipients during the same time period.

Patients and controls that did sustain a CIED infection required hospitalization, consultation with infectious disease and cardiac electrophysiology services, prolonged intravenous antibiotics, and, in the majority of cases, CIED explantation and replacement. Despite these efforts, 15% of patients died as a result of their infection.

The importance of preventing CIED infections cannot be overstated. CIED infections are associated with significant morbidity, mortality, and cost. The clinical management of CIED infections frequently includes device explantation and, if indicated, reimplantation.^{2,21,22} In an analysis of data from the National Hospital Discharge Survey, Voigt et al. found CIED infections to be associated with greater than twofold risk of in-hospital mortality.¹ de Bie et al. recently published a large, single center, retrospective study of CIED infection incidence and outcomes.¹⁴ They reported a 2.6% incidence of CIED infection at a median 30-month follow-up, with an adjusted odds ratio for mortality of 2.4 compared to patients without a device infection. In a recent analysis, the average hospital length of stay for a patient with a CIED infection was 13.8 days at a cost of \$146,000.⁴

Strategies for preventing CIED infections have been proposed.²³ These include the use of chlorhexidine-alcohol for skin preparation²⁴ and intravenous antibiotic prophylaxis⁶ prior to device implantation. In the COMMAND retrospective study, 624 patients with predefined risk factors for CIED infection underwent implantation of an AIGISRx® antibacterial envelope at the time of CIED implantation.¹⁶ During the relatively short follow-up period (mean 1.9 months), only three patients (0.5%) had a documented CIED infection. In contrast to the COMMAND study, we prospectively selected recipients for an antibacterial envelope based on the presence of CIED infection risk factors. Our study had a considerably longer follow-up period (minimum 90 days, mean 18.7 ± 7.7 months for cases and 42.4 ± 5.2 months for controls). For the first time, we report that antibacterial envelope recipients had a lower incidence of CIED infection compared to high-risk controls (0.4% vs 3%, $P = 0.04$).

Mechanisms of Action and Ease of Use of the Antibacterial Envelope

The AIGISRx® antibacterial envelope is a polypropylene mesh sleeve coated with a biopolymer that contains minocycline and rifampin, which, in combination, are highly active against CoNS and MRSA *in vitro*.¹⁶ The envelope elutes antibiotics locally into the device pocket for approximately 7–10 days. Hansen et al. evaluated the antibacterial envelope in an animal model of pocket infection.¹⁵ The investigators implanted paired pacemakers, one of which was placed in an AIGISRx® envelope, subcutaneously in adult rabbits. Each pocket was inoculated with bacterial strains, including *Staphylococcus epidermidis*, *Staphylococcus capitis*, *Escherichia coli*, and *Acinetobacter baumannii*, and after 7 days each animal was sacrificed and studied. They found no macroscopic, microscopic, or culture evidence of infection in the pockets treated with the antibacterial envelope, while the nontreated pockets invariably became infected. Systemic levels of minocycline and rifampin were undetectable.

In the COMMAND study of 624 patients who received an antibacterial envelope during CIED implantation, procedural success rate was reported to be 99.5% (621 of 624).¹⁶ Of the three failed procedures, only one (0.16% of the study cohort) was attributed to the antibacterial envelope. In our experience, there is a learning curve that applies to the use of the antibacterial envelope. However, we have found that its use does not significantly alter the duration or difficulty of CIED implants.

The AIGISRx® envelope is comprised of two flat, rectangular, polypropylene sheets that are closed on three sides with a 3-mm seam. The device comes sized for pacemakers (\$795) and ICD/CRT devices (\$895). The subcutaneous pocket must be enlarged by approximately 10–15% to accommodate the envelope. Over time, we have found that implantation is made easier by inversion of the envelope to place the seam on the inside and wetting of the envelope with saline just prior to its placement within the pocket.²³ According to the manufacturer, the envelope should not be left soaking in saline or antibacterial solution, as the antibiotic granules on the envelope will partially dissolve into the solution. Likewise, copious irrigation of the pocket with antibiotic solution after all components (including the envelope) have been inserted should be avoided. Our practice has been to insert the leads fully into the pocket, irrigate and aspirate the pocket, then wet and invert the antibacterial envelope, place the generator within the envelope, connect the leads to the device, and place the generator and envelope above the leads in the pocket. With this technique, implantation will maximize the efficacy of the antibiotic envelope and the ease of insertion.

