Gentamicin-collagen sponge and prevention of cardiac implantable electronic device infections: bargain basement or penthouse suite?

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Although cardiac implantable electronic device infections (CIEDI) remain a rare complication, its financial and human burdens are staggering [1, 2]. Thus, it is no wonder that CIEDI prevention has been the focus of multiple investigations and, currently, the only area in which clinical trial data are available regarding this syndrome. The search for cost-effective strategies to reduce the risk of CIEDI has led to the development of improved antibiotic prophylaxis (AP) protocols, drug-eluting envelopes, and novel device designs (i.e., leadless pacemakers) (Figure 1). For over two decades, meta-analysis [3] results have bolstered the notion that perioperative AP is beneficial in reducing the rate of CIEDI as a complication of surgical site infection. Since the bulk of these infections are due to staphylococcal species, one dose of pre-operative cefazolin has been advocated. A recent large, randomized, double-blind, placebo-controlled trial [4] demonstrated a five-fold lower incidence of CIEDI in the group who received pre-operative cefazolin vs. that of the placebo group (0.63% vs. 3.28%). As a result, the study was terminated early, and AP administration for the prevention of CIEDI was further solidified as a standard of care.

More recently, Krahn and colleagues [5] tested whether a single dose of pre-operative cefazolin was as efficacious as an "incremental" perioperative antibiotic regimen to reduce CIEDI in a cluster randomized crossover trial (PADIT Trial)

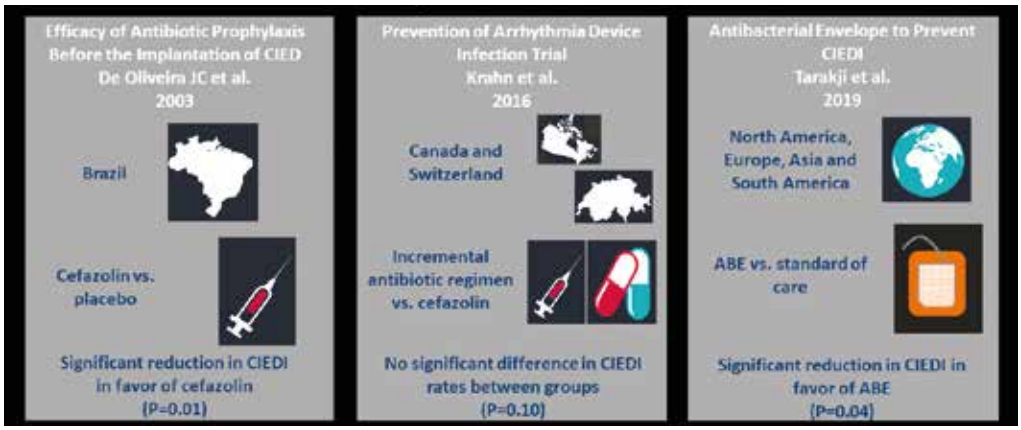

Figure 1. Summary of randomized clinical trials studying prevention of cardiovascular implantable electronic device infection

Abbreviations: ABE, antibacterial envelope; CIED, cardiovascular implantable electronic device; CIEDI, cardiovascular implantable electronic device infection

that included 28 institutions with over 19 000 patients. The incremental regimen consisted of pre-procedural cefazolin plus vancomycin, intraprocedural bacitracin pocket wash, and two-day post-procedural oral cephalexin. The reported CIEDI rates were lower (1.03% vs. 0.78%) than expected for both groups and were not statistically different.

Following the publication of multiple non-randomized trials of the efficacy of an absorbable "antibiotic envelope" impregnated with minocycline and rifampin in preventing CIEDI, a sentinel multinational, randomized controlled clinical trial was conducted with almost 7 000 patients enrolled in the WRAP-IT study [6]. Overall, the use of a "second generation" antibiotic envelope resulted in a 40% reduction in the major CIEDI rate (0.7% in the envelope group vs. 1.2% for the standard of care group) during a 12-month follow-up period. Moreover, there was a 60% reduction in CIEDI involving pocket sites, an infection presentation seen in 75% of randomized patients. Importantly, no increased risk of complications or allergic reactions among the envelope group was reported. However, the number needed to treat (NNT) to prevent one CIEDI was 200, raising concerns regarding the clinical impact and cost-effectiveness of this adjunct in the prevention of CIEDI.

