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SUPPLEMENT PAPER

Antibiotic eluting envelopes: evidence, technology, and defining high-risk populations

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Abstract

Cardiovascular implantable electronic devices (CIED) are effective and important components of modern cardiovascular care. Despite the dramatic improvements in the functionality and reliability of these devices, over time patients are at risk for developing several morbidities, the most feared of which are local and systemic infections. Despite significant financial investment and aggressive therapy with hospitalization, intravenous antibiotics, and transvenous lead extraction, the outcomes include a 1-year mortality rate as high as 25%. This risk of infection has increased over time, likely due to the increased complexity of the surgical interventions required to insert and replace these devices. The only way to reduce this morbidity and mortality is to prevent these infections, and other than preoperative antibiotics, there were little data supporting effective therapy until the WRAP-IT trial provided randomized data showing that pocket infections can be reduced by 60% at 12 months and major CIED infections reduced by 40% at 1 year with the use of the absorbable antibiotic eluting envelope in patient CIED procedures at high risk of infection. Not all CIED procedures are at high risk of infection and justify the use of the envelope, but cost-effectiveness data support the use of the antibiotic envelope particularly in patients with defibrillator replacements, revisions, and upgrades, such as to a resynchronization device and in patients with prior CIED infection, history of immunocompromise, two or more prior procedures, or a history of renal dysfunction.

Keywords

Cardiovascular implantable electronic devices • Pacemaker • Implantable defibrillator • Cardiac resynchronization • Infection • Antibiotic envelope

Introduction

The first fully implantable pacemaker (PPM) was placed in 1958 and ushered in an era of rapid development of cardiac implantable electronic devices (CIED). Pacemakers (PPM), internal cardiac-defibrillators (ICD), and later cardiac resynchronization pacemakers (CRT-P) and defibrillators (CRT-D) provided life changing and lifesaving therapy for disease processes for which previously there were few therapeutic options. Over the ensuing decades, the number of CIED implants rose dramatically. Improvements in surgical technique and available tools led to a decrease in many complications associated with CIED implantation, however, infection rates have increased despite advances. Infection remains one of the most difficult challenges associated with CIED implantation and is associated with high morbidity and mortality and costly treatment. While the incidence of CIED infections has increased, surprisingly few advances have been made to help prevent these infections. For decades after the first pacemaker implantation, the only proven prophylactic measure against CIED infection was preoperative antibiotic administration.[1]

In recent years, however, we have finally seen progress in the effort to prevent CIED infections. Advances in device technology such as subcutaneous ICDs and leadless pacemakers allow device implantation without the need for endovascular leads or a subcutaneous pocket, respectively. While these technologies show promise in smaller studies and in select patient populations, their ability to impact infection rates at a large scale in their current state seems unlikely.[2,3] In contrast, the antibiotic eluting envelope (AE) appears poised to make an impact immediately. In the largest cardiac device trial to date, the WRAP-IT investigators demonstrated a significant reduction in CIED infections with the use of the TYRX (Medtronic,

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What's new?

- Prospectively determined cardiovascular implantable electronic device major infection rate is 1.2% over 12 months.
- Absorbable antibiotic envelope use reduces major infections 40% and pocket infections 60% over 12 months.
- Cost effective use of the absorbable antibiotic envelope was observed in procedures in high-risk populations.
- High-risk populations include patients with prior cardiovascular implantable electronic devices infection, history of immunocompromise, two or more prior procedures for those with an implantable defibrillator or resynchronization defibrillator, history of renal dysfunction, or patients undergoing a revision or upgrade.

TM, USA) AE.[1] It remains to be seen whether the AE coupled with other measures such as strict surgical techniques and the use of preoperative antibiotics will finally begin to reverse the decades-long trend of increasing CIED infection rates.

