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The Final thesis

Infections in patients with implanted cardiac pacemakers and ICDs

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Summary

Cardiac implantable electronic devices are well established treatment options for many heart conditions, by implanting such a device many deaths have been prevented. At the same time new challenges have appeared, one of the most severe complications is a device infection, leading to a higher mortality rate, as well as longer hospital stay accompanied with a burden for the health system and patient. To deal with this problem clinicians and researchers have investigate different treatment options but haven not yet found a better solution than removing the device and simultaneously treating the infection with antibiotics. Not only does this require repeated surgical intervention which puts the patient at risk for complications, but it also increases the likelihood for reinfections. Due to drawbacks of present treatment methods the primary focus is laid on the prevention of infections. An evaluation of the patient for comorbidities is crucial, as they are known to increase the infection rate, the use of antibiotic prophylaxis has been proven to be successful. Prevention is not solely based on the patient's characteristic; it extends to the device and even the procedure itself. This literature review with a case report will be mainly focusing on determining the most significant risk factors and preventive measurements to decrease the infection rates that are reported post implantation, all this will be done while comparing the case to the found evidence from many different studies. The studies used include all types like meta-analysis, double-blinded studies, prospective and retrospective studies that are examining any type of cardiac device implantation.

Keywords

SCD, CIED, ICD, Infection, Risk factors, Prevention, CIEDI, Extraction surgery, Antibiotic prophylaxis, Diagnostic criteria

Introduction

Sudden cardiac death (SCD), also called sudden cardiac arrest is defined as an unexpected natural death that occurs due to a cardiac cause within one hour post symptoms development (1, 2). If no witness is present to confirm this, SCD is diagnosed, if the death of the person is noticed less than 24 hours after the person was seen alive (2). SCD along with arrhythmia account for approximately 15 – 20% of deaths worldwide, which requires immediate actions like resuscitation and defibrillation to save the patient's life (2). While many different aetiologies may cause SCD, coronary heart disease is yet known to be the leading risk factor (3). The risk of mortality from SCD in patient who have had previously survived cardiac

arrest, is extremely high, but not only those patients have an increased risk of SCD. After thorough evaluation of risk factors and past medical history of patients, indication for ICD will be made. The indications can be divided into primary or secondary preventive measurement (4,5).

In 1980, the first implantable cardioverter defibrillator (ICD) was introduced into clinical practice, which at first was met by distrust and was rather rejected as a new treatment option. Clinical trials made it possible to prove the benefit of an ICD in significantly decreasing the mortality rate in patients with life-threatening arrhythmias, and helped to implement the use of an ICD as a standard procedure for those patients (6). Over the past decades the indication for ICD implantation have been expanded for a variety of cardiological conditions. A similar path was achieved with the successful invention of a pacemaker in 1960, patients who suffered from bradyarrhythmia could be treated and death caused by this condition could be prevented (7). CIEDs, which includes any permanent device, that is used for the treatment of cardiac arrhythmias, have saved many lives over the last decades, but as with any other procedure implantation of any CIED come with risks. Complications like tamponade, haematoma, haemothorax, pneumothorax and lead dislodgment have been reported after CIED implantation (8). Infection of the devices however have been increasing out of proportion, and are the most challenging of the many possible complications, furthermore it is considered a very severe complication, which left untreated can lead to the death of the patient. (9–11).

ICD can be implanted for primary and secondary prevention of SCD. While primary prevention is targeted for patients without any documented life-threatening ventricular arrhythmias, but with potential risk for it, secondary prevention is indicated for patients who survived a cardiac death, hemodynamically instability or syncope due to ventricular tachyarrhythmias.