Study Limitations

As with all retrospective, nonrandomized studies, our study is subject to confounding and selection bias. We cannot exclude that important differences, which were not accounted for in our study, exist between the cases and controls that might explain the observed difference in CIED infection incidence, especially given that controls were selected to predate the use of the antibacterial envelope at our institution. These potential confounders include, but are not limited to, improved lab practices, different operators, and different practices in postoperative care.

There were potentially important differences in the prevalence of various CIED infection risk factors between the cases and controls in our study. This was a result of how the case and control cohorts were identified: cases were consecutive patients who had an antibacterial envelope implanted, whereas controls were derived by querying the electronic medical record for patients who had a CIED procedure, had CIED risk factors, and did not have an antibacterial envelope implanted. Importantly, the association between AIGIS Rx® envelope implantation and reduced risk of CIED infection persisted after adjustment for potential confounders and after propensity matching. As with many trials involving CIEDs,

women were underrepresented in our study, and important differences in CIED infection prevention might exist between men and women (e.g., body mass index and size of vascular structures affecting venous access). Finally, our trial was performed at a single academic tertiary center, and the results might not be generalizable to a broader population of patients in different practice settings.

Conclusions

In our retrospective cohort study of patients at high risk for device infection who received an AIGISRx® antibacterial envelope at the time of CIED implantation, we found that use of the antibacterial envelope was associated with a statistically significant decrease in CIED infections when compared to a matched control cohort. Previous data have demonstrated the high cost of hospitalization with increased mortality in the setting of CIED infection, and in our study, there was a 15% (3/20) mortality rate attributable to device-related infection. Our findings of a statistically significant association between antibacterial envelope use and reduced incidence of CIED infection in high-risk patients highlight the need for a prospective, randomized trial to further evaluate this potentially important strategy for CIED infection prophylaxis.

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Table I

Previously Described Risk Factors for Cardiac Implantable Electronic Device Infections

Risk Factor	Odds Ratios	Citations
Diabetes	3.2–3.4	9,10
Renal insufficiency	4.6–6.3	8-10
Systemic anticoagulation	2.8–3.4	9,10
Chronic steroid use	13.9	7
Preimplant fever	8.7	11
Prior device infection	–	7
3 leads	5.4	7
Early pocket reentry	7–16.3	6,11
Device revision [†]	1.7–3.1	6,9,10

[†] Includes generator changes, device upgrades, lead revisions, and other revisions.

Table II**Baseline Study Characteristics**

	AIGISRx® Cases (n = 260)	Controls (n = 639)	P Value
Age (years: mean, SD)	66.7 ± 12.5	67.8 ± 13	0.24
Sex (male)	70%	63%	0.048
Individual CIED-I Risk Factors (% , n)			
3 leads	62.7% (163)	26.5% (169)	<0.001
Anticoagulant use	59.2% (154)	67.9% (434)	0.013
Diabetes	40.8% (106)	54.1% (346)	<0.001
Renal insufficiency	36.5% (95)	46.3% (296)	0.007
Pacemaker dependence	32.3% (84)	31% (198)	0.699
Fever or leukocytosis	18.1% (47)	28% (179)	0.002
Early pocket reentry	15% (39)	3% (19)	<0.001
Corticosteroid use	7.3% (19)	14.6% (93)	0.003
Generator change/revision [†]	47.3% (123)	34% (217)	<0.001
Previous CIED-I	7.7% (20)	4.1% (26)	0.025
Mean number of risk factors	2.8 (±1.2)	2.8 (±1.2)	0.63

SD = standard deviation; CIED-I = cardiac implantable electronic device infection.

