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Original Article

Rate, Time Course, and Predictors of Implantable Cardioverter Defibrillator Infections: An Analysis From the SIMPLE Trial

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ABSTRACT

Background: The number of implantable cardioverter defibrillator (ICD) infections is increasing due to an increased number of ICD implants, higher-risk patients, and more frequent replacement procedures, which carry a higher risk of infection. Reducing the morbidity, mortality, and cost of ICD-related infections requires an understanding of the current rate of this complication and its predictors.

RÉSUMÉ

Contexte : L'incidence des cas d'infection du défibrillateur cardioverteur implantable (DCI) augmente en raison du nombre accru d'implantations, de l'emploi de ces dispositifs chez des patients exposés à un risque très élevé et de l'augmentation de la fréquence des interventions de remplacement, qui sont associées à un plus grand risque d'infections. Pour parvenir à réduire la morbidité, la mortalité et

Implantable cardioverter defibrillators (ICD) are widely used lifesaving treatments. Cardiac implantable electronic device infection occurs in approximately 1%-2% of all cases[1-6] or 4.82/1000 device-days.[7] It is a serious and potentially catastrophic consequence of these procedures.[2] Despite modern implant techniques, device infection rates are increasing[8,9] and infection is more common in patients undergoing generator replacement or having more complex procedures where the infection risk increases to 2%-3%. Recent data showed that although the implant rate increased by 12% in the United States from 2003 to 2006, the infection rate increased by 57% during the same period.[9] Early device infection is usually caused by skin pathogens that infect the device pocket and then may track along the leads with resultant intravascular sepsis. Device infection is costly as almost always managed with hospitalization and long courses of intravenous (IV) antibiotics.[3,10-12] In addition, system extraction is usually required and is associated with a risk of major complications (2.3%), including a 0.5%-1% mortality rate.[13,14] A 2008 study of 4.2 million device patients in the United States reported a cost of USD$146,000 per device system infection, and the risk of death associated with device infection was reported at 4.69%.[15] A recent Medicare cohort showed a cost per infection ranging from USD$45,006 to USD$77,397

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Ethics Statement: This research has adhered to relevant ethical guidelines.

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See page 358 for disclosure information.

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Methods: The **S**hock **Impl**ant **E**valuation Trial (SIMPLE) trial randomized 2500 ICD recipients to defibrillation testing or not. Over an average of 3.1 years, patients were seen every 6 months and examined for evidence of ICD infection, which was defined as requiring device removal and/or intravenous antibiotics.
Results: Within 24 months, 21 patients (0.8%) developed infection. Fourteen patients (67%) with infection presented within 30 days, 20 patients by 12 months, and only 1 patient beyond 12 months. Univariate analysis demonstrated that patients with primary electrical disorders (3 patients, $P = 0.009$) and those with a secondary prevention indication (13 patients, $P = 0.0009$) were more likely to develop infection. Among the 2.2% of patients who developed an ICD wound hematoma, 10.4% developed an infection. Among the 8.3% of patients requiring an ICD reintervention, 1.9% developed an infection.
Conclusions: This cohort of ICD recipients at high-volume centres have a low risk of device-related infection. However; strategies to reduce wound hematoma and the need for ICD reintervention could further reduce the rate of infection.

