Cardiac Implantable Electronic Device Infection in Patients at Risk

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Abstract

The incidence of infection following implantation of cardiac implantable electronic devices (CIEDs) is increasing at a faster rate than that of device implantation. Patients with a CIED infection usually require hospitalisation and complete device and lead removal. A significant proportion die from their infection. Transvenous lead extraction (TLE) is associated with rare but serious complications including major vascular injury or cardiac perforation. Operator experience and advances in lead extraction methods, including laser technology and rotational sheaths, have resulted in procedures having a low risk of complication and mortality. Strategies for preventing CIED infections include intravenous antibiotics and aseptic surgical techniques. An additional method to reduce CIED infection may be the use of antibacterial TYRX™ envelope. Data from non-randomised cohort studies have indicated that antibacterial envelope use can reduce the incidence of CIED infection by more than 80 % in high-risk patients and a randomised clinical trial is ongoing.

Keywords

Cardiovascular implantable electronic device infections, implantable cardioverter-defibrillators, antibacterial envelope, pacemaker, transvenous lead extraction

Disclosure: Professor Tarakji has received speaker fees and consulting honoraria from Medtronic, Professor Ellis has received advisory board/consultant fees from Atricure, SentreHeart, Boston Scientific, Medtronic and Spetranetics, and research grants from Medtronic, Atricure, Boston Scientific, Thoratec and HeartWare. Professor Defaye has no conflicts of interest to declare. Professor Kennergren has presented on behalf of, advised and/or performed scientific studies with Boston Scientific, Biotronic, ELA/Sorin, Medtronic/Vitatron/ TYRX, Mentice, Sim Suite and St Jude.

Acknowledgements: Medical Media Communications (Scientific) Ltd provided medical writing and editing support to the author, funded by Medtronic and Spectranetics.

Received: 30 November 2015 **Accepted:** 14 March 2016 **Citation:** *Arrhythmia & Electrophysiology Review* 2016;**5**(1):65–71 **Access at:** www.AERjournal.com

DOI: 10.15420/aer.2015.27.2

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Over the last few decades an increasing body of evidence has supported the role of cardiovascular implantable electronic devices (CIEDs) including permanent pacemakers (PPMs), implantable cardioverter-defibrillators (ICDs) and cardiac resynchronisation therapy (CRT-D [with defibrillator] and CRT-P [without defibrillator]) in improving quality of life and survival.[1] In addition, there has been a significant increase in the number of implantation procedures and subsequent replacements, revisions and upgrades.[2] Between 1993 and 2008, 4.2 million patients underwent implantation of a CIED.[3] A worldwide cardiac pacing and ICD survey, which included more than 80 % of all the pacemakers and ICDs implanted worldwide during 2009, reported 737,840 new implants and 264,824 replacements, a significant rise compared with a similar survey conducted in 2005.[4]

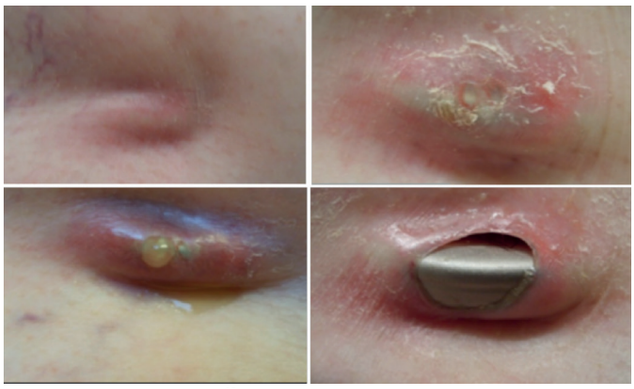
However, the cost and complications of device implantation, including infection or hardware malfunction in patients receiving CIEDs, have led to the concern that negative outcomes may partially counteract the expected benefits. The rate of CIED infection has been estimated at 0.5 % with primary implants and 1–7 % with secondary interventions.[3,5–8] It is difficult to give accurate estimates of infection rates, given the fact that figures are partly based on retrospective series of varying duration, and that different definitions of infection exist. However, the incidence of CIED infection is increasing out of proportion to CIED implantation.[3,5,9] A US study reported a 12 % increase in the number of CIED implantations from 2004 to 2006, with a 57 % increment in CIED infections during the same period.[9] Reasons for this rise in CIED infections include the fact that younger patients are receiving CIEDs, and therefore surviving long enough to require more pulse generator changes and lead revisions, which are associated with a higher infection rate.[7,10] In addition, there has been an increase in comorbidities, such as diabetes and kidney disease, resulting in poor wound healing and diminished immune responses.[3,9,11,12] Expanding indications for CIED use, coupled with an ageing population with more comorbidities, mean this trend is likely to increase.[2] Better awareness and improved reporting of CIED infections may, however, help to decrease the higher complication rates noted in recent years.

CIED infections also impose a substantial financial burden resulting from prolonged hospital stays, long duration of antibiotic therapy, management of sepsis and complications, device extraction and reimplantation.[3] These infections typically cost at least $52,000[13] and may exceed $100,000.[14] This article will review strategies for management and prevention of CIED infections, including lead extraction and the use of an absorbable antibacterial envelope.

Risk Factors for Cardiac Implantable Electronic Device Infections

Risk factors for CIED infections include patient factors such as medical comorbidities,[15] renal failure,[15–17] heart failure,[16,18] diabetes,[16,18] fever within

Figure 1: Images of Pocket Infection Over Two Years



Source: Tarakji and Wilkoff, 2013.[35]

24 hours before the implantation,[7] anticoagulation[17] and steroid use.[19] Important device-related risk factors include device revision or upgrade,[8] the use of more than two pacing leads and the need for early pocket re-exploration.[7,19] The presence of multiple leads increases the risk of central venous thrombosis in the area of the leads and is a potential site of secondary seeding of bacteria.[20] Procedure-related factors include procedure time, temporary pacemaker use prior to implantation, early re-intervention and postoperative haematoma at the device pocket site.[21] ICD replacement is associated with a 2.5x greater incidence of pocket-related events, and the need for re-intervention increases with every consecutive replacement.[10]

A registry study found that PPM and ICD generator replacements were associated with a substantial complication risk, particularly those with lead additions.[8] A study of 122 ICD patients undergoing generator replacement or surgical lead revision between January 2006 and July 2008 found that one-third of patients had an asymptomatic bacterial colonisation of the generator pocket. After revision, 7.5 % of these patients developed a device infection over 108 ± 73 days with the same species of microorganism.[22]

However, these risk factors have mostly been derived from small, single-centre studies. There is a need for larger, more representative studies to identify the most important factors that are responsible for the development of CIED infection. There is no consensus definition of patients at high risk of CIED infection; a composite risk score has been proposed,[23] but definitions of high-risk patients vary across studies.

