Clinical update

Infected cardiac-implantable electronic devices: prevention, diagnosis, and treatment

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Cardiac implantable electronic device (CIED) infection, according to current trends, appears to be an increasing problem. It can be indolent and its diagnosis challenging. Cardiac implantable electronic device infections are potentially lethal, and timely diagnosis and early initiation of correct treatment are of highest importance for patient prognosis. For reducing CIED infections, careful patient selection, preventative measures, and appropriate choice of device are key. The current review presents available data and consensus opinion within the field of CIED infection and identifies important current practice points and aspects for future development. Strategies for reducing CIED infection should be tested in sufficiently powered and well-designed multicentre randomized controlled trials.

Keywords Cardiac implantable electronic device • Infection • Prevention • Diagnosis • Treatment

Introduction

Cardiac implantable electronic device (CIED) therapy is safe and effective. Complications are infrequent, but among them, infection poses a major hazard, causing significant morbidity, increasing mortality, and generating considerable healthcare costs.1–4 Its incidence is growing, only partly explained by increasing numbers of CIED implants resulting from widening indications and increasing numbers of generator replacements. The absolute rate of device infection itself increased recently.2,5,6 Causes for this trend are uncertain, but likely relate to increasing proportion of implantable cardioverter defibrillator (ICD) and cardiac resynchronization therapy (CRT) devices implanted,2,7 coupled to implantations in ‘higher risk’ candidates, that is, patients with heart failure, diabetes, and renal failure.2

Current knowledge is mainly based upon observational data. While no international guidelines exists for handling infected CIED’s, an expert consensus statement on lead extractions,8 an American Heart Association scientific statement9 and a recent British guideline paper10 are useful for guiding decisions. This review aims to present available data and consensus opinion within the field of CIED infection and identify important current practice points and aspects for future development.

Incidence of cardiac implantable electronic device infection

Reported CIED infection rates vary according to definitions and follow-up duration. In a large cohort of pacemaker recipients, estimated incidence was 1.82/1000 device-years and higher within the first 12 months.11 Infection risk after pacemaker implant is 0.5–1% within the first 6–12 months.11–13 The more complex CIED system implanted the higher infection risk. Risk is higher with ICDs,14 recently estimated 1.7% within 6 months among 200 000 ICD recipients,15 even higher in CRT-recipients, 9.5% over 2 years15 and among these highest with defibrillators (CRT-D).16 Infection risk is higher for devices implanted at thoracotomy and may be 2–4× greater after device replacement and upgrades compared with primary implants.3,11–13,17

Pathogenesis and presentation

Breach of the skin barrier introduces bacteria into the pocket. These may colonize and not always cause clinically relevant infection. Pathogenesis of CIED infections is associated with biofilm formation on device surfaces, described as ‘a structured community of bacterial cells enclosed in a self-produced polymeric matrix and adherent to an inert or living surface’.18 Bacteria in biofilm are protected from killing by host defences and antimicrobial agents. Therefore, entire device removal is needed to treat infection. Most infections are caused by bacteria, which are part of the patient’s normal skin flora. Gram-positive species are most frequent, usually Staphylococcus species, less commonly Gram-negative bacteria. Fungi, anaerobes, or polymicrobial infections are rare.14,19 Cultures are negative in 15%. Pocket infection is the most common presentation of CIED infection.15,19,20 This should not be assumed localized since infection commonly tracks along leads and/or causes secondary
blood-stream infection and endocarditis. Less commonly, the mechanism of blood-stream infection is haematogenous spread of bacteria from another infection site with secondary involvement of intravascular CIED parts.

**Prevention of cardiac implantable electronic device infection**

Cardiac implantable electronic device infection is serious for the patient, potentially fatal, and virtually always necessitates complete CIED system removal. The most important issue within this field therefore is to prevent CIED infections.

**Before implantation**

Physicians should prescribe CIED treatment carefully. A thorough evaluation of its indication is mandatory for each patient with a balanced assessment of risks and benefits, accounting for individual patient characteristics and comorbidities. Lower infection risk with simpler CIED systems should be weighed against potential benefits of more complex systems. Use of smaller devices and shorter leads in asthenic patients reducing pocket bulk, or sub-pectoral implants to prevent erosions should be considered, and attention given to battery longevity to reduce anticipated generator replacements. Need for device upgrade should be evaluated extremely carefully, given the high infection risk.