Case presentation

Anamnesis and medical report

The 64 – years old male patient with a medical history of primary grade II arterial hypertension, ischaemic-hypertensive cardiopathy and dyslipidaemia, had in 2006 an anterior-lateral myocardial infarction, coronary blood flow was corrected by stent implantation. In 2017 the patient was running a marathon, when he suffered another MI, complicated by ventricular tachyarrhythmia, the patient was successfully resuscitated and required again coronary stenting. After the second infarction the patient experienced ventricular arrhythmias,

bradycardia and had a syncope. For secondary prevention of sudden cardiac death, the decision was made to implant a cardioverter defibrillator, because of concomitant sinus bradycardia the dual-chamber ICD was chosen. On the ECG prior to the implantation, the patient had sinus rhythm with the signs of an old infarction and QRS width of 108 ms, so he did not have complete criteria for cardiac resynchronization ICD (CRT-D) implantation.

Medical course

On the 30th of May 2018 the implantation was successfully performed, the patient received a dual-chamber ICD which was placed in his left pectoral region. Prior to the surgery and post-surgery, the patient received prophylactic 2 g of cefazolin. The patient stayed 7 days after the surgery in the hospital for observation, during this time no complications were observed, and he was discharged with a treatment plan and recommendations to be consulted by a cardiologist.

In September 2019 an echocardiography was performed, which revealed that the patient has an ischaemic cardiomyopathy with left ventricular (LV) dilatation, also a decreased LV ejection fraction of 30–35%. Additionally, a first-degree tricuspid valve regurgitation and a second-degree mitral valve regurgitation were noticed.

Two years after the device implantation, in March 2020, the patient had an accident, where he bumped into a table with the left side of his chest, following this incident the patient observed redness, and abrasion in the place of the ICD pocket, which he treated by himself. A few days later, patient noticed a skin defect through which the ICD device was visible, and he went to the hospital. Six days after the trauma a revision surgery was performed, where the altered area of the skin as well as the old ICD were removed, and a new ICD was placed in a slightly different place. The site of the old device was drained and connected to an active wash system, which was removed after two days. The patient received oral amoxicillin and clavulanic acid 500/125 mg, 3 times daily for a total of 4 weeks, and was discharged from the hospital, with instruction how to continue the treatment.

In May 2021, the patient complained about new appearing symptoms, like weakness while climbing the hill and discharge of ICD, during the interrogation of the ICD ventricular tachycardia was recorded.

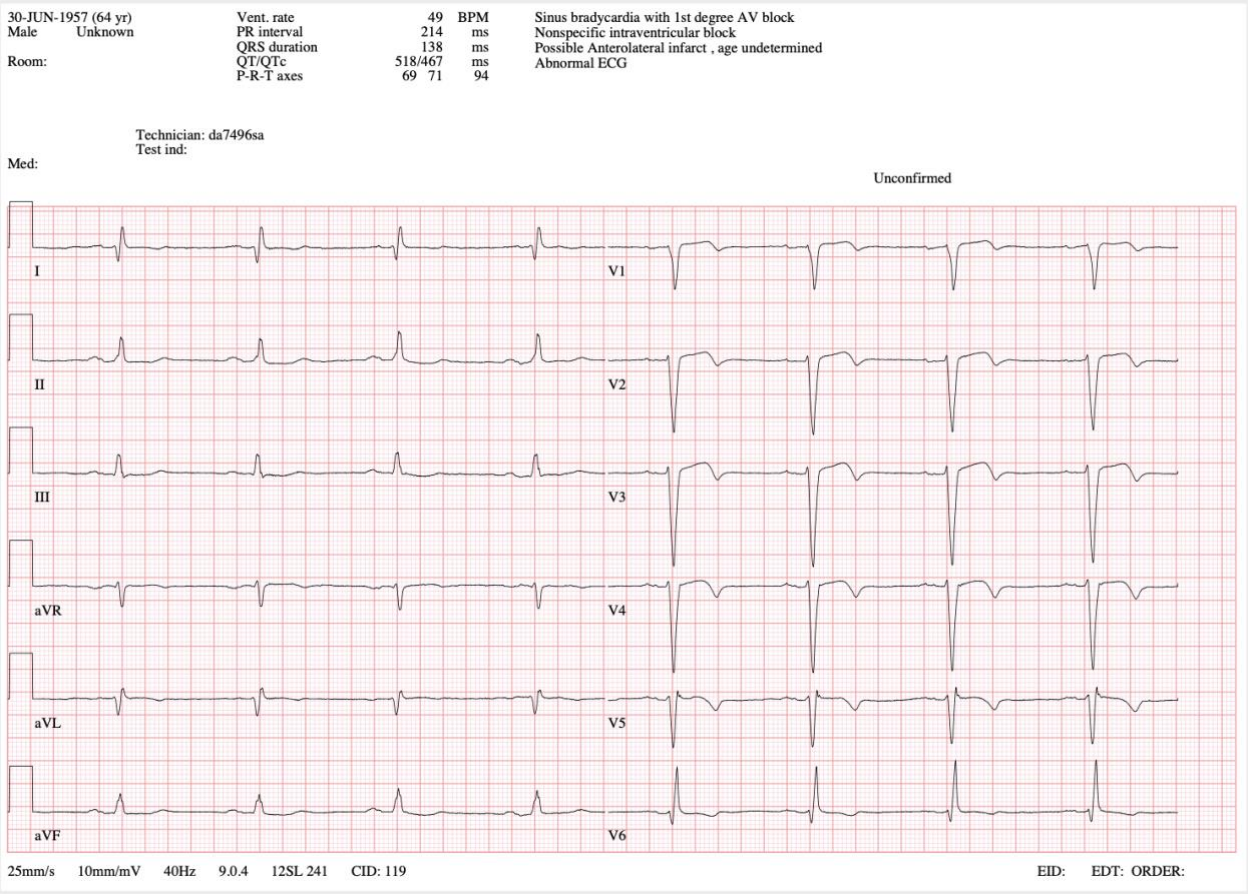
In the beginning of July 2021 an abscess formed at the implantation site, which got worse over time and was accompanied by increased redness and a feeling of stretching and soreness. On the 28th of July 2021 the patient was hospitalized for a removal of the entire ICD system, which was done on July 30th.