Pathogenesis, Presentation and Diagnosis of Cardiac Implantable Electronic Device Infection

CIED-related infections are mainly due to local contamination during implantation; breach of the skin barrier introduces bacteria into the device pocket.[24] The majority (88 %) of CIED infections are caused by Gram-positive organisms;[24–26] the most common organism is methicillin-sensitive *Staphylococcus aureus* (MSSA; 30.8 %), followed by coagulase-negative *Staphylococcus* (20.5 %). Around half of these *Staphylococcus* infections are methicillin-resistant *Staph. aureus* (MRSA).[25,27] The majority (60 %) of CIED infections are pocket infections, characterised by erythema, tenderness, warmth and erosion,[28] but infection can track along the intravascular portion of the leads, leading to intravascular infection, manifesting as bacteraemia and endocarditis.[29–32] A study found that, even when infection symptoms were limited to the device pocket, in 72 % of cases the intravascular segments of the leads had positive blood cultures.[31] Less commonly, the intravascular portion of the CIED can become infected as a result of haematogenous seeding from another infection site, and vegetations on the leads are frequently detected by transoesophageal echocardiography (TOE).[33] Early presentations typically result from wound infections, MRSA or MSSA. Late presentations are more likely to be related to vascular access.[12,34]

It can be hard to diagnose CIED infections since numerous conditions can present with the same symptoms. Clinical manifestations of CIED range from local device pocket erosion to full-blown sepsis,[25] and include symptoms such as erythema, warmth, tenderness, purulent discharge, erosion of generator or protrusion of leads through the skin (see *Figure 1*).[26,35] Furthermore, up to 30 % of patients present with nonspecific symptoms only, such as fever and malaise.

In order to diagnose systemic CIED infection, two sets of blood cultures should be obtained before initiating antibiotic therapy (class I recommendation). Percutaneous aspiration of the pocket should not be performed (class III recommendation). The use of transthoracic echocardiogram (TTE) should be mandatory to investigate the possibility of endocarditis.[28] The results should be interpreted according to the individual patient; for example a positive echo density does not always indicate infection and a lack of vegetation in the blood culture does not eliminate the possibility of CIED-related bacteraemia.

Patients with bacteraemia but no evidence of device pocket infection or endocarditis represent a diagnostic challenge. The use of TOE is essential in this group of patients as TTE lacks the necessary specificity.[36] The diagnosis may only be confirmed if infection relapses or persists after completion of the antibiotic course, particularly in the case of Gram-positive organisms other than *Staph. aureus*.[28,37] Given the increasing prevalence of CIED infections and the occasionally challenging nature of diagnosis, particularly in the absence of pocket involvement and with negative TOE, other diagnostic techniques have been investigated. Several show promise, including the use of ^{18}F-fluorodeoxyglucose–PET/CT.[38,39]

Management of Cardiac Implantable Electronic Device Infection

Correct management of patients with CIED infection depends on the clinical presentation and the causative pathogen. In mild cases such as superficial incision site infection or stitch abscess, conservative management strategies may suffice, such as 7–10 days of antimicrobial therapy and removal of the stitches.[40] When CIED infection is restricted to the pocket site, an American Heart Association (AHA) scientific statement recommends 7–10 days of therapy after device removal if no inflammatory changes are seen, otherwise 10–14 days of antimicrobial treatment is recommended.[28] At least one of the authors would extend the treatment until complete wound healing. Antibiotic treatment in cases of systemic CIED infection is more uniform, usually involving 4–5 weeks of IV treatment, also depending on the type of causative bacteria.

The Heart Rhythm Society (HRS) and European Heart Rhythm Association (EHRA) recommend complete device and lead removal in all patients with definite CIED systemic infection as evidenced by valvular endocarditis, lead endocarditis and sepsis. It is also recommended for all patients with CIED pocket infection as evidenced by pocket abscess, device erosion, skin adherence or chronic draining sinus without clinically evident involvement of the transvenous portion, patients with valvular

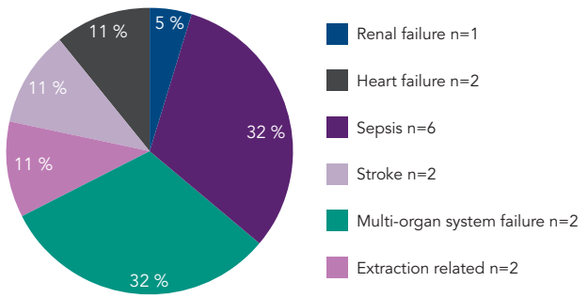
endocarditis without definite involvement of the leads and/or device and in patients with occult Gram-positive bacteria.[41,42] Complete device and lead removal is also reasonable in patients with persistent occult Gram-negative bacteria, but is not indicated for superficial or incisional infection without involvement of the device and/or leads, nor to treat chronic bacteraemia due to a source other than the CIED, when the source could not be eliminated and long-term antibiotic treatment is required.[41] Satisfactory control of the infection is required before implantation of a replacement device may be considered.

Transvenous device system explantation is the preferred technique; intraprocedural risks include haemothorax, laceration of the superior vena cava, damage to the tricuspid valve and cardiac tamponade.[25,26,28] However, without system removal the rate of relapse is high: rates of 50–100 % have been reported, compared with 0–4.2 % for complete system removal.[26,27,31,43,44] Mortality can be as high as 31–66 % if the device is not removed.[30,45] Using a combined approach with antibiotic and CIED removal, the one-year mortality is still approximately 20 %.[30,45,46] Data from the National Hospital Discharge Survey from 1996–2003 demonstrated that CIED infection doubles the rate of in-hospital mortality.[47] In one study that included 412 patients with CIED infection, the causes of in-hospital mortality are shown in *Figure 2*.Of note, only two out of the 19 in-hospital deaths were related to CIED extraction.[25] Delays to treatment and incomplete system removal are associated with higher mortality.[3,14] Recent data from the European multicentre study on lead extraction (ELECTRA) also show a significant in-hospital mortality of CIED infection patients, however only a minority of deaths were related to the extraction procedure.[48] In a study investigating the clinical predictors of short- and long-term mortality in patients with CIED infection, the following risk factors were identified: patient age (hazard ratio [HR] 1.20, 95 % CI [1.06–1.36]), heart failure (HR 2.01, 95 % CI 1.42–2.86), metastatic malignancy (HR 5.99, 95 % CI [1.67–21.53]), corticosteroid therapy (HR 1.97, 95 % CI [1.22–3.18]), renal failure (HR 1.94, 95 % CI [1.37–2.74]), and CIED-related endocarditis (HR 1.68, 95 % CI [1.17–2.41]).[49]

