Revista Portuguesa de Cardiologia 42 (2023) 719–721

Portuguese Society of CARDIOLOGY

Revista Portuguesa de
Cardiologia
Portuguese Journal of Cardiology
www.revportcardiol.org

EDITORIAL COMMENT

Cardiac implantable electronic device infections: An overwhelming tsunami

Infeções em dispositivos cardíacos eletrónicos implantáveis: um *tsunami* devastador

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Available online 8 June 2023

The incidence of infection in cardiac implantable electronic devices (CIEDs) is increasing at a faster rate than device implantation rates.[1] This is mostly due to older patients being implanted with more complex CIEDs and the fact that guidelines have significantly broadened the eligibility criteria for the use of CIEDs, now including patients with more comorbidities, who have a greater risk of infection.

Infection is one of the most serious complications of CIED therapy and is associated with significant mortality and morbidity. Patients undergoing extraction for a systemic-related device infection have about 25% one-year mortality despite successful extraction.[2] Another important consequence is the burden imposed on healthcare systems due to prolonged hospitalization, increased use of antibiotics, the need for device removal, as well as CIED reimplantation.[3]

Infections in CIEDs, including pacemakers, cardiac resynchronization therapy devices and implantable cardioverter-defibrillators (ICDs), can occur as a complication of device implantation, but occurs more often following revisions, upgrades and device replacements.[4] These infections are usually caused by bacteria entering the body during the procedure, but also, via the bloodstream or through the skin after a pressure lesion develops around the implant area.

Risk factors for CIED infection may be divided into patient-related, procedure-related, and device-related factors. The most common risk factors for infection, as well as factors of high clinical impact, have long been known: end-stage renal dysfunction, prior device infection, fever prior to implantation, corticosteroid use, renal insufficiency, procedure duration, hematoma, early reintervention, epicardial leads and diabetes.[5]

It is important to understand that recognition of these risk factors should be taken into consideration when deciding on the type of device chosen to treat different medical conditions. The availability of different technologies also means treatment can be tailored according to the risk of infection. Some of these technologies, like leadless pacing and extravascular ICDs, can significantly reduce or eliminate, respectively, the risk of intravascular infections. In the presence of infection, management of patients with extravascular ICDs is less challenging and as a result, mortality is diminished.

Prevention of infections is key. In order to optimize outcomes, preventative routine measures should be performed:

- Patients should be screened for active infection and antibiotics should be administered before the implantation procedure to prevent bacterial contamination (within 1 h of incision for cefazolin and flucloxacillin, within 90–120 min for vancomycin).[5]
- Sterile techniques during the implantation procedure should be optimized and assessed regularly. Surgical facilities should be routinely assessed and improved for better outcomes.

DOI of original article: https://doi.org/10.1016/j.repc.2023.01.023
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https://doi.org/10.1016/j.repc.2023.06.001

- Use of a prophylactic antibiotic envelope reduces the early risk of infection.
- Incisions and final stitching should routinely be performed as far as possible from all hardware components of the CIED, especially in device replacements, in which the risk of infection is higher.
- Unnecessary central or peripheral catheters should be removed as soon as possible after or even before device implantation. Whenever this cannot be achieved, extra careful aseptic management of these infection entry points is recommended.
- Patients with CIEDs should have early follow-up visits to detect any signs of early post-implantation superficial infection of the surgical wound that can be treated with antibiotics, before the infection reaches any component of the CIED.

It is important to highlight that despite these measures, CIED pocket infections will occur. Therefore, prompt diagnosis and treatment are essential to prevent serious complications such as sepsis or death.

Local administration of antiseptics and antibiotics in the pocket during device implantation is still controversial; according to the EHRA consensus document, this practice is contraindicated.[6] The same document recommends the use of antibiotic envelopes in patients at high risk of infection.[6]

Studies of multiple surgical procedures have reported reduced infection rates with the local application of antibiotics. Based on this evidence, the microbiology of CIED infections, and bactericidal data, current CIED envelope devices use either rifampin/minocycline or gentamicin for infection prophylaxis.

The TYRX Antibacterial Absorbable Envelope is a medical device designed to reduce the risk of infection associated with CIED implantation. The envelope is made of a mesh material that contains rifampin and minocycline, which are released over time to prevent bacterial colonization and biofilm formation around the device. It is fully absorbed within approximately nine weeks of implantation. This is probably the most extensively studied medical device developed specifically for this purpose.