During the revision surgery the ICD and both leads, and the infected skin area were removed, before closing the wound, the wound was washed with an antiseptic solution and a drainage was placed. Wound revision and haematoma evacuation was performed on 2nd of August 2021, with no more surgical complications.

Six days after the revision surgery an ultrasound of the patient's upper arm was performed, soft tissue oedema of the left arm, and haematoma of the soft tissue of the chest were detected.

During the hospital stay the patient had atrial flutter, and sinus rhythm was treated by amiodarone and electrical cardioversion. The patient stayed two weeks after the revision surgery in the Department of Cardiac Arrhythmias for observation, during this period the soft tissue haematoma had resolved, part of the sutures had been removed and the follow-up visit for removal of the remaining sutures had been scheduled. The patient was discharged with an updated treatment plan and recommendation on how to adjust his lifestyle.

Figure 1 ECG of the patient after device removal



This ECG done before hospital discharge reflects the medical history of the patient (two MIs, ventricular arrhythmias, syncope and the clinical death after the second MI) showing pathological findings like bradycardia, QT interval prolonged because of amiodarone, first

degree AV-block and QRS prolongation. A biventricular ICD is still indicated for SCD prevention and sinus bradycardia. When the wound healing is successfully completed, the patient will receive a new device, which will be placed in the opposite site, in his right pectoral region.

Discussion/Analysis of literature

Indications for cardiac implantable electronic device

While the indications for CIED were rather limited, when first introduced, their implantation is now well established for many different conditions. In the last few decades, the healthcare system has made the progress in the prevention of many diseases, that were causing early death in the population. These achievements led to a higher life expectancy in the population, and to some changes in the distribution of diseases. With higher life expectancy, many of the older population are suffering from various chronic conditions, which may require rather extensive and expensive therapies. One huge challenge, medicine is facing, is the increase of patients with heart failure, which can potentially cause life-threatening arrhythmias and SCD. When patients experience severe complications from heart failure, an implantation of CIED might be indicated as primary prevention measurement (12). Other indications for CIED are for secondary prevention, which is done in patients who experienced cardiac arrest previously and were resuscitated. In those patient CIED is implanted to decrease the chance to reexperience this event, which could end in the patient's death. As with the case described above, the patient had experienced two MIs, while one of those was complicated by ventricular tachyarrhythmia and required immediate resuscitation. After those two MIs, the patient did not recover fully, he was suffering from bradycardia, tachyarrhythmias and presented with syncope. Since it is well known that the risk for mortality from SCD is significantly increasing after the patient has already experienced one event this would justify the implantation of an ICD. In this patient the implantation of a dual-chamber ICD was performed, because of the coexisting bradycardia.