The need for transvenous lead extraction (TLE) has been increasing in proportion to the increased number of CIED implantations. In a study of patients undergoing TLE, a total of 5,973 (4,436 [74.3 %] PPM and 1,537 [25.7 %] ICD) leads were extracted during 3,258 TLE procedures.[50] Among these, 25 (0.8 %) patients experienced major complications requiring emergent surgical or endovascular intervention. Twenty patients (0.6 %) underwent sternotomy (n=18) or thoracotomy (n=2) for superior vena cava laceration (n=15) and right atrial (n=2) or ventricular (n=3) perforation. Two patients required vascular repair at the access site for subclavian vein or artery laceration. In-hospital mortality was 36 % including six procedural/operative deaths (0.2 %).[50] Factors associated with increased procedural complications (not mortality) risk include body mass index (BMI) <25 kg/m^2, damaged leads and ICD leads.[42] Predictors of major complications associated with TLE include cerebrovascular disease, ejection fraction ≤15 %, lower platelet count, international normalised ratio ≥1.2, mechanical sheaths and powered sheaths.[51] Thirty-day all-cause mortality following TLE has been associated with BMI, haemoglobin, end-stage renal disease left ventricular ejection fraction, New York Heart Association (NYHA) functional class, extraction for infection, number of prior lead extractions performed by the operator and extraction of a dual-coil defibrillator lead.[52]

Procedural success can be enhanced in lead extraction by the use of several tools and techniques such as locking stylets (Cook Medical and Spectranetics), powered and non-powered sheaths

Figure 2: Causes of Cardiac Implantable Electronic Devices Infection Mortality



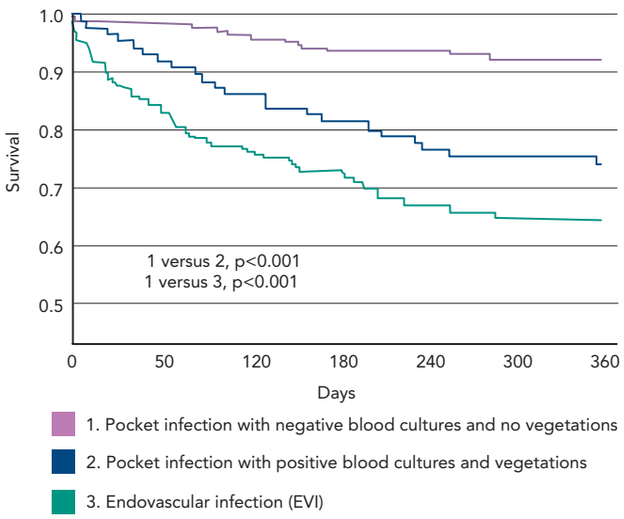
Source: Tarakji, 2010.[25]

(Evolution®, Cook Medical and TightRail™, Spectranetics) and laser technology[53,54] such as the Excimer and GlideLight™ (Spectranetics). An observational retrospective study concluded that lead extraction employing laser sheaths is highly successful with a low procedural complication rate, and that increasing experience is associated with greater success.[32] Several reports have described the effectiveness of the Evolution sheath.[55–58] The use of locking stylets placed in the lead to facilitate the application of traction and to stabilise the lead during sheath dissection of fibrotic tissue is essential.[59] However, the use of the electrosurgical technique for lead extraction seems to be decreasing according to data from the ELECTRA study.[48]

Although TLE intraprocedural mortality is very low, postprocedural and long-term mortality when extraction is performed for the indication of infection remain significant.[60–62] A recent study reviewed records of all patients with infected CIEDs who underwent TLE at a tertiary care centre between 2002 and 2008. Patients (n=502) were stratified into two groups: those presenting with pocket infection (n=289, 58 %), and those who presented with bacteraemia, with or without vegetation, and a pocket that appeared benign, termed endovascular infection (EVI) (n=213, 42 %). The one-year mortality rate was 20 %; EVI was associated with significantly higher one-year mortality (HR 2.1, p=0.0008). Among patients with EVI, 100 had vegetation on TOE however there was no difference in one-year mortality between patients with EVI and vegetation compared with patients with EVI and no vegetation. Risk factors for one-year mortality among patients with EVI included chronic renal insufficiency or history of renal insufficiency, end stage renal disease, NYHA functional class III or IV, prior valve surgery, diabetes and bleeding requiring transfusion. The presence of vegetations was not associated with increased one-year mortality (see *Figure 3*).[63]

A study of autopsy findings of patients with CIEDs found other issues relating to leads such as thrombi on ventricular/atrial leads (48 %), bipolar lead rings fixed by fibrous tissue (22 %), connective tissue bridges or tunnels in ventricle/atrium (71 %) and ventricular leads fixed to valve or penetrating chordae (46 %).[64] Depending on their location, such connective tissue surrounding the leads, as well as leads partially positioned outside the vessels or the heart, may increase the risk of complications during lead extraction. The present HRS and EHRA recommendations do not fully cover the timing of reimplantion or the treatment of pacemaker and ICD dependent patients, partially due to lack of studies comparing strategies. Amendments to the recommendations regarding these issues are highly desirable. Contralateral reimplantation in CIED infection patients is however always recommended, when possible. In summary, advances in TLE

Figure 3: Kaplan-Meier Survival Curves for One-year Mortality Among Patients with Cardiac Implantable Electronic Devices Undergoing Transvenous Lead Extraction



Source: Tarakji, 2010.[25]

have improved procedural safety for patients with CIED infection, but overall mortality remains high and there is a need for further studies to optimise treatment of at-risk patients.

Strategies to Prevent Cardiac Implantable Electronic Device Infection

The first preventive strategy against CIED infection is not reopening a CIED pocket unless necessary. ICD pulse generators in primary prevention systems may not always need replacement. It is possible to maximise battery longevity by setting the lower rate limit (LRL) at 50 bpm, choosing a better LV lead impedance vector for CRT, using devices with quadripolar LV leads or selecting high battery capacity devices, particularly with CRT-D systems. In addition, central lines (vascular catheters) should be avoided in patients with CIED devices, because they may be associated with higher risk of mortality from infection.[34]

Leadless pacemaker technology provides an alternative that does not require pockets or leads[65,66,67] and therefore avoids many of the problems associated with intravascular lead use, including pocket infection. This represents an important therapeutic advance in suitable patients.[68] In addition, subcutaneous ICDs (SICD) are now available. The SICD is implanted inferior and lateral to the left breast in mid-axillary line, and the lead is placed under the skin along the left side of the sternum. Therefore the lead is not intravascular or in contact with cardiac tissue, minimising intravascular infection risk.[69] However, to date, no comparative studies between the SICD and conventional ICDs have been reported. Therefore, the impact of SICD use on CIED infection rate is not yet known.