[†] Includes generator changes, device upgrades, lead revisions, and other revisions.

Table III

Cardiac Implantable Electronic Device Infections among Cases and Controls

	Infections (n, %)	Unadjusted OR	P Value	Adjusted OR	P Value
Entire Cohort					
AICISRx® Cases (n = 260)	1 (0.4%)	0.13 [0.02–0.95]	0.044	0.09 [0.01–0.73]	0.024
Controls (n = 639)	19 (3%)				
Propensity Score-Matched Cohort					
AICISRx® Cases (n = 209)	1 (0.5%)	0.11 [0.01–0.85]	0.035	–	–
Controls (n = 209)	9 (4.3%)				

CIED = cardiac implantable electronic device; OR = odds ratio, followed by 95% confidence interval.

Table IV
Characteristics of Control Patients with Cardiac Implantable Electronic Device Infections

Patient No.	Time Until Presentation (Months)	Presenting Symptoms	Microbiology	Treatment	Outcome
1	14	Systemic	<i>S. viridans</i>	Extraction	Survived
2	<1	Pocket	Negative	ABX only	Survived
3	10	Systemic	CoNS	ABX only	Died
4	2	Systemic	MRSA	ABX only	Died
5	4	Systemic	<i>E. faecalis</i>	ABX only	Survived
6	1	Systemic	MSSA	Extraction	Survived
7	2	Systemic	MRSA	Extraction	Survived
8	3	Systemic	CoNS	Extraction	Died
9	1	Pocket	Negative	Extraction	Survived
10	11	Pocket	Negative	Extraction	Survived
11	5	Systemic	<i>S. bovis</i>	Extraction	Survived
12	1	Pocket	Negative	ABX only	Survived
13	1	Pocket	Negative	Extraction	Survived
14	2	Systemic	<i>E. faecalis</i>	Extraction	Survived
15	4	Systemic	CoNS	Extraction	Survived
16	9	Systemic	<i>E. faecalis</i>	ABX only	Survived
17	3	Systemic	Negative	Extraction	Survived
18	14	Systemic	<i>S. epidermidis</i>	Extraction	Died
19	8	Pocket	MSSA	Extraction	Survived

ABX = antibiotics; CoNS = coagulase-negative *Staphylococcus*; *E. faecalis* = *Enterococcus faecalis*; MRSA = methicillin-resistant *Staphylococcus aureus*; *S. bovis* = *Streptococcus bovis*; *S. epidermidis* = *Staphylococcus epidermidis*; *S. viridans* = *Streptococcus viridans*.

Table V**Baseline Study Characteristics in Propensity-Matched Patients**

	AIGISRx® Cases (n = 209)	Controls (n = 209)	P Value
Age (years: mean, SD)	67.6 ± 12.3	66.8 ± 13.4	0.55
Sex (male)	74%	70%	0.38
Individual CIED-I risk factors (% , n)			
3 leads	60.3% (126)	60.3% (126)	1
Anticoagulant use	66% (138)	63.2% (132)	0.54
Diabetes	45% (94)	47.8% (100)	0.56
Renal insufficiency	44% (92)	47.4% (99)	0.49
Pacemaker dependence	34.4% (72)	28.7% (60)	0.21
Fever or leukocytosis	19.6% (41)	23.4% (49)	0.34
Early pocket reentry	7.7% (16)	7.7% (16)	1
Corticosteroid use	9.1% (19)	9.6% (20)	1
Generator change/revision [†]	49.8% (104)	52.2% (109)	0.63
Previous CIED-I	8.1% (17)	5.7% (12)	0.34
Mean number of risk factors	2.9 (±1.2)	2.9 (±1.1)	0.97

SD = standard deviation; CIED-I = cardiac implantable electronic device infection.

[†] Includes generator changes, device upgrades, lead revisions, and other revisions.