Pathogenesis and microbiology of cardiac implantable electronic device infections

The most common pathogens that are detected in CIED infections are Staphylococcal species, the two species, Staphylococcus aureus and coagulase negative staphylococci are responsible for more than 70% of all CIED infections. Also infections caused by gram-negative bacilli and in rare cases caused by fungi were reported (13). The major reason for the persistence of the infections are the virulence factors of the pathogens, Staphylococcus aureus, which is the

most common pathogen, once attached to the device will form a multi-layered biofilm, which is used to stay on the device surface, but it also prevents the penetration of antibiotics to the deeper layer of microbes. Depending on the causative agent, different mechanisms are used to decrease the antibiotic susceptibility, which is why there is a high rate of relapses. In order to definitely treat an CIED infection only a complete extraction of device will be successful in most cases (14). As for this patient, two microbiological tests were performed, one in 2020 and another one in 2021, both of those showed negative results. Regardless of the negative result, the decision was made to completely extract the device, because any type of infection, except for superficial incisional infection requires complete removal of the system, the worsening of the patient's condition confirmed this decision.

Diagnostic criteria

With the increased life-expectancy nowadays, much more CIEDs are implanted in older patients with multiple comorbidities, which puts them at higher risk for post-surgical complications, but not only older patients are at higher risk for development of complication. Different risk factors have impact on the post-surgical outcome, one complication, cardiac implantable electronic device infections (CIEDIs) seems to be extra challenging, they remain one of the most severe complications. Not only does it lead to prolonged hospital stay and enormous treatment cost, but it also increases the mortality rate during the hospital stay as well in long-term.

Diagnosing CIED infection early is of major importance, the early diagnosis can help to decrease the hospital stay, as well as the treatment costs and most important the mortality rate. What seems to be easy, is more challenging, since there is still not a single test, that can point to a definitive diagnosis, it is rather a combination of laboratory and microbiologic testing, clinical findings, and imaging techniques that help to establish a diagnosis of CIED infection (6,14). To ensure the most appropriate treatment for the patient, and to avoid severe complication a correct and prompt diagnosis is essential (15). The modified Duke and ESC 2015 guidelines criteria (Table 1) can be used to diagnose CIED infections and/or infective endocarditis. The patient can present with different types of CIEDI, "superficial incisional infection" is the only type of CIEDI, that can be treated without extraction surgery, considering that it only involves the skin and has no connection to the device or leads (15). Diagnosing it can be quite challenging, because it's presentation is similar to CIED pocket infection, while pocket infection can develop at any stage postsurgical, superficial incisional infection is limited to the very early time post-surgically (16).

Table 1 Recommendations for diagnosis of CIED infections and/or infective endocarditis: the Novel 2019 International CIED infection criteria (15)

