Therapy and outcomes of cardiac implantable electronic devices infections

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Abstract
Cardiac implantable electronic device (CIED) infection causes significant morbidity and mortality without appropriate treatment. It can present as incisional infection, pocket infection, systemic CIED infection, or occult bacteraemia. Complete percutaneous CIED extraction (excepted in case of incisional infection) and appropriate antibiotic therapy are the two main pillars of therapy. Device reimplantation, if needed, should be delayed sufficiently to allow control of the infection. Here, we address the differences in prognosis according to the clinical scenario and different treatment options.

Keywords
Antibiotic therapy • Implantable electronic device infection • Lead endocarditis • Percutaneous lead extraction • Reimplantation

Introduction
Implantation of pacemakers (PM) and implantable cardioverter-defibrillators (ICD) is on the rise, due to widening of indications and ageing population.1 Device-therapy is effective for the treatment of cardiac arrhythmias and improves prognosis and symptoms in selected patients.2–4 but cardiac implantable electronic device (CIED) infection is a feared complication causing significant morbidity and mortality. Despite technological improvements and standardized protocols, the rate of CIED infections increases even out of proportion to the rate of new device implants.5 In the recent report from the Danish device-cohort (1982–2018), the combined lifetime incidence of systemic endocarditis and pocket infection was reported to increase with the complexity of the devices from 1.19% for PM to 3.35% for CRT-D systems.6

Our review addresses the outcomes related (i) to the different clinical scenarios of CIED infection, (ii) to the extraction of infected leads, and (iii) to the available CIED reimplantation strategies in patients explanted because of device infection.

Clinical scenarios of cardiac implantable electronic device infection and their outcomes

Cardiac implantable electronic device infection occurs through contamination of leads and/or pulse generator during device procedures or by bloodstream infection at times of bacteraemia.7 Four main clinical scenarios can be differentiated, with major consequences on therapy. Figure 1 depicts our practical diagnosis and treatment approach for management of CIED infection.

Superficial incisional infection
A superficial incisional infection involves only the skin and the superficial subcutaneous tissue of the incision, but not the deep soft tissues (e.g. fascia, muscle, and/or pocket).8 Per definition it is associated with a recent device procedure (device implantation, revision, or replacement). Staphylococcus aureus is the most frequently involved pathogen. Wound cultures are recommended before initiation of...
oral antibiotic therapy covering *S. aureus* for 7–10 days. Importantly, close follow-up of the patient is mandatory to detect early extension of the infection to the pocket.\(^7\)

**Cardiac implantable electronic device pocket infection**

A CIED pocket infection is defined as an infection of the generator pocket (Figure 2A). It manifests with local inflammatory changes, including pocket erythema (41%), swelling (38%), pain and tenderness (28%), warmth (18%), drainage (38%), and/or device exposure (21%).\(^8,^9\) Once the generator and/or the proximal parts of the leads are exposed, the CIED system has to be considered infected irrespective of the Microbiological results, because it is in direct communication with the skin and its bacterial pathogens.\(^10\) Pocket infection can be isolated or associated to systemic CIED infection.\(^8,^9\) The accumulation of bacteria and extracellular polymeric matrix constitute a biofilm, which protects the microbes from antibiotics and host defenses,\(^11\) and helps the infection to track along the hardware to reach intravascular and intracardiac portions of the CIED system. In that view, vegetations were detected in 46% of patients presenting with clinical pocket infection in the cohort of Tarakji et al.\(^9\) and Bongiorni et al.\(^12\) reported that culture of the majority of their extracted electrodes (88.7%) resulted positive despite most of the patients (65.4%) had only local signs of infection. Therefore, blood cultures and transthoracic as well as transoesophageal echocardiography are recommended (statement class ‘green’) in all patients with clinical CIED pocket infection.