Meticulous attention to pre-operative preparation is necessary (Table 1). Fever <24 h before implant is associated with 5.8 times higher infection risk. It is therefore important to diagnose and treat ongoing infections before CIED implant. Patients presenting with need for acute cardiac pacing are challenging. It is unsettled whether the best management strategy is temporary transvenous pacing and treatment of infection, thus postponing permanent CIED implantation, or proceeding to primary permanent CIED implantation with concomitant treatment, particularly with ‘low-risk’ conditions such as urinary tract colonization. Most commonly, the first of these strategies is chosen to reduce potential infection of the permanent device. However, temporary pacing itself is associated with increased risk of CIED infection (odds ratio, OR 2.5) and should be performed under sterile conditions. Its duration should be minimized since longer hospital stay awaiting permanent CIED implantation is associated with significant complication risk.

Chronic skin conditions increase infection risk and should be appropriately treated to avoid skin defects especially around implantation site. Telemetry electrodes should not be mounting in an area of anticipated implantation to prevent skin reactions and defects.

Indwelling lines, for example, central venous catheters and chest tubes should be removed in timely fashion before CIED implantation. Ideal timeframe is unknown, most operators prefer >24 h.

Patients who are nasal carriers of Staphylococcus aureus (20–30% of population) are at increased risk of health care associated infections with this organism. Recently, a randomized controlled trial documented that screening and decolonizing of nasal carriers of these bacteria reduces number of surgical site infections (relative risk 0.42) among patients admitted to hospital for surgery. Whether such a strategy reduces CIED infection is unknown. No data support screening and treatment of health personnel.

### Table 1  Patient-, device-, and intervention-related factors associated with increased cardiac implantable electronic device infection risk

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early CIED re-intervention</td>
<td>2.7–15</td>
</tr>
<tr>
<td>Pocket haematoma</td>
<td>4.0–6.7</td>
</tr>
<tr>
<td>CIED replacement</td>
<td>2.7</td>
</tr>
<tr>
<td>More complex CIED</td>
<td>1.3–5.4</td>
</tr>
<tr>
<td>Temporary pacing</td>
<td>2.5–5.0</td>
</tr>
<tr>
<td>Prior device procedure</td>
<td>2.7–8.7</td>
</tr>
<tr>
<td>Prior CIED infection</td>
<td>11.3</td>
</tr>
<tr>
<td>Fever/systemic infection</td>
<td>5.8</td>
</tr>
<tr>
<td>Renal failure (no dialysis)</td>
<td>1.3</td>
</tr>
<tr>
<td>Haemodialysis</td>
<td>8.6</td>
</tr>
<tr>
<td>Chronic skin disease</td>
<td>10.6</td>
</tr>
<tr>
<td>Corticosteroid treatment</td>
<td>13.9</td>
</tr>
<tr>
<td>COPD</td>
<td>1.2–9.8</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.3</td>
</tr>
<tr>
<td>Higher Charlson comorbidity index</td>
<td>2.7–3.0</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.5</td>
</tr>
<tr>
<td>Younger age</td>
<td>1.4–4.5</td>
</tr>
<tr>
<td>Low body-mass index</td>
<td>NA</td>
</tr>
<tr>
<td>Heart failure</td>
<td>NA</td>
</tr>
<tr>
<td>Indwelling lines</td>
<td>NA</td>
</tr>
<tr>
<td>Anticoagulation/antithrombotic drugs</td>
<td>NA</td>
</tr>
<tr>
<td>Longer procedure time</td>
<td>NA</td>
</tr>
<tr>
<td>Low operator experience</td>
<td>NA</td>
</tr>
</tbody>
</table>

**Peri-operatively**

General recommendations for reducing surgical site infections should be applied. It is recommended to use appropriate anti-septic agents for skin preparation pre-operatively to minimize burden of microorganisms in normal skin flora. Comparative efficacy of chlorhexidine-alcohol vs. povidone-iodine for clean-contaminated surgery has yielded mixed results. Chlorhexidine-alcohol reduces surgical site infections following clean surgery compared with alcohol-based povidone-iodine. Use of transparent films or diathermia or substances preventing bleeding have not been proven beneficial.