Various prophylaxis strategies have been suggested, including skin and nasal infection treatment, device pocket irrigation and operative prep skin barriers, but there is no evidence to support their use in preventing CIED infections. Preoperative cleansing of the patient's skin with chlorhexidine–alcohol has been found to be superior to cleansing with povidone–iodine for preventing abdominal surgical site infection.[70] However, two recent studies showed no significant difference in infection risk among patients undergoing CIED procedure using chlorhexidine–alcohol or povidone–iodine for skin preparation.[71,72] In addition, the antimicrobial treatment of pacemaker casings with antiseptics has been investigated *in vitro* and early studies showed promising results.[73]

The most common strategy to reduce infections is intravenous prophylaxis using antibiotics.[74] A double-blind clinical trial randomised patients (n=649) to prophylactic antibiotics (intravenous administration of 1 g cefazolin immediately before the procedure) or placebo. The trial was terminated early after a significantly lower rate of infection was observed in the antibiotic arm (0.63 % in antibiotic arm versus control [3.28 %]; RR=0.19; p=0.016).[74] However, all infections in this study were caused by cefazolin-sensitive isolates and the study population had a low prevalence of methicillin resistance compared with US hospitals (13 % *Staph. aureus* and 60 % coagulase-negative *Staphylococcus* species in study versus 55–60 % and 80–90 % in US hospitals).

The use of postoperative antibiotics has been investigated in two recent studies. In a prospective randomised, single-centre study, patients (n=1,008) received standard systemic antibiotic prophylaxis and were then randomised into four groups receiving either povidone-iodine, neomycin, a sterile non-adherent pad or placebo ointment after procedure. All patients were followed for at least 12 months. Surgical site inflammation and infection were graded based on degree of inflammation, discharge, wound culture and blood culture. The surgical site infection rate was more than doubled in those with longer procedural time (HR=2.3, p=0.01) but the use of topical antibiotics after closure did not show significant benefit.[75] A prospective database on patients undergoing PPM implantation from 1991–2009 (n=3,253) found that over 19 years the incidence of CIED infections fell from 3.6 % with no antibiotics to 2.9 % (perioperative antibiotics), to 0.4 % (peri- plus postoperative antibiotics), suggesting that perioperative followed by postoperative antibiotics may minimise infections.[76] However, the REPLACE registry found no difference in infection rate between those who received postoperative antibiotics and those who did not.[6]

The Prevention of Arrhythmia Device Infection Trial (PADIT) clinical trial is currently recruiting and aims to compare a centre-wide policy of incremental antibiotic therapy with conventional antibiotic prophylaxis in high-risk patients undergoing CIED implantation. Centres (not patients) will be randomised to either conventional antibiotic therapy (cefazolin or vancomycin for penicillin-allergic patients) or incremental antibiotic therapy comprising a single preoperative dose of cefazolin and vancomycin (vancomycin only in patients allergic to penicillin), an intraoperative bacitracin pocket wash then two days of postoperative antibiotic therapy comprising cefalexin or cephadroxil (clindamycin in penicillin-allergic patients). Centres will be randomised to one therapy and then crossover after 6, 12 and 18 months. During each treatment period the randomised antibiotic therapy will be used on all patients undergoing a device implant procedure.[77,78]

An additional strategy to combat pocket infection involves the use of an antibiotic envelope. The TYRX™ non-absorbable envelope (Medtronic) has shown substantial efficacy in clinical studies in reducing the infection rate.[23,79,80] This has led to the development of the TYRX absorbable envelope, which is constructed from a fully bioabsorbable multifilament mesh (see *Figure 4*). The envelope holds the CIED in place, preventing device migration, elutes antimicrobial agents minocycline and rifampicin for a minimum of 7 days; and then is fully absorbed approximately 9 weeks after implantation.

The TYRX envelope received US Food and Drug Administration clearance in May 2013 and the CE Mark in September 2014.

A growing body of evidence has demonstrated the efficacy of the TYRX envelopes in the prevention of CIED infections. In a single-centre retrospective cohort study, the infection rate in patients with ≥2 risk factors for CIED infection was compared in patients receiving the TYRX absorbable envelope (n=135), the TYRX non-absorbable envelope (n=353) and controls who did not receive an envelope (n=636). After a minimum 300 days, CIED infections were reported in 0 % of patients receiving the absorbable TYRX, 0.3 % for the non-absorbable TYRX, and 3.1 % for controls (p=1 for absorbable versus non-absorbable TYRX; p=0.03 for absorbable TYRX versus controls, and p=0.002 for non-absorbable TYRX versus controls; see *Figure 5*). This represents a very low prevalence of infection in subjects at risk and suggests that the use of the TYRX absorbable antibacterial envelope is a promising strategy.[81]

Two large (n=1,129) prospective multicentre cohort studies are currently investigating the impact of the TYRX non-absorbable envelope on CIED major infections and mechanical complication rates. The Citadel (TYRX Envelope for Prevention of Infection Following Replacement with an Implantable Cardioverter-Defibrillator) and Centurion (TYRX Envelope for Prevention of Infection Following Replacement with a Cardiac Resynchronisation Therapy Device) studies aim to compare the rate of CIED infection and mechanical complication after CIED replacement with an ICD or CRT. Recently presented data indicated that the TYRX antibacterial envelope reduces the infection rate by 80 % compared with historical control data.[82] However, it should be noted that the comparison of data with historical controls has well-known limitations, and there is a need for randomised study data to confirm the effect of the TYRX envelope.

The Worldwide Randomised Antibiotic Envelope Infection Prevention Trial (WRAP-IT) is a multicentre, single-blinded, randomised study that aims to evaluate the ability of the TYRX absorbable antibiotic envelope to reduce major CIED infections during 12 months following CIED generator replacement, upgrade, revision or *de novo* CRT-D implant.[78] Patients (around 7,000) will be randomised 1:1 to envelope versus no envelope. The primary endpoint is the rate of major CIED infections leading to one or more of the following: CIED system removal, CIED pocket revision, antibiotic therapy or death. Secondary objectives include all cause mortality and CIED removal due to pain without obvious infection. The study also aims to determine the one-year incidence rate of CIED infection among a large cohort of patients undergoing CIED procedures, as well as elucidating risk factors for CIED infection.

A recent retrospective study analysed data from patients who underwent CIED implantations, with (n=365) or without (n=1,111) the TYRX envelope. In the non-TYRX group, 19 infections were observed (1.7 %), versus 0 in the TYRX group (p=0.006). It was estimated that the TYRX prevented 6.2 additional infections costing approximately $340,000. This cost was similar to the actual cost of the envelopes in the TYRX group, estimated at $320,000.[83] Therefore use of an antibacterial envelope as standard care appears to be economically reasonable.