The use of a gentamicin-collagen sponge (GCS) at the time of device placement to prevent surgical site infection has been investigated in other prosthetic device-related procedures [7] and showed promising results. The proposed mechanism of action involves the release of a high local concentration of gentamicin for several days, which prevents bacterial colonization of a prosthetic device. Furthermore, the collagen fibers promote blood coagulation and reduce the risk of hematoma formation, which is a well-recognized factor that predisposes to CIEDI. Its efficacy for CIEDI prevention, however, has not been widely studied.

In this issue of *Kardiologia Polska* (*Polish Heart Journal*), Kaczmarek et al. [8] present a single-center, retrospective study to evaluate the efficacy, safety, and cost-effectiveness of a gentamicin-collagen sponge (GCS) in preventing CIEDI in 312 patients with 6-month follow-up after device and sponge implantation.

Based on a comprehensive multi-component CIEDI risk score developed by the study group, patients considered to have a low risk of infection received ceftriaxone (or vancomycin if allergy reported) 60–120 minutes prior to the procedure. In contrast, high-risk patients received AP for 72 hours after CIED-GCS implantation. The authors report a single case of CIEDI (0.33%) and an NNT between 149 and 200, based on extrapolation from previously reported data [5]. No safety issues associated with the use of GCS were noted. The analysis of the cost associated with the management of CIEDI and that of GCSs to prevent one CIEDI concluded that the use of GCS may be a cost-effective intervention.

The authors acknowledge that relatively low rates of CIEDI observed in their study may not be solely attributed to the use of GCS. A predominant inclusion of patients at low risk of CIEDI, broad-spectrum AP (with longer duration in some cases [17%]), and the surgical technique employed (i.e., separate pocket closure with absorbable sutures) may have contributed to a low CIED rate.

In addition, the short follow-up (6 months) and exclusion of patients who did not survive the study period may have overestimated the effect of GCSs, as CIEDI can occur up to 12 months or longer following device placement [1, 9, 10]. Moreover, the lack of a control group prevented a comprehensive analysis of the cost-effectiveness of the proposed bundle strategies against standard of care.

The results of this study are encouraging; however, several questions remain. First, as suggested by this study, is it time to recommend GCSs for all patients undergoing CIED implantation?

The estimated cost of GCS can vary depending on the country, local geographic area, and, in some cases, type of healthcare system model and insurance coverage, if applicable. Kaczmarek and colleagues mentioned that the cost of one GCS at their institution was approximately 79 USD (we assume that this was an acquisition cost), which is considerably less than that of the currently available second-generation antibiotic envelope. Based on the reported low rates of CIEDI and high NNT, we believe that not all patients would benefit from GCSs. Whether this strategy would impact outcomes of patients at high risk of CIEDI is yet to be determined. However, it is important to highlight that although risk factors associated with CIEDI have been widely reported in the literature [1], at present, a risk score to define a population at high risk of CIEDI has not been validated, and a decision to use adjunctive local AP in a given patient is usually left at the discretion of the treating physician. Moreover, a comparison of the cost-effectiveness of this approach versus emerging technologies with a presumably lower risk of CIEDI, such as leadless pacemakers is lacking [11, 12]. Second, if a patient is deemed a candidate for a local antibiotic-delivered therapy at the time of CIED implantation, then should GCS or the minocycline and rifampin envelope be used?

To date, there are no clinical trial data that have examined outcomes in patients randomized to receive either of these two adjunctive therapies at the time of CIED implantation. In a comprehensive analysis of breakthrough CIEDI cases in the WRAP-IT study [13], a small but sizable proportion of cases were due to Gram-negative aerobic bacteria. The use of GCSs could, in theory, have better activity against this group of organisms compared to minocycline and rifampin. Although systemic absorption of locally delivered gentamicin is almost nil, it would also be important to examine if the broader-spectrum coverage of gentamicin could lead to breakthrough infections due to multidrug-resistant organisms or fungi. Lastly, the authors comment that the unit price of GCS is much lower than the minocycline and rifampin envelope. The cost may ultimately influence clinical decisions if similar efficacy and

adverse events related to the type of adjunct therapy are determined in future clinical trials.

Until randomized clinical trials compare the use of GCSs to the standard of care, other commercially available antibiotic envelopes [14], and newer device technologies become available, recommendations on the use of GCSs in patients undergoing CIED implantation will remain inconclusive.

Article information

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