Cardiac implantable electronic device infection—background

Cardiac implantable electronic device infections are one of the most common and devastating complications of CIED procedures with infection rates reported between 1% and 4%.[1,4–6] Alarmingly, multiple studies have reported a staggering increase in the incidence of CIED infection over recent decades. Joy *et al.*[7] reported an increase in the incidence of CIED infection from 1.45% in 2000 to 3.41% in 2008. The impact of these infections is profound. The 30-day mortality can be 5–8%, 1-year mortality up to 25%, and long-term mortality up to 1.5–2.4 times that of non-infected patients.[8–10]

Cardiac implantable electronic device infections are classified as pocket infections, limited to the pocket and surrounding tissue, or endovascular, including bacteraemia and endocarditis. Pocket infections are responsible for the majority of CIED infections and most commonly occur within 12 months of CIED surgery.[11,12] Staphylococcal species are the responsible organism in about 70% of CIED infections while gram-negative bacilli account for another 9%.[13,14] While multiple strategies of CIED infection prophylaxis have been investigated, until recently, only preoperative intravenous antibiotics have been shown to reduce the risk. Notably, local instillation of antibiotics into the pocket has not been demonstrated to reduce the risk of infection.[15]

Patient, procedural, and device factors have been associated with an increased risk of CIED infection (*Table 1*) and an increase in the presence of these risk factors in patients undergoing CIED implantation likely explains the increasing incidence.[16–18] Patient factors which increase risk include end-stage renal disease, prior CIED infection, diabetes mellitus, and immunosuppression.[15,19–21] Important procedural factors include haematoma formation, need for early reoperation, secondary procedures, and longer operative times. Device factors include CRT devices, high energy devices, and presence of multiple leads.[13,20,22] While understanding these relevant risk factors may help guide appropriate use of emerging prophylactic options, it is important to note that most of these data come from relatively small observational studies.

Antibiotic envelopes

Given the profound impact of CIED infections and with little else in the way of effective prophylaxis, the TYRX AE was developed to fill this clinical need. The multifilament mesh envelope was also intended to minimize migration of the CIED. While the initial envelope was non-absorbable, the newest generation's polymer comprised of glycolide, caprolactone, and trimethylene carbonate, is absorbed over the course of ~9 weeks.[23,24] An absorbable polyarylate polymer coating acts as a carrier for minocycline and rifampin.[23] Antibiotic dose varies based upon the size of the AE, with the medium AE, intended for PPM implantation, containing 8.0 mg rifampin and 5.1 mg minocycline and the large AE, intended for ICD implantation, containing 11.9 mg rifampin and 7.6 mg minocycline.[23] These antibiotics are eluted over a minimum of 7 days into the local tissue.[23,24]

Both rifampin and minocycline have a broad spectrum of activity, provide biofilm penetration, and are effective against most staphylococcal species making them choice candidates for prophylaxis against CIED pocket infections.[25] Preclinical, *in vitro* trials demonstrated antimicrobial activity of the TYRX AE against organisms including methicillin-resistant and methicillin-sensitive *Staphylococcus aureus, Staphylococcus epidermidis*, and *Escherichia coli* among others.[23] The TYRX AE also reduced infection after bacterial challenge in an animal model following CIED implantation.[26]

Early studies showed considerable promise for the non-absorbable AE with later studies supporting equal benefit from the absorbable envelope. Mittal *et al.*[27] reported a reduction of CIED infection by 79% and 100% in medium- and high-risk groups, respectively, with the use of the non-absorbable AE. The combined Citadel and Centurion trials examined clinical outcomes with the use of the non-absorbable AE for patients undergoing replacement or upgrade with an ICD or CRT. The non-randomized registries demonstrated 12-month infection rates of 0.2% in the ICD group and 0.7% in the CRT cohort which compared favourably with the published benchmark of 2.2% for ICD infection and 1.3% for comorbidity-match controls for the CRT group.[28] In a single-centre, retrospective cohort study, the non-absorbable and later the absorbable TYRX AEs were implanted in a total of 488 high-risk patients who were followed for a minimum of 300 days. Cardiac implantable electronic devices infection rates were 0% for the absorbable AE group, 0.3% for the non-absorbable AE group, and 3.1% for controls ($P = 0.03$ and 0.002, respectively).[29] A single study reported a higher incidence of major infection in patients implanted with the non-absorbable AE compared with controls (5.4% and 1.1%, respectively, $P = 0.048$), but was a retrospective study in which the study group was at higher risk of infection given higher rates of chronic steroid use, longer hospitalizations, a greater proportion of devices with more than two intracardiac leads, and a higher rate of CIED replacement or revision for the index procedure.[25]