Discussion

As a result of the increasing incidence and complexity of CIED treatment, infection is frequently encountered in clinical practice and is associated with significant morbidity and mortality. Moreover, the infection rate is rising faster than the rate of CIED implantation. Many questions remain unanswered, including the true infection incidence, clear infection definitions, better understanding of risk factors and the impact of implantation practices and techniques.

More experience and advances in TLE including laser technology and rotational sheaths have reduced procedural complications; however device infection, despite lead extraction, is associated with long-term mortality of 15–25 % at one year. The mortality risk is higher with endovascular infection than with pocket infection.

There is a need for further studies aimed at elucidating the complication and mortality risks associated with device and lead extraction: these may help guide CIED and lead management as well as extraction tool and technique development.

Figure 4: The TYRX™ Absorbable Antibacterial Envelope

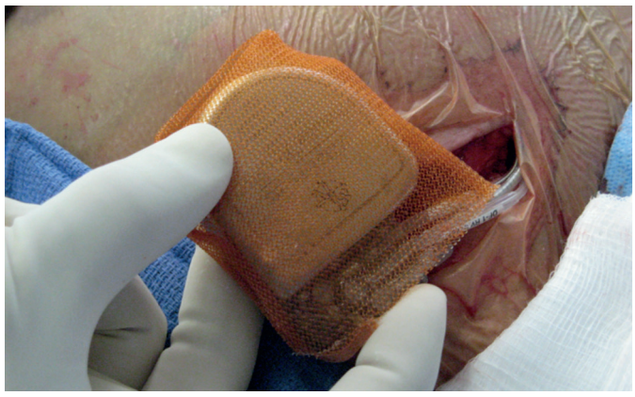
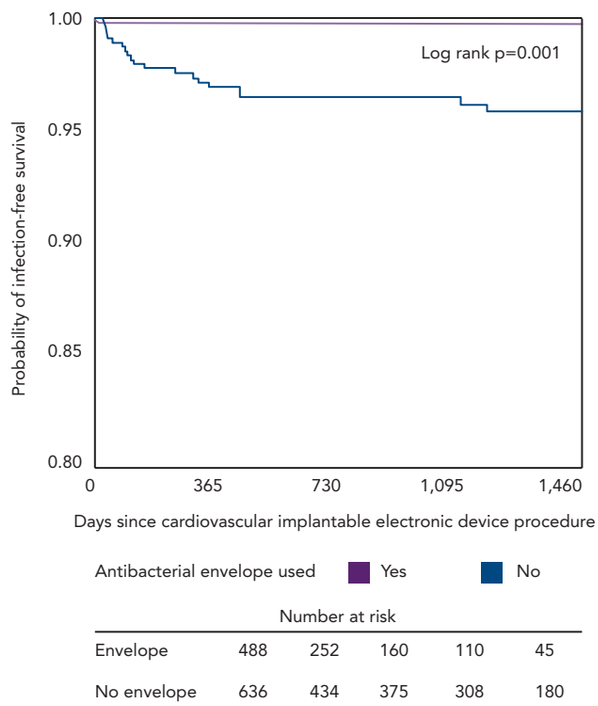


Photo courtesy of Dr Christopher R Ellis. Previously published in Ellis et al, 2011.[84]

Figure 5: Efficacy of TYRX™ Antibacterial Envelope in High-risk Subjects



Source: Kolek et al, 2015.[81]

In terms of preventing CIED infections, interim data from non-randomised studies indicate that the use of the TYRX antibacterial envelope appears to be one promising and cost-effective strategy in preventing CIED infections. The WRAP IT study will help assess the efficacy of the absorbable TYRX envelope in reducing infection in a prospective randomised large clinical trial. ■