A prospective multicenter randomized clinical trial published in the *New England Journal of Medicine* (WRAP-IT 2019), with 6983 patients (3495 to the envelope group and 3488 to the control group), demonstrated that adjunctive use of an antibacterial envelope resulted in a 40% lower incidence of major CIED infection than standard-of-care infection-prevention strategies alone at 12 months of the procedure (event rate was 0.7% vs. 1.2%, respectively; p=0.04).[7]

In addition, long-term follow-up (36 months) of WRAP-IT reported major CIED-related infections in 32 envelope patients and 51 control patients (Kaplan-Meier [KM] estimate 1.3% vs. 1.9%; hazard ratio [HR] 0.64; 95% confidence interval [CI] 0.41–0.99; p=0.046).[8] Any CIED-related infection occurred in 57 envelope patients and 84 control patients (KM estimate 2.1% vs. 2.8%; HR 0.69; 95% CI 0.49–0.97; p=0.030).

Although the results of the WRAP-IT trial achieved statistical significance (i.e., p<0.05), the findings were not as robust as expected, due to a lower than anticipated overall infection rate. Moreover, the number needed to treat in this trial to prevent one CIED infection was 200 patients, a large number compared to other preventive therapies. Therefore, further refinements are needed to optimize the clinical benefits and costs of these novel envelopes.

Overall, the available evidence suggests that the TYRX Antibacterial Envelope is an effective measure for reducing the risk of CIED infections. However, further independent studies may be needed to confirm these findings and to evaluate the device's long-term safety and effectiveness.

Although the TYRX is the best-known medical device in this field, there are other similar devices that are designed to reduce the risk of infection. These include:

- The AigisRx Antibacterial Envelope is the previous generation of the TYRX device and is also designed to release antimicrobial agents to prevent bacterial colonization and biofilm formation around the CIED. It contains a silver-based antimicrobial agent and is made of a non-absorbable mesh material. The fact of being non-absorbable constitutes one of the major differences from its successor, the TYRX, a characteristic that can become troublesome when device replacement becomes necessary.
- The CanGaroo® envelope is composed of decellularized extracellular matrix and was originally designed to stabilize the device within the pocket, limiting the risk of migration or erosion, and providing a substrate for tissue ingrowth. This device has shown promising results in a preclinical study and clinical studies with local delivery of gentamicin.[9]

Like the TYRX, these devices have shown to be effective in reducing the risk of CIED infections, however further studies may be needed to confirm their safety and effectiveness and in different patient populations and settings.

Future research that can determine the efficacy of new devices, as well as older technologies such as gentamicin-impregnated collagen sponges (GICSs),[10] that can be used in different settings from those they were initially produced for, is of paramount importance.

The article by Matteucci et al. published in this issue of the *Journal*[11] is an interesting example of a wise and practical approach with excellent results for the use of a device created and normally employed for reducing cardiac surgery wound infections, here applied in the prevention of CIED infection.

In this study, 2986 patients were randomized over a 10-year period, of whom 919 had additional treatment with GICSs and 2067 in the control group received only standard care with prophylactic antibiotics. The study's endpoints were the CIED infection rate at one year and the effectiveness of the use of GICSs in reducing CIED infection. It was demonstrated that adjunctive use of GICSs resulted in a reduction of the percentage of infected patients. CIED-related infections occurred in a total of 36 patients (1.2%); 30.8% of all non-infected patients received GICS therapy versus 13.9% of those in the infected group. Efficacy was statistically significant in treated patients (p<0.001, 95% CI: 0.03–0.001).[11] This study demonstrated for the first time that GICSs are effective in reducing CIED infection, although their efficacy needs to be tested

in randomized trials before they become routine practice.

It is essential to broaden the portfolio of this type of medical device. Increasing the availability and variety of such devices will mean that they can be more widely used and accessible at a lower cost.

New devices and large prospective studies are needed to help refine indications and to support judicious use of antibiotic envelopes to prevent CIED infection. This will certainly contribute to better treatments for reducing CIED infection, a complication that is growing at disproportionate speed and deserves our best efforts in order to reduce the burden of CIED-related side-effects.

Conflicts of interest

The author has no conflicts of interest to declare.

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