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The effect of an antibacterial envelope on cardiac implantable device-related infection — A real-world analysis from a tertiary center

Short title: **Effect of an antibacterial envelope on cardiac implantable device-related infection**

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Abstract

Background: Infections related to cardiac implantable electronic devices (CIED) are associated with significant morbidity and mortality. Antibiotic-eluting envelopes have been introduced as a technology to prevent CIED infections. The aim of this study was to evaluate the effectiveness of the antibacterial envelope in the real-world population of a tertiary center.

Methods: This cohort study includes consecutively enrolled patients undergoing a device procedure from 01/2014 to 12/2020 at the University Hospital in Zurich. During period A (01/2014-12/2019) antibacterial envelopes were not used, whereas during period B (01/2020-

12/2020) antibacterial envelopes were used in all device interventions. Follow-up was conducted by assessing all available patient records from patient visits and hospitalization.

Results: 1757 patients (male 70.5%, mean age 67.1 ± 16 years), were analyzed during a follow-up of 24 months. In 302 patients (17.2%) an antibacterial envelope was used. The overall occurrence of a device infection was low (n = 15, 0.85%). Factors that were associated with the incidence of an infection were not undergoing a primary implantation procedure (p = 0.024) and a CRT-P/D intervention (p = 0.022). There was no difference in the rate of infection between patients in whom a bacterial envelope was implanted vs. those in whom it was not used (0.6 vs. 0.9%, p = 0.693).

Conclusion: In a contemporary cohort of consecutive, unselected patients undergoing a device intervention at a large tertiary care center, the rate of device infection was low and not significantly different with vs. without the use of an antibacterial envelope. The data have important practical as well as economic implications for physicians performing such procedures.

Keywords: antibacterial envelope, cardiac implantable electronic device

Introduction

Cardiac implantable electronic device (CIED) infection occurs in 1–4% of all procedures [1] and is associated with an increase in morbidity and mortality, as well as with significant impacts on quality of life, healthcare utilization, and cost to global healthcare systems [2–4]. The most common manifestation of CIED infection is pocket infection. Typically, pocket infections develop in the first 12 months following implantation, although skin erosion late after implantation can also be observed [5]. As device infections usually require complete system removal, developing strategies to mitigate the risk of infection is of great importance. The TYRX absorbable antibacterial envelope (Medtronic, Inc., Minneapolis, MN) was designed to reduce infection rates as an adjunct to careful operative technique. Consisting of a multifilament mesh coated with a polymer containing rifampin and minocycline, the large-pore mesh envelope breaks down and is fully absorbed by approximately 9 weeks while eluting its antibiotics. The primary objective of minimizing infection was demonstrated in the Worldwide Randomized Antibiotic Envelope Infection Prevention (WRAP-IT) trial [6], which included 6983 patients randomized to antibacterial envelope vs. standard of care. The study demonstrated a 40% reduction in major infections occurring in 0.7% of patients receiving TYRX™ vs. 1.2% in controls. The aim of the current analysis was to evaluate the role of the newly introduced antibacterial envelope in a real-world population at a tertiary center.

Methods

Study design and cohort description

This retrospective cohort study includes 1757 consecutively enrolled patients undergoing a device procedure from 01/2014 to 12/2020 at the University Hospital in Zurich, Switzerland. Subcutaneous ICDs and leadless pacemakers were excluded. During period A (01/2014–12/2019) the antibacterial envelope was not used, while during period B (01/2020–12/2020) the antibacterial envelope was used consecutively in all device interventions. Follow-up was conducted by assessing all available patient records from patient visits and hospitalizations. The presence of a local or systemic device-related infection was counted as an infection event. Follow-up was 24 months for all patients.

Statistics

Continuous variables are reported as mean ± SD. Categorical variables are reported as counts (percentage). Comparisons between categorical variables were performed through contingency tables assessed using a χ^2 or Fisher's exact test, as appropriate. Student's t-test was used for comparison of normally distributed continuous variables and the Mann-Whitney U-tests for the other continuous variables. For univariate Cox regression analyses, time from index procedure to infection was the event of interest. Statistical significance was set for $p < 0.05$. Statistical analysis was performed using IBM SPSS Statistics (Ver.23).