Pre-operative antibiotics are mandatory for CIED procedures. Observational data indicate reduction in CIED infections to less than half with one single dose of pre-operatively intravenously administered antibiotics, and are supported by one meta-analysis (OR 0.26 with antibiotics). One randomized controlled trial confirmed these findings—risk of CIED infection within 6 months was reduced to 0.64% using single-dose cefalozin vs. 3.28% with placebo ($P = 0.016$). Topical antibiotics are often used additionally, but lacks supporting evidence.

Antibiotic regime differs widely with respect to type of antibiotics, treatment duration, and topical antibiotics. There is no documentation that one specific regime is superior. Most implanters use one dose of antibiotics 60–90 min pre-operatively. Antibiotic choice is influenced by local burden of methicillin-resistant Staphylococci that is increasing worldwide. An ongoing randomized cluster
crossover trial enrolling 10 800 patients compares single-dose pre-operative antibiotics (cefazolin or vancomycin) with an incremen- tal antibiotic strategy adding intra-operative wound pocket wash (bacitracin) and 2 days post-operative cephalaxin/cephadroxil/ clindamycin.11

The TYRX™ Envelope (Medtronic, Monmouth Junction, NJ, USA) is an antibacterial envelope made from polypropylene mesh releasing the antibiotics minocycline and rifampin in the generator pocket after CIED implantation. This envelope eliminates Staphylococcal species and prevents biofilm formation on implanted pacing devices in an animal model,32 and reduces CIED infections in high-risk patients in observational studies.33–35 Recently a bio-absorbable version, disappearing within 9 weeks after implantation was intro- duced. This will be evaluated in WRAP-IT (worldwide randomized antibiotic envelope infection prevention trial, NCT02277990, commen- ced 2015) aiming to enrol 7 764 patients scheduled for CIED re- placement or upgrade procedure, primary CRT-D implantation or late lead or pocket revision. Primary endpoint is major CIED infection within 12 months.

Meticulous surgical technique to prevent tissue damage, assure haemostasis, and ensure secure subcutaneous cover for the device should be standard. Shorter procedure times was associated with lower infection risk.16,30 Cephalic or axillary vein access is recom- mended for lead implantations, to better preserve long-term lead integrity and avoid re-operations. During device replacement procedures, some authors support capsulectomy. No controlled studies have tested this strategy. Benefit of removing avascular tissue must be weighed against risk of haematoma, associated with higher infection rates.16,22,30 Clopidogrel and aspirin increases risk threefold. Among anticoagulated patients, continued warfarin reduced risk of significant haematoma after CIED implantation mark- edly (OR 0.19) as compared with heparin bridging.36 How to handle patients treated with new oral anticoagulants is less clear. When hematoma occurs, management must be considered carefully. Early re-intervention probably is the strongest risk factor for later CIED infec- tion.3,12,16,17,23 Pocket re-entry should be avoided unless haema- toma is particularly tense or painful. Large haematomas gradually soften and resorb over few weeks. Appropriate education and a rea- sonable implant volume for each operator should be assured to de- crease risk of lead dislodgements and haematomas requiring early re-interventions.13

The high-risk patient

Several patient-related factors are associated with heightened risk of CIED infection, such as gender, age, body-mass index, renal failure and dialysis, heart failure, diabetes (especially with hyperglycaemia), respiratory failure, corticosteroid treatment, chronic skin conditions, indwelling lines, and higher comorbidity index (Table 1). Since these conditions are largely irreversible/unavoidable, attention should focus on optimization before CIED implantation. Conceivably, this patient group may benefit most from innovations as leadless pacemakers and subcutaneous ICD systems. Leadless pacemakers17 are likely to bear lower risk of device infection than systems used today. However, long-term efficacy and safety that is at least non-inferior to traditional pacemakers needs confirmation in randomized controlled trials before advocating for their widespread utilization. In event of their infection, extraction risk is unknown. Subcutaneous ICD systems using a subcutaneous shock electrode was intro- duced.38 It is unlikely that pocket infection rate is much lower than for traditional pacemakers. However, this system does not bear the risk of blood-stream infection or device endocarditis and thus could be attractive for patients not needing bradycardia or anti- tachycardia pacing and at particularly high risk of CIED infection, for example, renal failure patients treated with haemodialysis. Again, documentation of at least non-inferiority with respect to effi- cacy and safety as compared with transvenous ICD systems is needed before expanding this treatment to larger patient groups. Extraction risk is however negligible.