**Cardiac implantable electronic device systemic infection**

A CIED systemic infection is caused by infection of the intravascular parts of the device (Figure 2B). The diagnosis of CIED systemic infection without pocket infection is especially challenging and approximate the one of infective endocarditis. The symptoms are usually non-specific and include fever, chills, night sweats, and weight loss.\(^13\) Addressing the need for more specific diagnostic criteria for patients implanted with CIED, the ‘Novel 2019 International CIED Infection Criteria’\(^7\) added specific CIED-related infection criteria to the ‘ESC 2015 modified criteria for the diagnosis of infective endocarditis’.\(^7\) In that view, clinical or radiological signs of pocket infection or lead vegetations are considered major criteria.\(^7\)

More patients (58–65%) present with pocket infections rather than systemic CIED infection.\(^9,12,14\) Although CIED infection within 6 months following device surgery seems to present more likely with pocket infection while late CIED infection are more often systemic, the timing of the infection after CIED procedure alone does not reliably suggest whether an infection is localized or systemic.\(^15\)
Positive blood cultures in patients with cardiac implantable electronic device

Blood cultures are the first-line tool for the diagnosis of bloodstream infections. Their main weaknesses are the risk of contamination during sampling and false-negative results due to previous antibiotic therapy. The prevalence of blood culture contamination varies from 0.6% to 17%, explained by hospital-, staff- and patient-related factors, such as teaching-hospital labelling, workload of medical staff, and patients’ comorbidities. Patients undergoing CIED extraction because of infection are no exception, and the species isolated from blood cultures have been shown to often differ from those found on lead culture, being therefore rather likely the result of contamination. The most important predictor of contamination is the identity of the microorganism isolated in blood culture, with coagulase-negative Staphylococci (CoNS). Micrococcus spp., viridans group streptococci, Propionibacterium acnes (Cutibacterium acnes), Corynebacterium spp., Clostridium perfringens, and Bacillus spp. being most often cited. In that view, at least three sets of blood cultures should always be acquired before antibiotic therapy in case of clinically suspected CIED infection, and every effort should be made to perform clean samplings.

Cardiac implantable electronic device infection is monomicrobial in the majority of cases. Consistent with our report, CoNS were the most frequently isolated pathogens (69%) in consecutive patients (n = 1204) with infected PM or ICD who underwent transvenous removal in Pisa 2000–2011, followed by S. aureus (13.8%). Only 6.1% of CIED infections were caused by gram-negative bacilli and CIED fungal infection is uncommon, identified in only 1%. Although one single blood culture positive for CoNS provides insufficient evidence to dictate a therapeutic strategy in patients with CIED, S. aureus should always be considered as pathogen, and evaluation for a source should be undertaken besides the workup of possible CIED infection.

As shown in Table 1, the prevalence of CIED infection in patients presenting with positive blood cultures varies from 4% to 45% depending on the isolated pathogen. At least a transthoracic and transoesophageal echocardiography should be performed in bacteraemic patients with suspected CIED infection, with recommended repetition of the examinations within 5–7 days if clinical suspicion of CIED-related endocarditis remains high. In the absence of signs of pocket or systemic CIED infection at initial presentation, the outcomes depend on the pathogen isolated in blood cultures. The reported rates of CIED infection in patients presenting with S. aureus bacteraemia range from 30% to 75% depending on definition and time delay from implantation.

Figure 2 (A) Device pocket infection with perforation 1 week later. (B) Transoesophageal echocardiography showing a large vegetation attached to the tricuspid valve and right ventricular lead.
Table 1. Prevalence of intracardiac electronic device infection at initial evaluation and outcomes according to type of pathogen in CIED patients with bacteraemia