Results

Patient demographics

A total of 1757 patients were included in this study, of whom the majority were male (70.5%, n = 1238). The mean age (± SD) at intervention was 67.1 ± 16.0 years. In 302 patients (17.2%) a device with an envelope (TYRX) was implanted, while 1455 (82.8%) received an implantation of a device without an envelope. The most frequently implanted devices were pacemakers (51.5% [n = 904]), followed by ICDs (26.1% [n = 458]), and CRT-P/Ds (22.5% [n = 395]). In 68.5% (n = 1203) of the patients the intervention was a first implant procedure, while 31.5% (n = 554) of patients already had a device in place and underwent replacement, upgrade, or revision surgery. 42.1% (n = 740) and 46.3% (n = 814) of patients were on oral anticoagulation and antiplatelet therapy, respectively. Baseline characteristics are shown in Table 1.

Risk factors associated with infection

Pocket infections or systemic infections occurred in 0.85% (n = 15) of patients. Characteristics of patients with device infection are presented in Table 2. On χ^2 or Fisher's exact test, intake of oral anticoagulation therapy (p = 0.028) and antiplatelet therapy (p = 0.001) as well as undergoing a box change/upgrade/revision procedure (p = 0.017) or CRT-P/D intervention (p = 0.016) were associated with the risk of infection.

In the univariate Cox regression analysis, the two factors that were significantly associated with infection were undergoing an intervention other than *de novo* implantation (p = 0.024), as well as undergoing a CRT-P/D intervention (p = 0.022; Tab. 3).

Infection rate with vs. without use of an antibacterial envelope

Patients receiving a cardiac device procedure with vs. without use of an antibacterial envelope revealed a similar rate of infection: 0.6% (n = 2 of 302) vs. 0.9% (n = 13 of 1455; Tab. 3). All patients with infections underwent lead and device extraction and anti-infective therapy. The rate of infection with vs. without use of an antibacterial envelope is shown in Figure 2.

Discussion

In this study, we systematically assessed the rate of infection in patients undergoing a cardiac implantable electronic device intervention between 01/2014 and 12/2020 at our institution. The main findings are as follows:

1. The overall infection rate during follow-up over a minimum of 2 years was low (n = 15, 0.85%).
2. Factors associated with the incidence of an infection were undergoing a procedure other than a *de novo* device implantation and undergoing a CRT-P/D intervention.
3. The addition of an antibacterial envelope had no significant effect on the overall low rate of infection.

Factors associated with an elevated risk of CIED infection

Previous studies reported a 1–4% infection rate in CIED procedures during follow-up [1]. Generally, factors associated with higher CIED infection risk can be grouped into patient-related, procedure-related, and device-related [7]. Among the numerous patient-related factors, end-stage renal disease, prior CIED infection, advanced age, and preprocedural fever are associated with the highest infection risk. Procedural factors associated with greatest risk are pocket hematoma formation, early reintervention, procedure duration more than one hour,

as well as system revision/lead revision, upgrade, or generator replacement [7, 8]. The BRUISE CONTROL INFECTION study included 659 patients with CIED infection from the original study population and demonstrated that development of hematoma was associated with a more than 7-fold increased risk of infection within one year of follow-up [9]. An analysis of the WRAP-IT population with 6800 participants demonstrated a 2.2% incidence of hematoma 30 days after the device implantation. The risk for CIED infection in patients with hematoma was 11-fold higher vs. uncomplicated cases [10]. In our data, the use of oral anticoagulation and antiplatelet drugs was no longer significantly associated with the incidence of infection in univariate Cox regression analysis, which might be due to the relatively low event rate. Randomized data from the PADIT study demonstrated the importance of the procedure type as a risk factor for CIED infection, with the highest risk in device revisions/upgrade and generator replacements [11]. The reason for this is not always unanimous, but the presence of bradytrophic scar tissue as well as “dormant” bacteria within the device pocket have been postulated [12]. Consistently, in our analysis, such procedures had a higher risk of infection than the first implantation of a device.