Méthodologie : Lors de l'essai ***S**hock **Impl**ant **E**valuation Trial* (SIMPLE), 2 500 patients ayant reçu un DCI ont été répartis aléatoirement en deux groupes, l'un subissant des tests de défibrillation et l'autre, non. Sur une période de 3,1 ans en moyenne, les patients ont été vus en consultation tous les 6 mois et examinés à la recherche de signes d'infection du DCI, définie comme étant une infection exigeant le retrait du dispositif et/ou l'administration d'antibiotiques par voie intraveineuse.
Résultats : Au total, 21 patients (0,8 %) ont présenté une infection dans les 24 mois suivant l'implantation. Quatorze patients (67 %) ont présenté une infection dans les 30 jours suivant l'intervention; à 12 mois, 20 patients avaient présenté une infection. Un seul patient a présenté une infection plus de 12 mois après l'intervention. Les résultats d'une analyse univariée ont démontré qu'une infection était plus probable chez les patients qui présentaient un trouble électrique primaire (3 patients, $p = 0{,}009$) et chez ceux qui avaient reçu un dispositif en prévention secondaire (13 patients, $p = 0{,}0009$). Parmi les patients qui présentaient un hématome après l'implantation du DCI (2,2 %), 10,4 % ont présenté une infection. Parmi les patients qui ont eu besoin d'une nouvelle intervention relative au DCI (8,3 %), 1,9 % ont présenté une infection.
Conclusions : Les patients de cette cohorte ayant reçu un DCI dans des établissements à haut volume étaient exposés à un faible risque d'infection du défibrillateur. Des stratégies visant à réduire les hématomes et la nécessité d'une nouvelle intervention sur les DCI pourraient toutefois contribuer à réduire encore plus la fréquence des infections.

associated with a 25.3% mortality rate at 1 year.[16] Recent Canadian data reported a mean cost of CAD$30,000 for extraction.[17] Importantly, mortality is increased far beyond the initial infection event.[15,18]

Multiple risk factors have been reported such as multiple leads, diabetes, renal and respiratory failure, chronic steroid use, early reintervention, hematoma,[19] fever in the preceding 24 hours, and the use of a temporary pacing lead.[20-22] A recent **P**revention of **A**rrhythmia **D**evice **I**nfection **T**rial (PADIT) risk score identified in a validated cohort 5 independent predictors of infection.[23]

Prevention of Device Infection

Current guidelines recommend that a single preoperative dose of a cephalosporin be used at the time of surgery to reduce the risk of device infection.[6,24,25] Nonetheless, a variety of additional preventive measures are often used but never been proven effective in randomized trials. These include (1) additional preoperative antibiotics; (2) use of intraoperative wound pocket irrigation (with saline or antibiotics); (3) skin barriers; and (4) postoperative antibiotics. Oral postoperative antibiotics are supported by data from other cardiac surgical site infection trials, where the pathophysiology and microbial pattern are similar.[6,8,26-28]

Methods

The **S**hock **Impl**ant **E**valuation Trial (SIMPLE) is a multicentre trial evaluating whether ICD implantation without defibrillation test (DFT) is not inferior to implantation with DFT.[29]

Patients receiving an ICD for either primary or secondary prevention, with or without cardiac resynchronization (CRT), were randomized to have DFT or no DFT at the time of the device implant. A total of 2500 patients were recruited and followed up for at least 2 years after enrollment of the last patient (mean follow-up, 3.1 years). Prespecified data collection included infection rates and related risk factors.

Infection was defined as requiring IV antibiotics, hospital admission, or device and lead removal. Minor skin infections resolved with oral antibiotics were not included in this study because no detailed data were collected. Hematomas were defined according to a previously published SIMPLE substudy.[19]

Primary electrical disorders included patients with no structural heart diseases (chanellopathies, Brugada syndrome, Long QT, cathecolaminergic ventricular tachycardia, etc.).

The aim of our study was to analyze the frequency and the clinical and operative predictors of infection from the time of implant up to 24 months after implantation. Preventive measures and risk factors such as age, complex procedures, upgrades, CRT implantation, diabetes, renal failure, hematomas, and lead dislodgments were collected.