1. Beck H, Boden WE, Patibandla S, et al. 50th anniversary of the first successful permanent pacemaker implantation in the United States: historical review and future directions. *Am J Cardiol* 2010;**106**:810–8. PMID: 21391322.
2. Uslan DZ, Tleyjeh IM, Baddour LM, et al. Temporal trends in permanent pacemaker implantation: a population-based study. *Am Heart J* 2008;**155**:896–903. DOI: 10.1016/j.ahj.2007.12.022; PMID: 18440339; PMCID: PMC2597171.
3. Greenspon AJ, Patel JD, Lau E, et al. 16-year trends in the infection burden for pacemakers and implantable cardioverter-defibrillators in the United States 1993 to 2008. *J Am Coll Cardiol* 2011;**58**:1001–6. DOI: 10.1016/j.jacc.2011.04.033; PMID: 21867833.
4. Mond HG, Proclemer A. The 11th world survey of cardiac pacing and implantable cardioverter-defibrillators: calendar year 2009 – a World Society of Arrhythmia's project, *Pacing Clin Electrophysiol* 2011;**34**:1013–27. DOI: 10.1111/j.1540 8159.2011.03150.x; PMID: 21707667.
5. Cabell CH, Heidenreich PA, Chu VH, et al. Increasing rates of cardiac device infections among Medicare beneficiaries: 1990-1999. *Am Heart J* 2004;**147**:582–6. PMID: 15077071.
6. Uslan DZ, Gleva MJ, Warren DK, et al. Cardiovascular implantable electronic device replacement infections and prevention: results from the REPLACE Registry. *Pacing Clin Electrophysiol* 2012;**35**:81–7. DOI: 10.1111/j.1540-8159.2011.03257.x; PMID: 22077194.
7. Klug D, Balde M, Pavin D, et al. Risk factors related to infections of implanted pacemakers and cardioverter-defibrillators: results of a large prospective study. *Circulation* 2007;**116**:1349–55. PMID: 17724263.
8. Poole JE, Gleva MJ, Mela T, et al. Complication rates associated with pacemaker or implantable cardioverter-defibrillator generator replacements and upgrade procedures: results from the REPLACE registry. *Circulation* 2010;**122**:1553–61. DOI: 10.1161/CIRCULATIONAHA.110.976076; PMID: 20921437.
9. Voigt A, Shalaby A, Saba S. Continued rise in rates of cardiovascular implantable electronic device infections in the United States: temporal trends and causative insights. *Pacing Clin Electrophysiol* 2010;**33**:414–9. DOI: 10.1111/j.1540-8159.2009.02569.x; PMID: 19793359.
10. Borleffs CJ, Thijssen J, de Bie MK, et al. Recurrent implantable cardioverter-defibrillator replacement is associated with an increasing risk of pocket-related complications. *Pacing Clin Electrophysiol* 2010;**33**:1013–9. DOI: 10.1111/j.1540-8159.2010.02780.x. PMID: 20456647.
11. Kurtz SM, Ochoa JA, Lau E, et al. Implantation trends and patient profiles for pacemakers and implantable cardioverter defibrillators in the United States: 1993-2006. *Pacing Clin Electrophysiol* 2010;**33**:705–11. DOI: 10.1111/j.1540-8159.2009.02670.x; PMID: 20059714.
12. Greenspon AJ, Patel JD, Lau E, et al. Trends in permanent pacemaker implantation in the United States from 1993 to 2009: increasing complexity of patients and procedures. *J Am Coll Cardiol* 2012;**60**:1540–5. DOI: 10.1016/j.jacc.2012.07.017; PMID: 22999727.
13. Centers for Medicare & Medicaid Services. U.S. Department of Health and Human Services Inpatient Prospective Payment System (IPPS) Final Rule FY2013. http://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/AcuteInpatientPPS/index.html?redirect=/AcuteInpatientPPS/IPPS2013/list.asp (accessed 14 January 2016).
14. Sohail MR, Henrikson CA, Braid-Forbes MJ, et al. Mortality and cost associated with cardiovascular implantable electronic device infections. *Arch Intern Med* 2011;**171**:1821–8. DOI: 10.1001/archinternmed.2011.441; PMID: 21911623.
15. Greenspon AJ, Patel JD, Lau E, et al. Inpatient vs. outpatient device implantation surgery: impact on cardiac implantable electronic device infection. Poster presented at the Heart Rhythm Society 34th Annual Scientific Session, Denver, CO, 8-11 May 2013. Po02–43.
16. Bloom H, Heeke B, Leon A, et al. Renal insufficiency and the risk of infection from pacemaker or defibrillator surgery. *Pacing Clin Electrophysiol* 2006;**29**:142–5. PMID: 16492298.
17. Lekkerkerker JC, van Nieuwkoop C, Trines SA, et al. Risk factors and time delay associated with cardiac device infections: Leiden device registry. *Heart* 2009;**95**:715–20. DOI: 10.1136/hrt.2008.151985; PMID: 19036758.
18. Herce B, Nazeyrollas P, Lesaffre F, et al. Risk factors for infection of implantable cardiac devices: data from a registry of 2496 patients. *Europace* 2013;**15**:66–70. DOI: 10.1093/europace/eus284; PMID: 23097224.
19. Sohail MR, Uslan DZ, Khan AH, et al. Risk factor analysis of permanent pacemaker infection. *Clin Infect Dis* 2007;**45**:166–73. PMID: 17578774.
20. Howarth DM, Curteis PG, Gibson S. Infected cardiac pacemaker wires demonstrated by Tc-99m labeled white blood cell scintigraphy. *Clin Nucl Med* 1998;**23**:74–6. PMID: 9481492.
21. Romeyer-Bouchard C, Da Costa A, Dauphinot V, et al. Prevalence and risk factors related to infections of cardiac resynchronization therapy devices. *Eur Heart J* 2010;**31**:203–10. DOI: 10.1093/eurheartj/ehp421; PMID: 19875388.
22. Kleemann T, Becker T, Strauss M, et al. Prevalence of bacterial colonization of generator pockets in implantable cardioverter defibrillator patients without signs of infection undergoing generator replacement or lead revision. *Europace* 2010;**12**:58–63. DOI: 10.1093/europace/eup334; PMID: 19861383.
23. Mittal S, Shaw RE, Michel K, et al. Cardiac implantable electronic device infections: incidence, risk factors, and the effect of the AigisRx antibacterial envelope. *Heart Rhythm* 2014;**11**:595–601. DOI: 10.1016/j.hrthm.2013.12.013; PMID: 24333543.
24. Da Costa A, Lelievre H, Kirkorian G, et al. Role of the preaxillary flora in pacemaker infections: a prospective study. *Circulation* 1998;**97**:1791–5. PMID: 9603533.
25. Tarakji KG, Chan EJ, Cantillon DJ, et al. Cardiac implantable electronic device infections: presentation, management, and patient outcomes. *Heart Rhythm* 2010;**7**:1043–7. DOI: 10.1016/j.hrthm.2010.05.016; PMID: 20470904.
26. Sohail MR, Uslan DZ, Khan AH, et al. Management and outcome of permanent pacemaker and implantable cardioverter-defibrillator infections. *J Am Coll Cardiol* 2007;**49**:1851–9. PMID: 17481444.
27. Margey R, McCann H, Blake G, et al. Contemporary management of and outcomes from cardiac device related infections. *Europace* 2010;**12**:64–70. DOI: 10.1093/europace/eup362; PMID: 1991031.
28. Baddour LM, Epstein AE, Erickson CC, et al. Update on cardiovascular implantable electronic device infections and their management: a scientific statement from the American Heart Association. *Circulation* 2010;**121**:458–77. DOI: 10.1161/CIRCULATIONAHA.109.192665; PMID: 20048212.
29. Greenspon AJ, Rhim ES, Mark G, et al. Lead-associated endocarditis: the important role of methicillin-resistant Staphylococcus aureus. *Pacing Clin Electrophysiol* 2008;**31**:548–53. DOI: 10.1111/j.1540-8159.2008.01039.x; PMID: 18439167.
30. Klug D, Lacroix D, Savoye C, et al. Systemic infection related to endocarditis on pacemaker leads: clinical presentation and management. *Circulation* 1997;**95**:2098–107. PMID: 9133520.
31. Klug D, Wallet F, Lacroix D, et al. Local symptoms at the site of pacemaker implantation indicate latent systemic infection. *Heart* 2004;**90**:882–6. PMID: 15253959.
32. Wazni O, Epstein LM, Carrillo RG, et al. Lead extraction in the contemporary setting: the LExICon study: an observational retrospective study of consecutive laser lead extractions. *J Am Coll Cardiol* 2010;**55**:579–86. DOI: 10.1016/j jacc.2009.08.070; PMID: 20152562.