| Population | Definition of positive blood culture for inclusion | Definitions of CIED infection | Prevalence of intracardiac electronic device infection at initial evaluation and main outcomes |
|------------|---------------------------------------------------|------------------------------|-----------------------------------------------------------------------------------|
| S. aureus18 | 131 consecutive CIED patients presenting at Mayo Clinic Rochester 2001–2011 with S. aureus bacteraemia and no clinical evidence of pocket infection. Any positive blood culture. 'Definite CIED infection': vegetations on echocardiography, fulfilment of modified Duke criteria for 'definitive endocarditis', or positive cultures from the generator pocket or leads. | Definite CIED infection: 45/131 (34.3%) • Vegetations in 41/45 (91.1%) patients |
| S. aureus19 | 33 consecutive CIED patients presenting to Duke University Medical Center 1994–2000 with S. aureus bacteraemia. >1 blood culture positive for S. aureus, or a single blood culture positive for S. aureus in a patient with clinical evidence of infection. 'Confirmed CIED infection': vegetations on echocardiography, fulfilment of the Duke criteria or positive cultures from the generator pocket or leads. 'Rejected CIED infection': no evidence of CIED infection at time of blood culture, no CIED extraction, no recurrent infection within 12 weeks, no evidence of CIED infection at autopsy. 'Possible CIED infection': death before confirmation or rejection. | Confirmed CIED infection: 15/33 (45.5%), clinically 3/15, and microbiologically 12/15 Possible + confirmed CIED infection: 24/33 (72.7%) Rejected CIED infection: 9/33 (27.3%) Mortality at 12 weeks: 10/21 (47.6%) patients without vs. 2/12 (16.7%) patients with CIED extraction, P = 0.13 |
| CoNS20 | 44 consecutive CIED patients presenting to Mayo Clinic Rochester 2001–2007 with CoNS bacteraemia. Any non-contaminated blood culture from a peripheral blood sample. Blood cultures were considered to be contaminated and excluded if CoNS, Micrococcus species, enterococci, or viridans group streptococci were identified in only 1 set of culture. 'Definite CIED infection': clinical pocket infection, vegetations on echocardiography, fulfilment of the modified Duke criteria or positive cultures from the generator pocket or leads. | Definite CIED infection: 16/44 (36.4%) • Vegetations in 10/16 (62.5%) patients Relapse at 12 weeks: 5/16 (31.3%) patients without initial CIED infection, no CIED extraction, no in-hospital death, and no lost to follow-up. |
| Non-Staphylococcal gram-positive coccus bacteraemia20 | 30 consecutive patients presenting to Mayo Clinic Rochester 2001–2007 with non-staphylococcal gram-positive coccus bacteraemia. | Definite CIED infection: 6/30 (20.0%) • Vegetations in 5/6 (83.3%) patients Relapse at 12 weeks: 0/16 (0.0%) patients without initial CIED infection, no CIED extraction, no in-hospital death, and no lost to follow-up. |
| Gram-negative bacteraemia21 | 49 consecutive patients hospitalized at Mayo Clinic Rochester 1998–2005 with gram-negative bacteraemia. Any blood culture from a peripheral sample. 'Definite CIED infection': clinical pocket infection, presence of vegetations on echocardiography, or fulfilment of Duke criteria, or positive culture from the generator pocket or lead(s). 'Rejected CIED infection': no evidence of CIED infection at the time of initial blood culture, no CIED extraction, and no relapse of infection during a 12-week follow-up period. | Definite CIED infection: 2/49 (4.1%) • 2/2 (100.0%) patients with clinical pocket infection • 0/49 (0.0%) patients with systemic CIED infection Rejected CIED infection: 34/49 (69.4%) Relapse at 12 weeks: 2/34 (6%) patients without initial evidence of CIED infection, no CIED extraction, and no death. • 2/2 (100.0%) clear alternative source of relapse other than CIED and no evidence of CIED infection at time of relapse. |

CIED, cardiac implantable electronic device; CoNS, coagulase-negative Staphylococci.
Treatment of cardiac implantable electronic device infection

Antibiotic therapy is the first pillar in CIED infection management. It should be started promptly following blood culture sampling, and follow the principles of treatment of infectious endocarditis. Table 2 summarizes the recommended empiric antibiotic therapy regimens until identification of the microbiological aetiology according to the clinical scenarios. Once the pathogen is identified (usually within 48 h), the antibiotic treatment has to be tailored to the antimicrobial susceptibility pattern. The collaboration between cardiologists and microbiologists with expertise in the field of CIED infection is of paramount importance concerning antibiotic therapy. The duration of therapy depends on the presence or not of concomitant systemic infection and vary from 10 to 14 days in case of isolated pocket infection to typically 4–6 weeks in case of positive blood cultures, vegetations, and/or prosthetic valves (Figure 1). Two weeks of parenteral antimicrobial therapy after device extraction has been advocated by some experts in case of non-S. aureus systemic CIED infection without valvular involvement and adequate clinical improvement. In the absence of systemic CIED infection, switch to oral treatment after device removal is possible since the remaining infection only involves skin and soft tissue. The day of lead extraction or first negative blood cultures (whichever occurred last) should be considered as reference for the calculation of therapy duration.