Statistical analysis

The baseline characteristics were summarized as mean and standard deviation for normally distributed continuous

Table 1. Baseline characteristics

Variables	No infection N = 2479 (%)	Infection N = 21 (%)	*P* value
Age < 70	1697 (68.5)	18 (85.7)	0.102
Age ≥ 70	782 (31.5)	3 (14.3)	0.102
Male	2006 (80.9)	18 (85.7)	0.782
Female	473 (19.1)	3 (14.3)	0.782
BMI (kg/m^2), mean (SD)	28 (5.2)	27 (4.3)	0.575
ICD indication			
Ischemic heart disease	1609 (64.9)	11 (52.4)	0.255
Dilated cardiomyopathy	800 (32.3)	6 (28.6)	0.818
Hypertrophic cardiomyopathy	95 (3.8)	0 (0.0)	1.000
Primary electrical disease	50 (2.0)	3 (14.3)	**0.009**
Other	187 (7.5)	3 (14.3)	0.187
Medical condition			
LVEF %, mean (SD)	32 (12.6)	38 (13.3)	**0.036**
Hypertension	1572 (63.4)	6 (28.6)	**0.002**
Diabetes	734 (29.6)	3 (14.3)	0.153
Renal failure	477 (19.2)	2 9 (9.5)	0.403
Atrial fibrillation	581 (23.4)	3 (14.3)	0.441
Previous heart surgery	546 (22.0)	2 (9.5)	0.286
Chronic oral anticoagulation	527 (21.3)	4 (19.0)	1.000
ASA	1577 (63.6)	8 (38.1)	**0.002**
Thienopyridine	511 (20.6)	4 (19.0)	1.000
Low−molecular-weight heparin	443 (17.9)	6 (28.6)	0.247
Previous pacemaker implant	109 (4.4)	2 (9.5)	0.239
Paced QRS	102 (4.1)	2 (9.5)	0.217

ASA, aspirin; BMI, body mass index; LVEF, left ventricular ejection fraction; SD, standard deviation.

Bold indicates *P* value < 0.05 is statistically significant.

variables, median and interquartile range for non-normally distributed variables, and frequency and proportion for categorical variables. A comparison between patients with and without infection was performed using an independent *t* test or Wilcoxon rank-sum test for continuous variables and a χ^2 test or Fisher's exact test for categorical variables. Univariate logistic regression analysis was applied to investigate the effect of individual predictors, and subsequently multivariable logistic regression model was applied to potential predictors selected from univariate analysis based on statistical significance ($P < 0.1$). Statistical analyses were conducted using SAS 9.2 software (SAS Institute, Inc, Cary, NC). A 2-sided *P*-value of ≤ 0.05 was considered statistically significant.

Results

Population

From the main SIMPLE trial, all 2500 patients were included in the study: 2479 with no infection and 21 with infection. Baseline characteristics are detailed in Table 1. Most implants were in men, for ischemic heart disease and for a primary prevention indication. Compared with patients with no infection, primary electrical disease indication and secondary prevention indication were statistically more likely to develop infection. Interestingly, patients who developed infection had less often history of hypertension, better left ventricular ejection fraction, and did not use aspirin. There was no statistical difference between patients who did not develop infection for other risk factors such as diabetes, renal failure, use of oral anticoagulation, or previous pacemaker implantation.

Table 2. Procedural characteristics

Variables	No infection N = 2479 (%)	Infection N = 21 (%)	*P* value
Primary prevention	1805 (72.8)	8 (38.1)	**0.001**
Secondary prevention	671 (27.1)	13 (61.9)	**0.001**
Implantation			
Subcutaneous	2413 (97.3)	20 (95.2)	0.436
Subpectoral	27 (1.1)	1 (4.8)	0.211
DFT testing	1200 (48.4)	9 (42.9)	0.666
No DFT testing	1261 (50.9)	12 (57.1)	0.663
Single chamber	1112 (44.9)	9 (42.9)	1.000
Dual chamber	634 (25.6)	9 (42.9)	0.081
Resynchronization therapy	711 (28.7)	3 (14.3)	0.223
Mean surgery duration (min) (SD)	69 (48.1)	61 (27.3)	0.468

DFT, defibrillation test; SD, standard deviation.

Bold indicates *P* value < 0.05 is statistically significant.

Procedural characteristics

Table 2 describes the procedural characteristics of the study population. There was no statistical difference regarding the implant location (subcutaneous or subpectoral), the device model implanted (CRT or no CRT), or the surgery duration between the 2 groups.