Diagnosis of cardiac implantable electronic device infection

There are intra- and extra-cardiac components. Diagnosis may be dif- ficult and a high index of clinical suspicion is warranted. Presentation demonstrates a wide spectrum from subtle complaints of mild pain without pocket abnormalities, device migration occurring years after implant, erosion, to a hot, red pocket, and septic shock. Uniden- tified or partially treated low-grade chronic sepsis can result in multi- system disease processes. Cardiac implantable electronic device infection commonly presents as local infection around the device. Such pocket infection usually occurs within 12 months post-implant, but may occur later. Blood-stream infection is less common, may appear with or without concomitant pocket infection, and with or without valve endocarditis.39 Symptoms and blood tests may be mis- leadingly normal. Bacteraemia may occur during the entire CIED life- time. Blood-stream infection is particularly common among patients with end-stage renal failure and haemodialysis.39,40

Any symptom from the device pocket should raise suspicion of CIED pocket infection, and the patient referred to a CIED specialist for evaluation (Figure 1). When using remote monitoring for device follow-up, educating patients about this topic is especially important. In particular, this form of follow-up, if initiated at implant, does not obviate need for standard 2-week wound check and 3-month in person evaluation post-implant.41 Typical signs are local erythema, warmth, pain, and swelling, adherence of skin to device, and incipient or overt erosion of skin with a draining sinus.42 Erosion is de facto infected. Early post-operatively it may be difficult to differentiate between CIED pocket infection and superficial wound infection. Diagnostic percutaneous puncture with pocket fluid aspiration should be avoided.

In CIED patients developing systemic infection without any obvious focus, blood-stream infection affecting the CIED should be suspected, and repeated blood cultures obtained. At least two sets of blood cultures should be obtained before starting empiric antibiotic treatment. Growth of bacteria typical for CIED infections, Staphylococcal species, Corynebacteria or Propiono- bacteria, support the diagnosis. If suspecting CIED infection, echocardiography is indicated. Transoesophageal imaging more accurately visualizes leads, valvular involvement, and vegetation. However, echocardiography cannot discriminate infective vegetation from non-infected thrombotic or fibrous masses, often prevalent on chronic indwelling leads.43 Absence of CIED lead vegetation does not rule out CIED blood-stream infection. Occult Gram-positive
bacteraemia is indicative for CIED blood-stream infection and Class 1 indication for explantation.8 Systemic symptoms may warrant pulmonary or brain imaging for septic emboli.

Recently, fluorine-18 marked fluorodesoxyglucose (18F-FDG) positron emission tomography and computed tomography was found useful for differentiating patients with CIED infection from those without.44 Yet experience is limited, and further validation of this method is needed.

Treatment of cardiac implantable electronic device infection

Confirmation of CIED infection—systemic or localized to pocket—mandates removal of all hardware (generator and leads), antibiotic therapy, and a strategy for re-implant. Only exception to this rule is for minor incisional/suture abscesses few days after implantation, not communicating with the pocket, which may be treated with antibiotics and careful follow-up. Timely, correct and complete treatment are of highest importance for patient prognosis. Delay further increases morbidity and mortality. Partial procedures, for example, generator removal and capping of leads are associated with almost invariable relapse,20,42,45,46 even if presentation is pocket infection. Percutaneous extraction is favoured though associated with a small risk of major complications, particularly vascular lacerations causing hemothorax and death. Mortality rates are 0.3–0.8%.47 Given this, risk–benefit ratio favours extraction, which should be performed in centres with procedural volume sufficient to maintain operator skills and capacity for immediate surgical backup. Primary surgical extraction may be considered with failed/incomplete percutaneous extraction, epicardial leads, and valvular endocarditis demanding surgical repair. A hybrid approach is sometime necessary.48