Complete extraction of the infected CIED system and of any other device fragments, independently of their location, constitute the second pillar in CIED infection management. Although the need for device extraction is obvious in case of lead vegetations or pocket infection, complete device and lead removal is also recommended for all patients with valvular endocarditis without definite involvement of the CIED system. Complete CIED removal can be curative for patients with CIED infection even in the presence of prosthetic heart valves and thus helps to prevent repeated valve surgery. Antimicrobial therapy without device removal was associated with a seven-fold increase in 30-day mortality in a retrospective review of all cases of CIED infections seen at Mayo Clinic Rochester between 1991 and 2008, and CIED infection relapse has been described in 70% of patients with incomplete system removal. Although patients suffering from systemic infection might need stabilization before the extraction procedure, there should be no unnecessary delay between diagnosis and device extraction, as immediate device removal was shown to be associated with a three-fold decrease in 1-year mortality [hazard ratio (HR) 0.35, 95% confidence interval (CI) 0.16–0.75]. On short-term, transvenous lead extraction within 3 days from admission has been correlated with shorter hospitalization and better survival.

Percutaneous transvenous lead extraction is superior to surgical open extraction in terms of patients’ safety and comfort, and is recommended as first extraction strategy in most patients with transvenous CIED. In the ELECTRA Registry (6493 leads with a median dwelling time 5.0 years, inter-quartile range 2.0–9.0; 34.9% dual coil ICD leads) complete lead extraction was achieved in 6212/6493 leads.

Table 2 Recommended empirical antibiotic therapy regimens until identification of the microbiological aetiology according to the clinical scenarios (patients with normal renal function)

| Clinical scenario | Recommended empirical antibiotic therapy regimens |
|-------------------|--------------------------------------------------|
| Superficial incisional infection | Flucloxacillin p.o. 1 g every 6–8 h |
| | If high MRSA prevalence or penicillin-allergy: clindamycin p.o. 450 mg every 6 h, doxycyclin p.o. 100 mg every 12 h, and linezolid p.o. 600 mg every 12 h |
| Isolated CIED pocket infection | Vancomycin i.v. 30–60 mg/kg/day in 2–3 doses |
| | Alternative: daptomycin i.v. 8–10 mg/kg every 24 h |
| | If systemic symptoms: add ceftriaxone i.v. 2 g every 24 h (or a broader betalactam antibiotic) OR gentamycin i.v. 5–7 mg/kg every 24 h |
| CIED systemic infection (including suspicious positive blood cultures in a patient with a CIED) | Vancomycin i.v. 30–60 mg/kg/day in 2–3 doses |
| | Alternative: daptomycin i.v. 8–10 mg/kg every 24 h |
| | AND |
| | Ceftriaxone i.v. 2 g every 24 h (or a broader betalactam antibiotic) OR gentamycin i.v. 5–7 mg/kg every 24 h |
| | If staphylococcal prosthetic valve infection: add rifampicin p.o. or i.v. 900–1200 mg/day in 2 doses after 5–7 days |

CIED, cardiac implantable electronic device; i.v., intravenous; MRSA, methicillin-resistant Staphylococcus aureus; p.o., per oral.
Recently been shown to be safe and highly successful (>90%) in common vegetation size, particularly in the context of right-to-left shunt. Therefore, surgical CIED extraction may be considered in case of presence of right-sided vegetations and right-to-left shunt.

During percutaneous lead extraction procedures, with PFO being independently associated with stroke occurrence, in the presence of right-sided vegetations and right-to-left shunt. Therefore, surgical CIED extraction may be considered in case of large vegetation size, particularly in the context of right-to-left shunt without available percutaneous vegetation aspiration. Obviously, surgery should be the preferred technique when a combined surgical treatment (e.g. valve repair or replacement) is indicated.

Chronic antibiotic suppression has been proposed in case of refusal of the extraction or comorbidities precluding the intervention. Tan et al. reported a median survival of only 1.43 years (95% CI 0.27–2.14) with chronic antibiotic suppression, with 18% of their patients suffering an infection relapse within 1 year. Finally, some authors have described successful treatment, at least on short-term, of isolated pocket infection with surgical debridement, negative pressure, and/or closed irrigation systems with antibiotics. However, these almost palliative procedures have to be reserved for very selected patients who are too frail or sick to undergo lead extraction.