Device-related factors mainly include system size and complexity. Of these, implantation of CRT (cardiac resynchronization therapy) devices, the presence of more than two leads, and high-energy devices have consistently been associated with increased infection risk [8, 13]. In a large Danish registry including 97,750 patients with 1827 CIED infections, there was a significantly increased infection risk in patients with complex devices with hazard ratios (HR) of 1.26, 1.67, and 2.22 for ICD, CRT-P, and CRT-D systems, respectively, compared to conventional pacemakers [13]. As such, it comes as no surprise that also in our study cohort interventions involving CRT-P/D systems were associated with the highest risk of infection.

Use of an antibacterial envelope in unselected patients undergoing CIED procedures

In our study cohort, the use of an antibacterial envelope had no significant influence on the rate of infection. In contrast, the randomized WRAP-IT study demonstrated a significant 40% reduction in major infections over 12 months following the operation. There are several reasons for this observed difference. First, our study was not randomized, and we cannot exclude bias due to its retrospective design. However, our study consisted of a consecutive all-comer population of patients undergoing device procedures, whereas patients included in the WRAP-IT trial were a pre-selected, enriched population at increased risk of CIED infection (implantation of a *de novo* CRT-D; generator replacement or an upgrade of a previous implanted device; and pocket revision of an existing device) [6]. Second, group sizes were smaller in our analysis, and it is conceivable that in a larger population the numerical

difference in infections observed in our study (0.6% vs. 0.9% with vs. without antibacterial envelop, respectively) may become significant. Finally, the overall event rate in our study was very low and may represent the background level of risk, which may to a large extend not lend itself to prevention by the use of an antibacterial envelope.

Implications for clinical practice

While data from the WRAP-IT trial indicated that the use of an antibacterial envelope may lower the risk of CIED infection in selected patients at high risk, our data do not support the unrestricted use of such a strategy in unselected all-comer patients. These real-world observational data have important practical as well as economic implications for physicians performing such procedures, with the lack of necessity for an antibacterial envelope resulting in relevant cost savings in most procedures.

It is important to note that these implications are only valid in the presence of a low overall infection rate. Conversely, if *overall* rates of CIED infection in an individual center are substantially higher, even the use of an antibacterial envelope will most likely not result in a relevant reduction. Therefore, in such situations, procedural, logistical, as well as hygiene rules need to be reviewed and optimized first. In contrast, in high-risk situations such as re-interventions, long procedure duration, CRT-P/-D implantation, and/or the presence of patient-related risk factors (chronic kidney disease, anticoagulant use, etc.) the use of an antibacterial envelope may well be considered to further reduce the residual risk of infection in such procedures.

Conclusions

In a contemporary, unselected cohort of device implantations at a large tertiary care center, the rate of device infection was low and not significantly different with vs. without the use of an antibacterial envelope. These data have important practical as well as economic implications for physicians performing such procedures.