33. Golzio PG, Fanelli AL, Vinci M, et al. Lead vegetations in patients with local and systemic cardiac device infections: prevalence, risk factors, and therapeutic effects. *Europace* 2013;**15**:89–100. DOI: 10.1093/europace/eus240; PMID: 22968846.
34. Kim DH, Tate J, Dresen WF, et al. Cardiac implanted electronic device-related infective endocarditis: clinical features, management, and outcomes of 80 consecutive patients. *Pacing Clin Electrophysiol* 2014;**37**:978–85. DOI: 10.1111/pace.12452; PMID: 25060820.
35. Tarakji KG, Wilkoff BL. Management of cardiac implantable electronic device infections: the challenges of understanding the scope of the problem and its associated mortality. *Expert Rev Cardiovasc Ther* 2013;**11**:607–16. DOI: 10.1586/erc.12.190; PMID: 23621142.
36. Rundstrom H, Kennergren C, Andersson R, et al. Pacemaker endocarditis during 18 years in Göteborg. *Scand J Infect Dis* 2004;**36**:674–9. PMID: 15370655.
37. Madhavan M, Sohail MR, Friedman PA, et al. Outcomes in patients with cardiovascular implantable electronic devices and bacteremia caused by Gram-positive cocci other than Staphylococcus aureus. *Circ Arrhythm Electrophysiol* 2010;**3**:639–45. DOI: 10.1161/CIRCEP.110.957514; PMID: 20852296.
38. Sarrazin JF, Philippon F, Tessier M, et al. Usefulness of fluorine-18 positron emission tomography/computed tomography for identification of cardiovascular implantable electronic device infections. *J Am Coll Cardiol* 2012;**59**:1616–25. DOI: 10.1016/j.jacc.2011.11.059; PMID: 22538331.
39. Ahmed FZ, James J, Cunnington C, et al. Early diagnosis of cardiac implantable electronic device generator pocket infection using (1)(8)F-FDG-PET/CT. *Eur Heart J Cardiovasc Imaging* 2015;**16**:521–30. DOI: 10.1093/ehjci/jeu295. Epub 2015 Feb 3; PMID: 25651856. PMCID: PMC4407104.
40. Sohail MR, Sultan OW, Raza SS. Contemporary management of cardiovascular implantable electronic device infections. *Expert Rev Anti Infect Ther* 2010;**8**:831–9. DOI: 10.1586/eri.10.54; PMID: 20586567.
41. Wilkoff BL, Love CJ, Byrd CL, et al. Transvenous lead extraction: Heart Rhythm Society expert consensus on facilities, training, indications, and patient management. *Heart Rhythm* 2009;**6**:1085–104. DOI: 10.1016/j.hrthm.2009.05.020; PMID: 19560098.
42. Deharo JC, Bongiorni MG, Rozkovec A, et al. Pathways for training and accreditation for transvenous lead extraction: a European Heart Rhythm Association position paper. *Europace* 2012;**14**:124–34. DOI: 10.1093/europace/eur338; PMID: 22167387.
43. Chua JD, Wilkoff BL, Lee I, et al. Diagnosis and management of infections involving implantable electrophysiologic cardiac devices. *Ann Intern Med* 2000;**133**:604–8. PMID: 11033588.
44. del Río A, Anguera I, Miró JM, et al. Surgical treatment of pacemaker and defibrillator lead endocarditis: the impact of electrode lead extraction on outcome. *Chest* 2003;**124**:1451–9. PMID: 14555579.
45. Cacoub P, Leprince P, Nataf P, et al. Pacemaker infective endocarditis. *Am J Cardiol* 1998;**82**:480–4. PMID: 9723637.
46. Le KY, Sohail MR, Friedman PA, et al. Impact of timing of device removal on mortality in patients with cardiovascular implantable electronic device infections. *Heart Rhythm* 2011;**8**:1678–85. DOI: 10.1016/j.hrthm.2011.05.015; PMID: 21699855.
47. Voigt A, Shalaby A, Saba S. Rising rates of cardiac rhythm management device infections in the United States: 1996 through 2003. *J Am Coll Cardiol* 2006;**48**:590–1. PMID: 16875991.
48. Bongiorni MG. ELECTRa (European Lead Extraction ConTRolled Registry: preliminary data on Transvenous Lead Extraction in Europe, Presented at the ESC Congress, Barcelona, Spain, 30 August 2014.
49. Habib A, Le KY, Baddour LM, et al. Predictors of mortality in patients with cardiovascular implantable electronic device infections. *Am J Cardiol* 2013;**111**:874–9. DOI: 10.1016/j.amjcard.2012.11.052; PMID: 23276467.
50. Brunner MP, Cronin EM, Wazni O, et al. Outcomes of patients requiring emergent surgical or endovascular intervention for catastrophic complications during transvenous lead extraction. *Heart Rhythm* 2014;**11**:419–25. DOI: 10.1016/j.hrthm.2013.12.004; PMID: 24315967.
51. Brunner MP, Cronin EM, Duarte VE, et al. Clinical predictors of adverse patient outcomes in an experience of more than 5000 chronic endovascular pacemaker and defibrillator lead extractions. *Heart Rhythm* 2014;**11**:799–805. DOI: 10.1016/j.hrthm.2014.01.016; PMID: 24444444.
52. Brunner MP, Yu C, Hussein AA, et al. Nomogram for predicting 30-day all-cause mortality after transvenous pacemaker and defibrillator lead extraction. *Heart Rhythm* 2015;**2**:2381–6. DOI: 10.1016/j.hrthm.2015.07.024; PMID: 26190318.
53. Byrd CL, Wilkoff BL, Love CJ, et al. Clinical study of the laser sheath for lead extraction: the total experience in the United States. *Pacing Clin Electrophysiol* 2002;**25**:804–8. PMID: 12049372.
54. Wilkoff BL, Byrd CL, Love CJ, et al. Pacemaker lead extraction with the laser sheath: results of the pacing lead extraction with the excimer sheath (PLEXES) trial. *J Am Coll Cardiol* 1999;**33**:1671–6. PMID: 10334441.
55. Oto A, Aytemir K, Canpolat U, et al. Evolution in transvenous extraction of pacemaker and implantable cardioverter defibrillator leads using a mechanical dilator sheath. *Pacing Clin Electrophysiol* 2012;**35**:834–40. DOI: 10.1111/j.1540-8159.2012.03385.x; PMID: 22486778.
56. Kocabas U, Duygu H, Eren NK, et al. [Evaluation of lead extraction procedures using the Evolution Mechanical Dilatator Sheath lead extraction system: A single centre experience]. *Turk Kardiyol Dern Ars* 2015;**43**:350–5. DOI: 10.5543/tkda.2015.76329; PMID: 26142788.
57. Aksu T, Guray U, Sen T, et al. Use of the mechanical dilator sheath for removal of endocardial leads: a single center experience. *Pacing Clin Electrophysiol* 2012;**35**:514–8. DOI: 10.1111/j.1540-8159.2012.03329.x; PMID: 22353144.
58. Hussein AA, Wilkoff BL, Martin DO, et al. Initial experience with the Evolution mechanical dilator sheath for lead extraction: safety and efficacy. *Heart Rhythm* 2010;**7**:870–3. DOI: 10.1016/j.hrthm.2010.03.019; PMID: 20346418.
59. Kennergren C, Schaerf RH, Sellers TD, et al. Cardiac lead extraction with a novel locking stylet. *J Interv Card Electrophysiol* 2000;**4**:591–3. PMID: 11141204.
60. Maytin M, Jones SO, Epstein LM. Long-term mortality after transvenous lead extraction. *Circ Arrhythm Electrophysiol* 2012;**5**:252–7. DOI: 10.1161/CIRCEP.111.965277. PMID: 22362891.
61. Deckx S, Marynissen T, Rega F, et al. Predictors of 30-day and 1-year mortality after transvenous lead extraction: a single-centre experience. *Europace* 2014;**16**:1218–25. DOI: 10.1093/europace/eut410; PMID: 24569572.
62. Hamid S, Arujuna A, Ginks M, et al. Pacemaker and defibrillator lead extraction: predictors of mortality during follow-up. *Pacing Clin Electrophysiol* 2010;**33**:209–16. DOI: 10.1111/j.1540-8159.2009.02601.x; PMID: 19889182.
63. Tarakji KG, Wazni OM, Harb S, et al. Risk factors for 1-year mortality among patients with cardiac implantable electronic device infection undergoing transvenous lead extraction: the impact of the infection type and the presence of vegetation on survival. *Europace* 2014;**16**:1490–5. DOI: 10.1093/europace/euu147; PMID: 25087154.
64. Novak M, Dvorak P, Kamaryt P, et al. Autopsy and clinical context in deceased patients with implanted pacemakers and defibrillators: intracardiac findings near their leads and electrodes. *Europace* 2009;**11**:1510–6. DOI: 10.1093/europace/