Infection-prevention strategies

Overall, 98.7% of patients with no infection and 100% of patients who did develop infection received preoperative IV antibiotics, not statistically different. Additional infection prevention strategies used during the study are presented in Table 3 and were left to the implanter's decision, and included additional doses of IV antibiotics, dual antibiotic regimens, skin barriers, postoperative IV antibiotics, and pocket wash with antibiotics. The use of these additional interventions was similar amongst patient who did and did not develop infection (Table 3). In the early postoperative phase (predischarge, 3 days), more than 50% of patients in both groups also received antibiotics, not statistically different between groups.

Table 3. Infection prevention strategies

Variables	No infection N = 2479 (%)	Infection N = 21 (%)	*P* value
Perioperative			
IV cefazolin	861 (34.7)	9 (42.9)	0.492
IV meropenem	35 (1.4)	1 (4.8)	0.263
IV vancomycin	62 (2.5)	0 (0.0)	1.000
IV clindamycin	76 (3.1)	1 (4.8)	0.483
Other antibiotics	635 (25.6)	6 (28.6)	0.802
All preop antibiotics	2448 (98.7)	21 (100)	1.000
Skin barrier during surgery	1802 (72.7)	14 (66.7)	0.623
Pocket wash with antibiotics	2448 (98.7)	21 (100.0)	1.000
Postoperative			
IV cefazolin	861 (34.7)	9 (42.9)	0.492
IV meropenem	35 (1.4)	1 (4.8)	0.264
IV vancomycin	62 (2.5)	0 (0.0)	1.000
Other antibiotics	352 (14.2)	2 (9.5)	0.757
All postop antibiotics	1308 (52.8)	12 (57.1)	0.827

IV, intravenous.

Table 4. Clinical outcomes

	30 d (%)	12 mo (%)	24 mo (%)	Cumulative (%)
Infection, N (%)	14 (0.6)	6 (0.2)	1 (0.04)	0.840
Removal, N (%)	10 (0.4)	3 (0.1)	0 (0.00)	0.500
Any reintervention	208 (8.3)	0	0	208 (8.3)
Hematoma	56 (2.2)	0	0	56 (2.2)

Clinical outcomes

Infection outcomes are depicted in Table 4. At 30-day follow-up, infection occurred in 14 patients (0.6%) and 10 required system removal (0.4%). At the 12-month follow-up, 6 additional patients had device infection (0.2%) and 3 of those required system removal (0.1%). At the 24-month follow-up, only 1 additional patient had device infection. The cumulative incidence of infection was 0.84% and system removal was required in 0.50% of the entire population and 62% of patients who had infection. During study follow-up, 208 patients (8.3%) required any type of reintervention, such as lead or generator revision. Of these patients, 4 developed an infection (1.9%).

As shown in Table 5, primary electrical disease and secondary prevention patients had more infections. After adjustment, secondary prevention patients were still significantly more at risk.

As previously published, 56 patients in the SIMPLE trial (2.2%) experienced a clinically significant hematoma after ICD implant, from which 6 patients later developed an infection (10.7%).[19]

Discussion

This large modern cohort of ICD patients implanted in high volume centres and followed for 24 months had a low rate of infection at 0.84% compared with previous studies.[1-6,8,9] This low infection rate was observed despite a population with many known risk factors for infection. In our cohort, diabetes (29.6%), renal failure (19.2%), anticoagulation (21.3%), and CRT implantation (28.7%) were prevalent and were not associated with a significant increase in the infection rate. This may be explained by our small population and our low infection rate overall. However, as reported by others, hematomas and reinterventions were associated with a higher infection rate at 10.7% and 1.9%, respectively. As shown with the PADIT risk score[23] and a previous meta-analysis,[30] we also found more infections in the younger population and patients with no hypertension. Patients with primary electrical disease indication are often younger with preserved left ventricular ejection fraction, and this may explain their higher infection rate. The higher risk seen in our secondary prevention group has not been well defined in the literature. However, these patients are often hospitalized, been resuscitated, and have IV lines and other procedures that confer risk factors for infection.