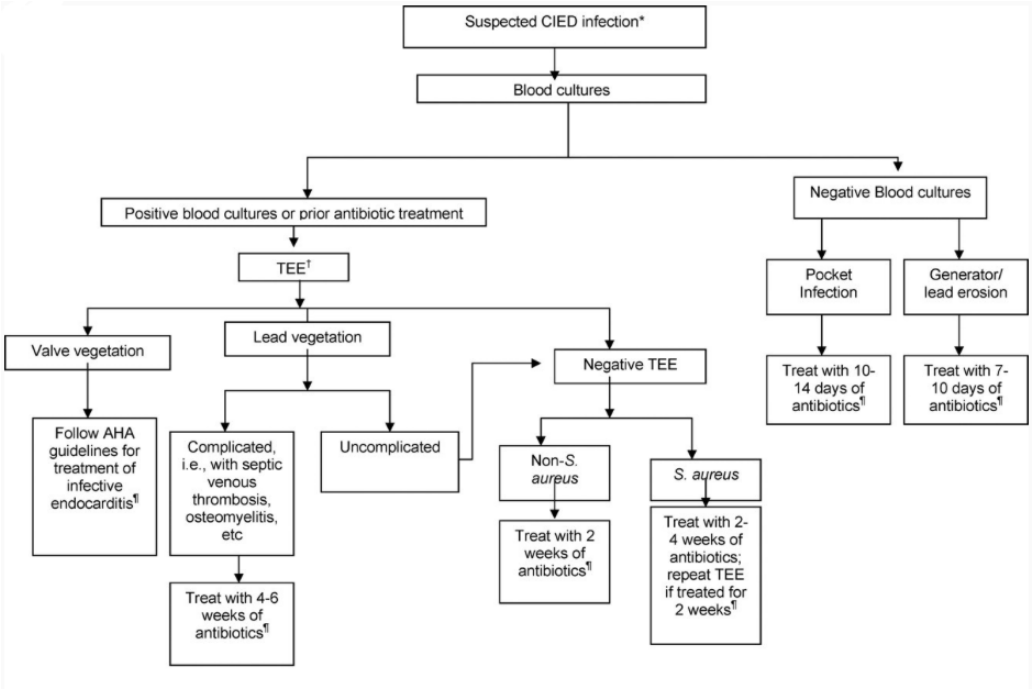
Consensus statement	Statement class	Scientific evidence coding	Reference
'Definite' CIED clinical pocket/generator infection = generator pocket shows swelling, erythema, warmth, pain, and purulent discharge/sinus formation OR deformation of pocket, adherence and threatened erosion OR exposed generator or proximal leads			
'Definite' CIED/IE = presence of either 2 major criteria or 1 major + 3 minor criteria			
'Possible' CIED/IE = presence of either 1 major + 1 minor criteria or 3 minor criteria			
'Rejected' CIED/IE diagnosis = patients who did not meet the aforementioned criteria for IE			
Major criteria		E	59
Microbiology	A. Blood cultures positive for typical microorganisms found in CIED infection and/or IE (*Coagulase-negative staphylococci, S. aureus*) B. Microorganisms consistent with IE from 2 separate blood cultures: a. Viridans streptococci, *Streptococcus gallolyticus* (*S. bovis*), HACEK group, *S. aureus*; or b. Community-acquired enterococci, in the absence of a primary focus C. Microorganisms consistent with IE from persistently positive blood cultures: a. ≥2 positive blood cultures of blood samples drawn >12 h apart; or b. All of 3 or a majority of ≥4 separate cultures of blood (first and last samples drawn ≥1 h apart); or c. Single positive blood culture for *Coxiella burnetii* or phase I IgG antibody titre >1:800		
Imaging positive for CIED infections and/or IE	D. Echocardiogram (*including ICE*) positive for: a. CIED infection: i. Clinical pocket/generator infection ii. Lead-vegetation b. Valve IE i. Vegetations ii. Abscess, pseudoaneurysm, intracardiac fistula iii. Valvular perforation or aneurysm iv. New partial dehiscence of prosthetic valve E. [^{18}F]FDG PET/CT (caution should be taken in case of recent implants) or radiolabelled WBC SPECT/CT detection of abnormal activity at pocket/generator site, along leads or at valve site F. Definite paravalvular leakage by cardiac CT		
Minor criteria		E	59
a. Predisposition such as predisposing heart condition (e.g. new onset tricuspid valve regurgitation) or injection drug use			
b. Fever (temperature >38°C)			
c. Vascular phenomena (including those detected only by imaging): major arterial emboli, septic pulmonary embolisms, infectious (mycotic) aneurysm, intracranial haemorrhage, conjunctival haemorrhages, and Janeway's lesions			
d. Microbiological evidence: positive blood culture which does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with IE or pocket culture or leads culture (extracted by non-infected pocket)			

Based on merging of the modified Duke and ESC 2015 Guidelines criteria, see text.[59,60] Green text refers to CIED-related infection criteria.
CIED, cardiac implantable electronic device; CT, computerized tomography; E, expert opinion; ICE, intracardiac echocardiography; IE, infective endocarditis; M, meta-analysis; O, observational studies; R, randomized trials; SPECT, single-photon emission tomography; WBC, white blood cell.