Given the initial promise of these non-randomized studies, the WRAP-IT trial was designed as the largest prospective, randomized CIED trial in history. 6983 patients were randomized in a 1 : 1 fashion to treatment with the absorbable TYRX AE or standard of care.[1] The

Table 1 Factors associated with increased risk of CIED infection

Patient factors	Odds ratio	Source	Device factors	Odds ratio	Source
ESRD	8.73	19,20	Epicardial leads	8.09	19,20
History CIED infection[a]	7.84	19,20	Abdominal pocket	4.01	19,20
Age ≥75	5.93	21	CRT[b]	2.87	15
Fever prior[a]	4.27	19,20	≥2 leads	2.02	19,20
Immunosuppression	3.44	19,20	ICD[a]	1.83	15
Renal insufficiency[a]	1.48–3.02	19,20	Dual chamber device	1.45	19,20
COPD	2.95	19,20			
NYHA Class ≥2	2.47	19,20	**Procedural factors**	**Odds ratio**	**Source**
Skin disorder	2.46	19,20	<30 days reintervention[a]	16.29	21
Immunocompromised	2.24	15	Duration >1 h	13.96	21
Malignancy	2.23	19,20	Haematoma	8.46–4.95	19–21,35
Diabetes mellitus[a]	2.08	19,20	Revision/upgrade[b]	6.46–4.16	15,21
Heparin bridging	1.87	19,20	Lead repositioning	6.37	19,20
CHF	1.65	19,20	Replacement[b]	4.93–1.7	19,20
Age <60	1.63	15	≥2 prior procedures	3.37	15
Oral anticoagulants[a]	1.59	19,20	Inexperienced operator	2.85	19,20
Age 60–69	1.43	15	Temporary pacing	2.31	19,20
			1 prior procedure	1.51	15

CIED, cardiovascular implantable electronic devices; COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure; CRT, cardiac resynchronization therapy; ESRD, endstage renal disease; ICD, implantable cardiac-defibrillator.
[a]Prespecified risk factor for CIED infection in an observational AE trial.
[b]Prespecified risk factor for CIED infection in a prospective, randomized AE trial.

inclusion criteria specifying patients undergoing de novo CRT-D implantation, patients with an existing CIED undergoing generator replacement or upgrade or patients with an existing CIED undergoing system revision ensured a higher risk population.[23] Notably, however, certain high-risk patients were excluded. Patients undergoing revision in whom the pocket had been opened in the previous 365 days were not included. Additionally, patients on chronic oral immunosuppression, on haemodialysis or peritoneal dialysis, patients requiring long-term vascular access, and those with prior CIED or endovascular infection within the prior 12 months were excluded.[23] Exclusion of very high-risk populations may, in part, explain the low incidence of CIED infection seen in controls.

The WRAP-IT investigators reported that at 12 months, the primary endpoint of major infection occurred in 0.7% of patients implanted with the TYRX absorbable AE and 1.2% of patients in the control group which amounted to a 40% reduction in major infections.[1,24] The benefit persisted in long-term follow-up with rates of major CIED infections of 1.3% in the envelope group and 1.9% in the control group for a hazard ratio of 0.64. The benefit of the envelope was driven by a 60% reduction in pocket infections which represented 75% of all major infections at 12 months. There was no reduction in the incidence of endocarditis or bacteremia.[1] Within the subgroup receiving a high-power device (ICD or CRT-D), an approximate 50% reduction in major CIED infections was seen. No significant difference in major infections was observed in the low-power subgroup or in patients receiving a de novo CRT-D.[1] The TYRX AE was successfully implanted in 99.7% of cases and there was no increased risk of procedure or system-related complications. Additionally, there were no reports of allergic reactions to the TYRX AE.[24]