eup216; PMID: 19684037.
65. Reddy VY, Knops RE, Sperzel J, et al. Permanent leadless cardiac pacing: results of the LEADLESS trial. *Circulation* 2014;**129**:1466–71. DOI: 10.1161/CIRCULATIONAHA.113.006987; PMID: 24664277.
66. Fudim M, Fredi JL, Ball SK, et al. Transcatheter leadless pacemaker implantation for complete heart block following CoreValve transcatheter aortic valve replacement. *J Cardiovasc Electrophysiol* 2016;**27**:125–6. DOI: 10.1111/jce.12745; PMID: 26100053.
67. Steinwender C, Hönig S, Saleh, K, et al. First-in-man experience with a minimally invasive transcatheter pacemaker. Presented at Cardiostim 2014, Nice, France, 19 June 2014. Abstract 83/1.
68. Gold MR. Are leadless pacemakers a niche or the future of device therapy? *J Am Coll Cardiol* 2015;**65**:1505–8. DOI: 10.1016/j.jacc.2015.02.021; PMID: 25881931.
69. Chang PM, Doshi R, Saxon LA. Subcutaneous implantable cardioverter-defibrillator. *Circulation* 2014;**129**:e644–6. DOI: 10.1161/CIRCULATIONAHA.113.006645; PMID: 24914020.
70. Darouiche RO, Wall MJ Jr, Itani KM, et al. Chlorhexidine–alcohol versus povidone–iodine for surgical-site antisepsis. *N Engl J Med* 2010;**362**:18–26. DOI: 10.1056/NEJMoa0810988; PMID: 20054046.
71. Qintar M, Zardkoohi O, Hammadah M, et al. The impact of changing antiseptic skin preparation agent used for cardiac implantable electronic device (CIED) procedures on the risk of infection. *Pacing Clin Electrophysiol* 2015;**38**:240–6. DOI: 10.1056/NEJMoa0810988; PMID: 20054046.
72. Da Costa A, Tulane C, Dauphinot V, et al. Preoperative skin antiseptics for prevention of cardiac implantable electronic device infections: a historical-controlled interventional trial comparing aqueous against alcoholic povidone-iodine solutions. *Europace* 2015;**17**:1092–8. DOI: 10.1093/europace/euu293; PMID: 25917024.
73. Marsch G, Mashaqi B, Burgwitz K, et al. Prevention of pacemaker infections with perioperative antimicrobial treatment: an in vitro study. *Europace* 2014;**16**:604–11. DOI: 10.1093/europace/eut222; PMID: 23928734.
74. de Oliveira JC, Martinelli M, Nishioka SA, et al. Efficacy of antibiotic prophylaxis before the implantation of pacemakers and cardioverter-defibrillators: results of a large, prospective, randomized, double-blinded, placebo-controlled trial. *Circ Arrhythm Electrophysiol* 2009;**2**:29–34. DOI: 10.1161/CIRCEP.108.795906; PMID: 19808441.
75. Khalighi K, Aung TT, Elmi F. The role of prophylaxis topical antibiotics in cardiac device implantation. *Pacing Clin Electrophysiol* 2014;**37**:304–11. DOI: 10.1111/pace.12280; PMID: 24164587.
76. Senaratne JM, Jayasuriya A, Irwin M, et al. A 19-year study on pacemaker-related infections: a claim for using postoperative antibiotics. *Pacing Clin Electrophysiol* 2014;**37**:947–54. DOI: 10.1111/pace.12403; PMID: 24766534.
77. Connolly SJ, Philippon F, Longtin Y, et al. Randomized cluster crossover trials for reliable, efficient, comparative effectiveness testing: design of the Prevention of Arrhythmia Device Infection Trial (PADIT). *Can J Cardiol* 2013;**29**:652–8. DOI: 10.1016/j.cjca.2013.01.020; PMID: 23702356.
78. Prevention of Arrhythmia Device Infection Trial (PADIT). https://clinicaltrials.gov/ct2/show/NCT01628666 Accessed 25 January 2016.
79. Bloom HL, Constantin L, Dan D, et al. Implantation success and infection in cardiovascular implantable electronic device procedures utilizing an antibacterial envelope. *Pacing Clin Electrophysiol* 2011;**34**:133–42. DOI: 10.1111/j.1540-8159.2010.02931.x; PMID: 20942819.
80. Kolek MJ, Dresen WF, Wells QS, Ellis CR. Use of an antibacterial envelope is associated with reduced cardiac implantable electronic device infections in high-risk patients. *Pacing Clin Electrophysiol* 2013;**36**:354–61. DOI: 10.1111/pace.12063; PMID: 23252988.
81. Kolek MJ, Patel NJ, Clair WK, et al. Efficacy of a bio-absorbable antibacterial envelope to prevent cardiac implantable electronic device infections in high-risk subjects. *J Cardiovasc Electrophysiol* 2015;**26**:1111–6. DOI: 10.1111/jce.12768. Epub 2015 Sep 6; PMID: 26222980.
82. Henrickson CA, Sohail MR, Simons GR, et al. CITADEL/CENTURION study interim analysis: use of an antibacterial envelope is associated with very low 90-day CIED infection rates. Presented at 34th Annual Scientific Sessions, Heart Rhythm 2013, Denver, Colorado, 11 May 2013. Abstract LB03-01.
83. Shariff N, Eby E, Adelstein E, et al. Health and economic outcomes associated with use of an antimicrobial envelope as a standard of care for cardiac implantable electronic device implantation. *J Cardiovasc Electrophysiol* 2015;**26**:783–9. DOI: 10.1111/jce.12684; PMID: 25845917.
84. Ellis CR, Kolek MJ. Rising infection rate in cardiac electronic device implantation; the role of the AIGISRx® antibacterial envelope in prophylaxis. *Comb Prod Ther* 2011;1:1–9.