Our low rate of infection could also be explained by rigorous and standard operating procedures and high volume centres and mostly first implants included. In addition, antibiotics were administered preoperatively in 98.7% of patients and postoperatively in more than 50% of patients. Furthermore, other preventive measures were used such as pocket wash with antibiotics in 98.7% of patients and the use of skin barriers in the majority of patients. All those measures may all have contributed to this low overall infection rate. Because there was no randomization for any infection preventive measures in this trial, no definitive conclusions can be derived from our study for individual strategies.

The recently published PADIT trial prospectively randomized 19,603 patients to a conventional preoperative IV cefazolin (or vancomycin in allergic patients) dose to a more aggressive strategy of preoperative IV cefazolin + IV vancomycin, pocket wash with bacitracin, and 2 days of postoperative oral cefazolin. Infection occurred in 1.03% of patients in the conventional arm compared with 0.78% in the aggressive arm ($P = 0.10$),[31] similar to our results.

The **W**orld-wide **R**andomized **A**ntibiotic Envelo**p**e **I**nfection Preven**t**ion trial randomized 6983 patients to receive an antibacterial envelope (n = 3495) or not (n = 3488). Adjunctive use of an antibacterial envelope resulted in a significantly lower incidence of major device infections (0.7%) than standard-of-care infection-prevention strategies alone (1.2%),[32] again with similar infection rate in their control group.

We thus need to target the highest risk population. Validated risk scores and strategies to reduce the overall complication rate, including decreasing reintervention and hematoma, 2 important risk factors for device infection well identified in the **B**ridge or Contin**u**e Coumad**i**n for Device **S**urg**e**ry Randomized **Control**led Trials I and II[33-35] and the NCDR registry,[36] must be reinforced. The recently published PADIT risk score identified 5 independent predictors of device infection and can be used clinically to choose the best preventive strategies. This could have a major impact on morbidity, mortality, and health care costs in the higher risk population.[23]

Limitations

It is possible that some infections were treated as outpatients, not required hospitalization and/or extraction, and could not be captured in our trial. However, infection was a

Table 5. Association between infection and underlying conditions

Characteristics	Infection group (N = 21), n (%)	No infection group (N = 2479), n (%)	No adjustment		With adjustment	
			OR (95% CI)	*P* value	OR (95% CI)	*P* value
Primary electrical disorder	3 (14.3)	50 (2.0)	8.1 (2.3, 28.4)	0.0011	4.6 (0.9, 22.8)	0.0595
Secondary prevention	13 (61.9)	671 (27.1)	4.4 (1.8, 10.6)	0.0011	7.4 (2.8, 19.8)	< 0.0001

Adjustment includes age, gender, diabetes, reintervention, hematoma, and antibiotic regimen.
CI, confidence interval; OR, odds ratio.

prespecified outcome in this trial and was collected at each follow-up. In 25% of patients, the IV antibiotic received was not specified. Because this percentage was not different between groups (25.6% no-infection and 28.6% in patients who develop infection, P = ns), this should not have influenced the results. Our small sample size and low infection rate may explain why some risk factors such as aspirin, diabetes, chronic renal failure, and CRT cases were not associated with more infections. Because the first follow-up was at 30 days and every 6 months thereafter, this may have caused an excess in early ascertainment.

Conclusions

In this large modern cohort of ICD implantation in high volume centres, we observed a low rate of device infection at 0.84% and most occurred early after implantation. Standard operating procedures and strict adherence to infection preventive measures may all have contributed to this lower rate of infection compared with previous trials. Additional efforts should be made to use clinical scores and to decrease the rate of reintervention and hematoma where the infection risk is still significantly increased.

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Disclosures

The authors have no conflicts of interest to disclose.

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