Economic analyses have reported that the TYRX AE is cost-effective. In a cost analysis of the practice of implanting an AE as standard of care during CIED implantation, revision or replacement, one group estimated the cost of additional infections in the control group was $340 000 compared to the cost of the device in the AE group estimated at $320 000.[30,31] The number needed to treat in the WRAP-IT trial was 200 while the base incremental cost-effectiveness of the TYRX AE was $112 603 per quality-adjusted life year.[32,33] However, the cost-effectiveness of the AE was far more pronounced in certain subgroups such as those with prior CIED infection, history of immunocompromise, two or more prior procedures for those with a high power device, history of renal dysfunction, or undergoing a revision or upgrade[33] (*Figure 1*).

Defining high risk

While no increased risk of procedure or device-related complications was seen in WRAP-IT or most of the other AE studies, not all patients derive equal benefit from the device. Not surprisingly, economic analyses suggest the patients that reap the greatest risk reduction from the TYRX AE are those at greatest risk for pocket infection. How we determine those at greatest risk for infection and most likely to benefit from AE implantation remains a challenge. Given its large size and prospective, randomized design, the WRAP-IT inclusion criteria, de novo CRT, generator change or upgrade, and CIED system revision, are the best supported indications for AE implantation.[1,19] However, the trial excluded certain high-risk populations that are likely to benefit. For instance, early reoperation for CIED revision or upgrade has been shown to dramatically increase

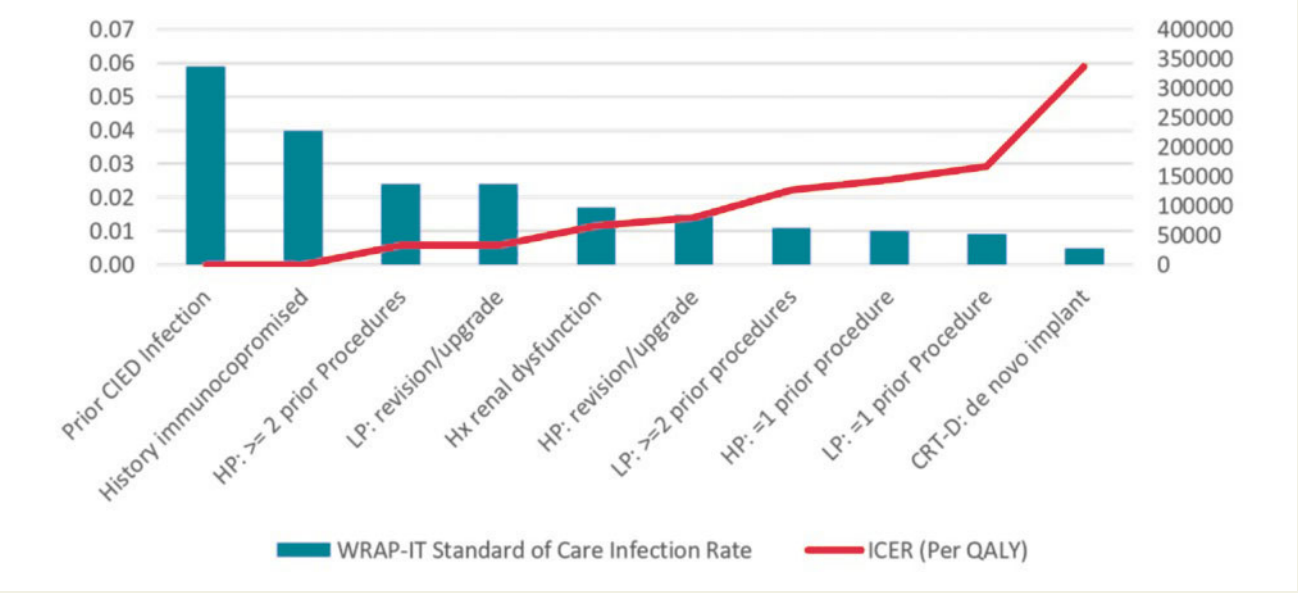

Figure 1 Incremental Cost-Effectiveness Ratio of Subgroups per Quality Adjusted Life Year.

risk of CIED infection, yet patients with revision <365 days removed from prior CIED surgery were excluded to prevent confusion over the timing and source of the infection.[21,34] While a host of other patient, device and procedural factors have been associated with increased risk of CIED infection (*Table 1*), these data come largely from observational studies with low event rates and the impact of AE implantation in the setting of many of these factors is unstudied.