Figure 1. Manifestations of implantable electronic cardiac device infection

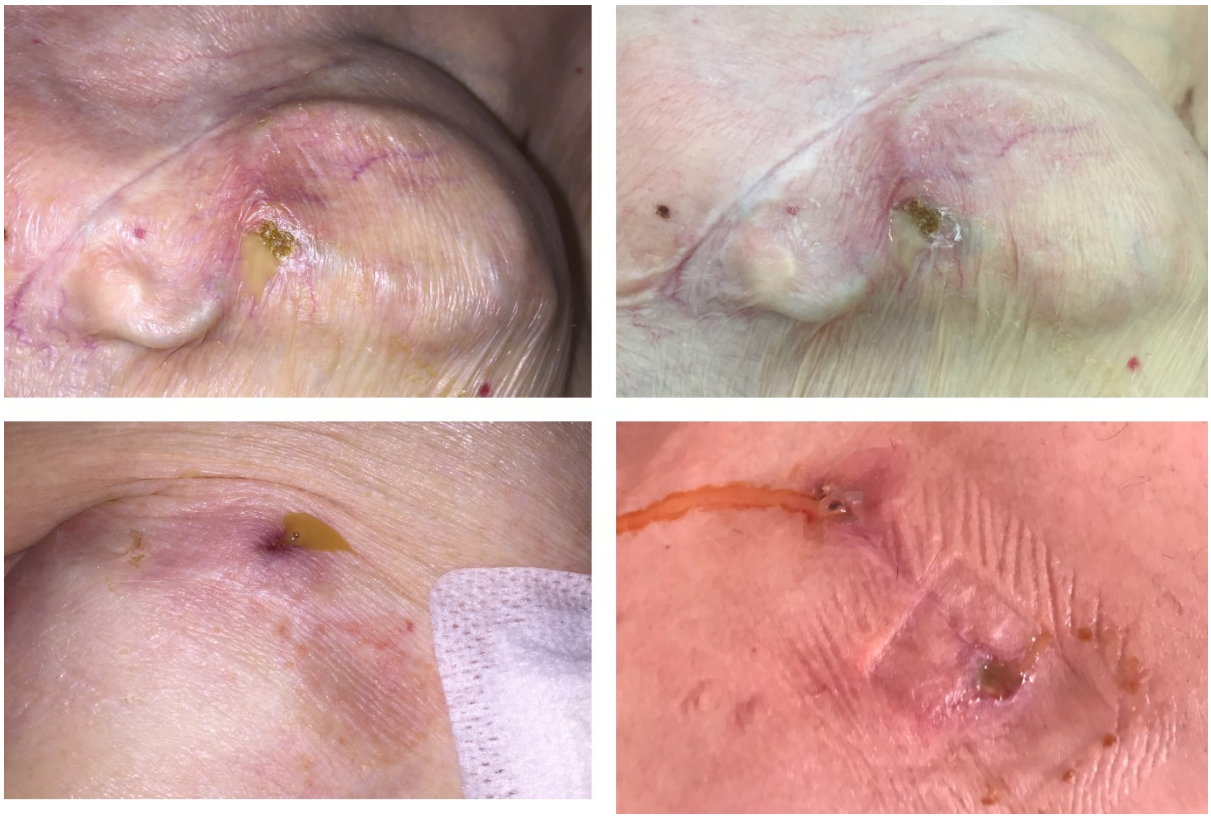

Figure 2. Rate of infection with vs. without use of an antibacterial envelope

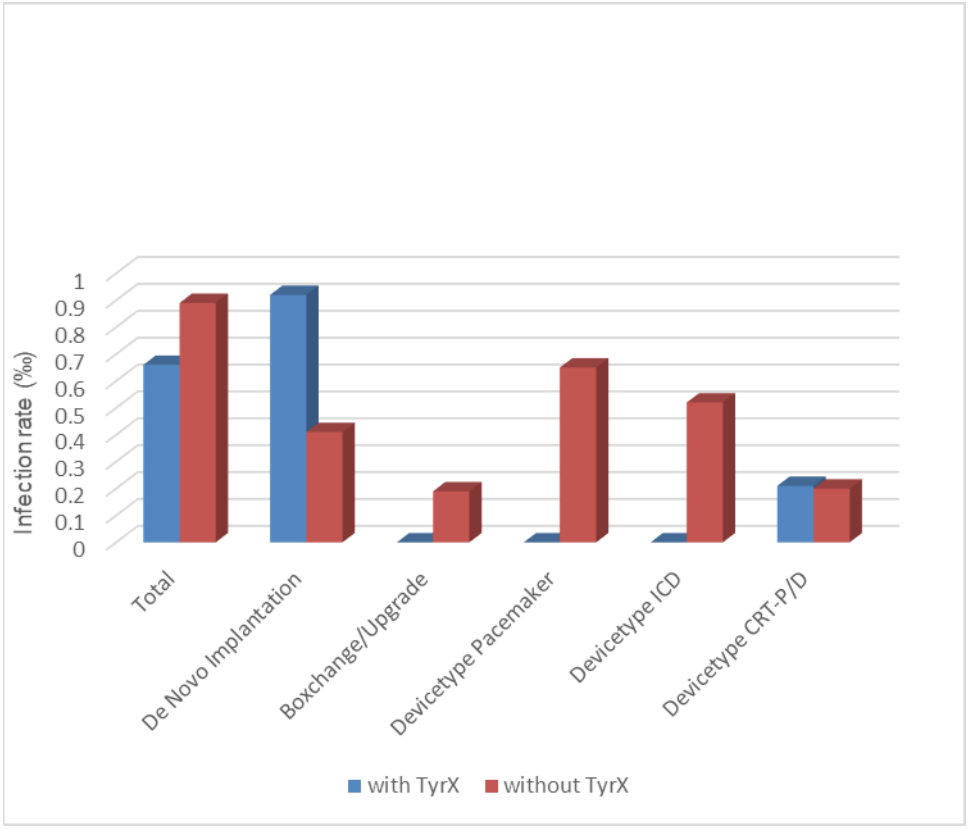

Table 1. Baseline characteristics of patients undergoing a device procedure with and without use of an antibacterial envelope