While there are many similarities in the management of CIED infection whether it presents as pocket infection or systemic infection, the overall prognosis of these two types of presentation is different, with a significantly higher overall mortality (OR 4.93, 95% CI 2.72–8.93, P < 0.0001) in case of systemic infection. This difference remains not completely explained, and might results from differences in decisions concerning reimplantation, duration of antibiotic therapy, and comorbidities.

**Device reimplantation and outcomes**

The indication, approach, and timing for device reimplantation are often challenging. Obviously, no part of the removed CIED should be reused.

First, the indication for reimplantation should be thoroughly reevaluated following complete CIED system extraction. Some patients might have had improvement in rhythm or cardiac function and no longer meet a guideline indication for permanent PM, ICD, or resynchronization therapy, while others might not wish to receive a new device. In that view, reported reimplantation rates vary from 58% to 86%. Secondly, the replacement device should be implanted at a different anatomical site with use of an alternative lead access such as the contralateral subclavian vein, an iliac vein, or by surgical epicardial lead placement.

Finally, the reimplantation should be deferred until signs and symptoms of local and systemic infection have resolved, and postponed to allow blood culture to remain negative during 48–72 h. A delay of 14 days has been proposed in case of valve vegetations. Tan et al. reported an increased risk of infection relapse at one year in patients implanted during the same hospitalization as hardware removal (2.6% vs. 1.9% for the overall cohort). This finding stresses the importance of a sufficient waiting period before safe device reimplantation. Obviously, such a delay is especially challenging in pacing-dependent patients. Due to the inerrant risks of lead displacement or ventricular perforation, and to avoid complications resulting from immobilization, passive fixation temporary PM leads are not recommended for bridging the stimulation. Instead, the implantation of an epicardial device before extraction, or the use of an ipsilateral screwed-in provisory PM lead with a view to definitive delayed endocardial reimplantation, have been proposed as alternatives in those patients (Figure 3).

In our retrospective single-centre study including two cohorts of consecutive PM-dependent patients who underwent transvenous lead extraction at our tertiary hospital, we found no difference in long-term mortality between epicardial device reimplantation before extraction or bridging stimulation with a screwed-in provisory PM lead. The strategy of provisory pacing with a significantly reduced risk of late endocarditis and device reintervention (HR 0.25, 95% CI 0.09–0.669, P = 0.01). In facts, ~25% of our patients with an epicardial CIED required reimplantation of an endocardial device, mainly for cardiac resynchronization or anti-tachycardia protection. Based on those finding, epicardial CIED reimplantation should be primarily reserved for patients needing anyways heart surgery. That be, stressing the difficulty of infect control in systemic CIED infection, 25% of our patients with a provisory screwed-in pacing wire were finally reimplanted epicardially, mainly because of infection of their provisory lead despite guideline-conform antibiotic therapy. In case of epicardial reimplantation, every efforts should be made to immediately implant the most suited device according to the clinical condition, to avoid future reinterventions. In consequence to the reported increased risk of epicardial lead fracture, we consider in particular situations the implantation of a second ventricular epicardial lead, which we leave capped in the abdominal device pocket. In case of a lead issue during follow-up, only a pocket revision with connection of the backup lead is needed in those patients.

New kinds of CIED have been designed recently to reduce the amount of intravascular material or suppress it completely. A single-chamber ventricular PM can be implanted trough femoral venous access directly into the right ventricle. Also, a completely extra-thoracic subcutaneous defibrillator system is available for patients having an indication for ICD implantation but no need for pacing or...
cardiac resynchronization therapy. Making those devices especially interesting following CIED extraction due to infection, all serious infectious events (endocarditis or bacteraemia) in the investigational device exemption study of the leadless PM could be treated successfully with antibiotics, and the consequences of systemic infection are obviously lessened by the absence of endovascular material in patients with extra-thoracic subcutaneous ICD.

Conclusion

Cardiac implantable electronic device infection remains a major matter of concerns in cardiology. In-hospital mortality is impressive (4.1%) and worsened long-term prognosis has been suggested. Every effort must be made to ensure that care providers have good knowledge of the different clinical scenarios of CIED infection and offer guideline-conform management to affected patients. Reassuringly, patients treated according to guidelines in the present era seem to have similar prognosis to CIED patients without device infection.

That be, the main focus in management of CIED infection should obviously remain the prevention of its occurrence.

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