Pocket infection can also be further divided into "isolated pocket infection", "isolated pocket erosion", "pocket infection with lead/valvular endocarditis" and "pocket infection with bacteraemia". In case of isolated pocket infection/erosion the blood culture will be negative in both cases, but the clinical presentation might be different. As the name is indicating in case of infection, the patient will be complaining about typical signs of local infection, like erythema, tenderness, wound discharge etc., in case of infected pocket erosion, signs of local infection are not always present, but to make the diagnosis there is a skin damaged above the device, which leads to the exposure of the device (17). Blood culture has to be positive and the patient has to present with any sign of local infection in pocket infection with bacteraemia and in pocket infection with lead/valvular endocarditis, the difference is that one type there are vegetation which can be presented by different imagining tools (17,18). Some patients

develop CIED infections, with positive culture but they do not show any signs of local infection, this presentation is diagnostic for CIED-related endocarditis without pocket infection, in this case there might or might not be any evidence of vegetation. And lastly there is another type which is diagnosed based on exclusion criteria, the patient presents with bacteraemia which cannot be explained by any other condition of the patient and which resolves with the removal of the device (17). While the treatment for all except local incisional infection requires extraction surgery combined with antibiotics, it is still essential to distinguish what type of infection it is, to choose the correct timeline for the antibiotic treatment, "Figure 2" shows the appropriate antibiotic course for each time of CIEDI (19). The patient was diagnosed with CIED infection, based on the clinical picture, the patient presented with an abscess that had formed at the implantation site, and which was accompanied by erythema, pain, purulent discharge, and a feeling of stretching and soreness. Negative blood cultures, and no signs of vegetations and all laboratory test that were performed to check for systemic infections signs were without any pathological findings.

Figure 2 Antibiotic therapy in patients with CIED infection (20)



CIED, cardiac implantable electronic device; TEE, transoesophageal echography; AHA, American heart association

Risk factors

Any procedure, where a foreign object is placed inside the patient's body, has the potential to get infected, while in some locations the management is fairly easy, in patients with CIED,

infections due to the proximity to the bloodstream the management is a huge challenge and is a major cause of mortality. Therefore, it is extremely important to detect all risk factors that increase the chances of developing a CIED infection. When it comes to the evaluation those risk factors for CIED infections, can be categorized into patient-associated, procedure-associated, and device-associated risk factors. Among those categories they can be further divided into modifiable and non-modifiable risk factors. By identifying all modifiable risk factors, different measures can be planned to eliminate those and decrease the potential risk of CIED infections. Although non-modifiable risk factors cannot be eliminated, it is of great importance to identify them as well and to search for alternative strategies or methods to decrease the risk of CIED infection (15). In the past few decades many studies have been conducted, which emphasized on risk factors for CIED infections. A meta-analysis published in 2015, with a total of 206,176 patients from 60 studies determined the most important risk factors. They categorized those risk factors according to the source, which could be patient-related, procedure-related, and device-related. Patients that had certain comorbidities, like diabetes mellitus (DM), renal disease, chronic obstructive pulmonary disease, malignancy, heart failure were at significantly higher risk of developing a device related infection, according to more than 5 studies. Additionally the usage of corticosteroids and anticoagulants impacts the post procedure infection rate (21). In another study, performed in Japan, including 1749 patients with CIED implantations, they not only determined the risk factor, but also observed the rising trend of CIED infections from 0.7% (1999-2009) to 1.7% (2009-2019). Furthermore, they noticed that late CIED infections are increasing. Other factors such as the age of the patients (< 50 years) and revision surgery were linked to a higher infection rate, possible explanations for the increased risk in younger patients could be that they have a more active immune system, which could cause more severe reactions, another possibility is that they undergo more complex procedures or maybe simply because of their longer life expectancy, they may require a revision or exchange procedures, which is linked to a higher infection rate (22). Between 2006 and 2009, 200,909 ICD implantations have been performed in Medicare patients, out of those 3390 patients developed an ICD infection. The list of risk factors, that were related to the increased ICD infection was quite extensive, patients with any heart condition, related to the rhythm, valves, blood supply, pump function impairment were at higher risk. In this study patients with chronic lung diseases, kidney failure needing dialysis, DM, and those using anticoagulation experience ICD infections more frequently, which agrees with the findings of the meta-analysis described before (23). Another study determined that patients who had fever 24 h before the device inserting procedure were at a