	Total n (%)	**With TyrX**	**Without TyrX**	**P-value**
Age ± SD [years]	71.0 ± 16.0	66.6 ± 16.1	67.2 ± 16.0	0.540
Female gender [n]	519 (29.8%)	97 (32.1%)	422 (24.0%)	0.494
Type of device • **Pacemaker** • **ICD (implantable cardioverter-defibrillator)** • **CRT-P/D**	 904 (51.5%) 458 (26.1%) 395 (22.5%)	 129 (42.7%) 77 (25.5%) 95 (31.5%)	 774 (53.2%) 382 (26.3%) 300 (20.6%)	< 0.001
Type of device intervention • **New implantation** • **Follow-up procedure**	 1203 (68.5%) 554 (31.5%)	 217 (71.9%) 85 (28.1%)	 986 (67.8%) 469 (32.2%)	0.003
Oral Anticoagulation Medication	740 (42.1%)	142 (47.0%)	598 (41.1%)	0.058
Antiplatelet Medication	814 (46.3%)	115 (38.1%)	699 (48.0%)	0.002

Table 2. Characteristics of patients with device infection

Patient	**Age at date of infect**	**Device type**	**Device indication**	**LV EF, left ventric**	**TyrX**	**Time to infection (days**	**Microbiology**	**D.m.**	**Immune suppression**	**Pre-procedural elevated Inflammatory**

	ion			**ular ejection fraction (%)**		**)**				**parameters**
1	43	PM	AVB III°	30	No	13	–	No	Yes	No
2	61	PM	AVB III°	30	No	76	*S. aureus*	Yes	No	No
3	69	CRT-D	HFrEF (DCM)	55	No	691	*S. epidermidis*	No	No	No
4	84	CRT-D	HFrEF (DCM)	63	No	28	–	Yes	No	No
5	67	PM	AVB III°	63	No	8	*S. epidermidis*	No	No	No
6	49	ICD	HFrEF (ICM)	15	No	540	*Streptococcus sanguinis*	No	No	Yes
7	62	PM	AVB III°	63	No	371	–	No	No	Yes
8	59	CRT-D	HFrEF (DCM)	40	No	24	–	No	No	No
9	76	ICD	HFrEF (DCM)	35	No	264	*Campylobacter*	No	No	No
10	26	ICD	ARVC	60	No	75	–	No		No
11	69	CRT-D	HFrEF (DCM)	20	No	34	–		No	No
12	52	CRT-D	HFrEF (DCM)	35	No	44	*Bacillus cereus*	No	No	No
13	78	CRT-D	HFrEF (DCM)	20	No	3	*S. aureus*	Yes	No	No
14	68	CRT-D	HFrEF (ICM)	29	Yes	138	*S. aureus*	Yes	No	No
15	65	CRT-D	HFrEF (DCM)	23	Yes	10	–	Yes	No	No

Table 3. Univariate analysis of factors associated with increased risk of infection

	P-value	**HR (95% CI)**
Type of device (CRT vs. rest)	0.022	3.693 (1.208–11.289)

Type of device intervention (Others vs. *de novo*)	0.024	3.281 (1.168–9.219)
Oral Anticoagulation Medication	0.866	0.915 (0.326–2.571)
Antiplatelet Medication	0.978	1.014 (0.368–2.797)
Antibacterial Envelope	0.693	0.741 (0.167–3.283)

Data availability statement: Data are available on reasonable request. On urgent request and associated need, our data are available, while our utmost intention is to protect our patients' privacy.

Ethics statement: The study is performed according to the Declaration of Helsinki and guidelines for good clinical practice.

Author contributions: Conceptualization: AB, JS. Data curation: PR, DA, VG, NM. Analysis of data: NM. Drafting the Manuscript: NM, JS. Review and editing: AB, JS, VG, DH, NM.

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