Beyond the WRAP-IT inclusion criteria, data defining high-risk patients likely to benefit from AE implantation become murky. Other pre-specified risk factors from observational AE trials may be cautiously considered. A meta-analysis of AE studies found a significant reduction in the incidence of major infection for high-power devices, but no significant difference for low-power devices.[30] Mittal *et al.*[27] found implantation of the TYRX AE reduced infections by 79% and 100% in medium- and high-risk groups and defined risk using a multivariate logistic regression analysis to weight factors including early pocket re-exploration, male gender, diabetes mellitus, device upgrade, congestive heart failure, hypertension, and renal impairment. While a reduction in major CIED infection was reported by Kolek *et al.*[29] in their single-centre retrospective study, AE implantation was reserved for patients deemed high risk by virtue of two or more risk factors for infection including diabetes mellitus, chronic renal disease, systemic anti-coagulation, chronic daily corticosteroid use, fever ≥100.5°F, or leucocytosis ≥11 000 WBC/μL 24 h prior to implantation, prior documented CIED infection, presence of three or more transvenous leads, pacemaker dependence, or early pocket reentry within 2 weeks of the original implantation. While these studies may suggest other high-risk patients likely to benefit from AE implantation, additional research is clearly needed.

The benefit of AE implantation in the setting of other risk factors is unproven. For some, the benefit of AE implantation would seem plausible from a mechanistic standpoint while for others, the benefit seems less likely. Pocket haematoma is associated with a seven-fold increase in risk of CIED infection, and while it seems reasonable that an AE would be of benefit in these cases, to date, there are no subgroup analyses examining AE efficacy in patients who develop a haematoma subsequent to their CIED procedure.[16,20,29,35,36] The route of entry for most pocket infections is thought to be contamination during CIED surgery.[19,37] Longer procedure times and operator inexperience may increase the risk of CIED infection. Perhaps longer exposure times or a less refined surgical prep or technique leads to an increased risk or burden of contamination. Again, the benefit of an AE implantation is such cases, while mechanistically plausible, is unproven. Age, young and old, has been variably reported as a risk factor for CIED infection, but the impact AE implantation in specific age groups is unknown.[21,38] Finally, end-stage renal disease is one of the most powerful determinants of risk for CIED infection, but perhaps that risk will not be significantly impacted by an intervention with demonstrable effect against pocket infection, but no significant effect on endovascular infection.[15,16,21,32,39] Future studies including planned analyses of the WRAP-IT data should further clarify the role of AEs.

Conclusion

Much work remains in the effort to eliminate CIED infections and their attendant morbidity, mortality risk, and economic burden. While the decades since the implantation of the first pacemaker saw incredible technological development and an explosion in implantation volumes, few advances were made in CIED prophylaxis. More recently, however, early retrospective and non-randomized studies of AE implantation showed promise with reductions in the incidence of CIED infection in high-risk patients.[27–29,31] The WRAP-IT trial, the largest, randomized, prospective CIED trial to date, corroborated early findings, demonstrating a 40% reduction in CIED infections and a 60% reduction in major pocket infections.[1,24] Numerous studies have demonstrated cost-effectiveness of the TYRX AE, but subgroup analyses reveal marked disparities with high-risk populations deriving the lion's share of the benefit. Future studies should clarify which high-risk

populations stand to benefit most from AE implantation during CIED surgery. In the interim, we will wait with great anticipation to see if this is the decade we finally see CIED infection rates begin to fall.

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