Pre-operative evaluation

Adequate inter-disciplinary preparation is mandatory. Infection disease specialists may direct antibiotic therapy. This may be commenced before system explant after blood and incisional drainage cultures. Septic shock requires immediate explant. There are few data regarding course of antibiotic therapy. Generally, courses of 10–14 days after pocket infection, 14 days for bacteraemia, and 4–6 weeks for endocarditis are used.9 When long-term intravenous antibiotics are needed, venous access sites not interfering with future
implantations should be considered. Temporary pacing needs careful planning. Following extraction, we use a ‘permanent’ active fixation endocardial right ventricular pacing electrode. Externally, this is anchored to sterilized skin using an anchoring sleeve, covered, and connected to a generator, which may be affixed externally to the skin of the shoulder or chest at a convenient location. Heart failure teams should be involved when anticipating haemodynamic support after CRT device removal.

All hardware, including abandoned leads, even if contralateral to infected system, must be removed. Risks of explant increase with older leads and superior vena cava coils. A chest X-ray is important. Imaging may discover unreported leads, leads jailed by stents, or unusual trajectories suggestive of extravascular or even arterial courses. This may require contrast CT-scan for visualization of, for example, perforated tips of endocardial leads, epicardial leads, and loculated pericardial collections, which may affect choice of approach.

Transoesophageal echocardiography is an important part of evaluation. Large vegetation particularly when adherent to the tricuspid valve must be assumed infected, and may indicate surgical explant (Figure 2). Traditionally, transvenous extraction is avoided for vegetations >2 cm. Most are friable, and even at open surgical explant tend to disintegrate on handling and cannot be removed en masse. These disintegrate during transvenous extraction and seldom cause pulmonary artery obstruction. They may be visualized with intra-cardiac echo (Figure 3). However, dispersion may cause sepsis syndrome and hypotension.

A thorough evaluation of the individual patient’s condition, risks, and benefits must be taken into account. For example, in someone very fragile or with poor prognosis due to overwhelming comorbidities presenting with localized pocket infection of a 10-year-old dual coil ICD system, best management may be pocket debridement and commitment to chronic antibiotic therapy, or tailored salvage therapy.Operative procedure

Extraction methodology is beyond this article’s scope. However, surgical principles need to be followed with debridement of necrotic-infected tissue and drainage of purulent abscesses. This includes pocket capsulectomy with removal of avascular tissues. Lead tip and pocket culture are important. Re-implantation

Firstly, the original indication needs re-evaluation. Some arrhythmia problems may resolve, for example, post-operative atrioventricular...
block or sinus node disease, as confirmed by 0% pacing on explanted device diagnostics. Alternatively, indication for a more complex CIED may have developed, for example, need for CRT in a patient with previous single-lead device. Other comorbidities may have overtaken the risk from cardiovascular disease, for example, malignancy in patients with prophylactic ICD, or significant renal disease. In such cases, there may be merit in not re-implanting at all. When re-implantation is necessary, this should be done on opposite side of the chest, or via transiliac approach.

There are no randomized trials guiding appropriate timing of re-implantation. Carefully attention to an adequate period of antibiotic therapy and indication for CIED is needed. Decisions must be individualized. Epicardial placement of pacemaker leads may be considered for those at high risk of re-infection or with limited vascular access, for example, dialysis patients. A continued dialogue, commencing pre-operatively, among electrophysiologist, surgeon, and infection disease specialist, is critical to ensuring individual management plans.

Conclusion
Cardiac implantable electronic device infection, according to current trends, appears to be an increasing problem. It can be indolent and its diagnosis challenging, and potentially lethal if left untreated. Its trends, appears to be an increasing problem. It can be indolent and its diagnosis challenging, and potentially lethal if left untreated. Its treatment—exploration and eradlicative antibiotic therapy—may be challenging and without risk. These include risks associated with device removal and re-implantation, adverse reactions to antibiotics and generation of resistant bacteria, and risks of long-term vascular access. Given this backdrop, careful patient selection, preventative measures, and appropriate choice of device, are key. Future strategies for reducing CIED infection should be tested in sufficiently powered and well-designed multicentre randomized controlled trials.

Conflict of interest: none declared.

References