higher risk of developing an infection (24). Other factors that are related to the procedure itself, could also increase the risk for developing CIED infections. Any type of revision surgery (for example device replacement, lead replacement) is increasing the risk of developing an CIED infection, according to different studies (21–24). Multiple studies that were conducted to research the effect of antibiotic prophylaxis prior to CIED implantation, concluded that the lack of antibiotic administration is directly correlated to an increased infection rate (25–27). Others examined the correlating between the hospital and their staff that are performing those procedures and the rate of CIED infections rates. The outcomes of those studies indicate that patients receiving their CIED in non-teaching hospitals, hospitals with low CIED implantation rates, as well as in hospitals that do not perform coronary artery bypass graft are developing CIED infections more often, than patients treated in other hospitals. The features of the hospital are not exclusively causing a higher infection rate, additionally untrained and unexperienced surgeons as well as a longer surgery time are contributing to a higher infection rate (23,28). Since there are many different indications for a CIED, there is not a single device that can serve all the different demands. Before performing the surgery where a device needs to be implanted, it is crucial to select the most suitable device for each patient. If suitable it is recommended to choose devices with lower number of leads, since multiple leads are possibly increasing the risk of developing an infection (29,30). Despite the number of leads that a device has, the device itself correlates with different CIED infection rates, when comparing the infection rate of different devices that have been implanted cardiac resynchronizing therapy devices (CRT) seem to cause the highest complication rates which includes infection (31). Going back to the medical history of the patient that has been presented, the patient has been diagnosed with heart failure with ischaemic cardiomyopathy with LV dilatation, additionally the patient was on oral anticoagulation (OAC) therapy which is considered as a risk factor. Before and after the surgery antibiotic was administered to the patient, to reduce the infection rate, which was initially successful. Only after one incident, where the patient suffered form an injury directly in the area where the device was placed, did an infection occur. The primary injury was superficial and did not cause a systemic infection, also the two cultures from the infected area that were performed during two different hospital stays were negative. The treatment for this patient was to remove the current ICD device and to replace it with a new one in a slightly different area with a long course of antibiotic therapy. As has been described by many studies on revision surgery, the use of OAC therapy as well as a prior infection increases the risk of recurrent device infection, so now after re-evaluating the patient’s situation his risk of

developing an infection is much higher. A year later the situation got worse, and the patient developed again an infection, which was accompanied by systemic symptoms like fatigue and reduced exercise tolerance, dyspnoea, and the area where the device was located started to discharge purulent secret, it became red, and the patient complained of pain and soreness. Due to his complains and after a thorough examination, the patient was scheduled for a surgery to remove the complete device with all leads and the affected skin area. The surgery was scheduled within few days to prevent the spread of the infection, causing sepsis or heart valve vegetation, which are life threatening complications. After the removal of the device, the medical condition of the patient was re-evaluated to check if an ICD is required. With the past medical history of the patient and the tachyarrhythmias that required cardioversion and amiodarone therapy after the device removal the indication for an ICD still exists. Another surgery is planned in the future after the patient has fully recovered from the infection. Even though the new device will be placed on the other side of his chest, he is now at even higher risk of developing again an infection. To reduce his risk, it is essential to eliminate all modifiable risk factors and to fulfil all safety measures. The most important risk factors are summarized in Table 2, while Figure 3 is providing an algorithm which can be used primarily to recognize all possible risk-factors, furthermore it helps with possible adjustments that can be done to reduce the risk for developing an CIED infection.

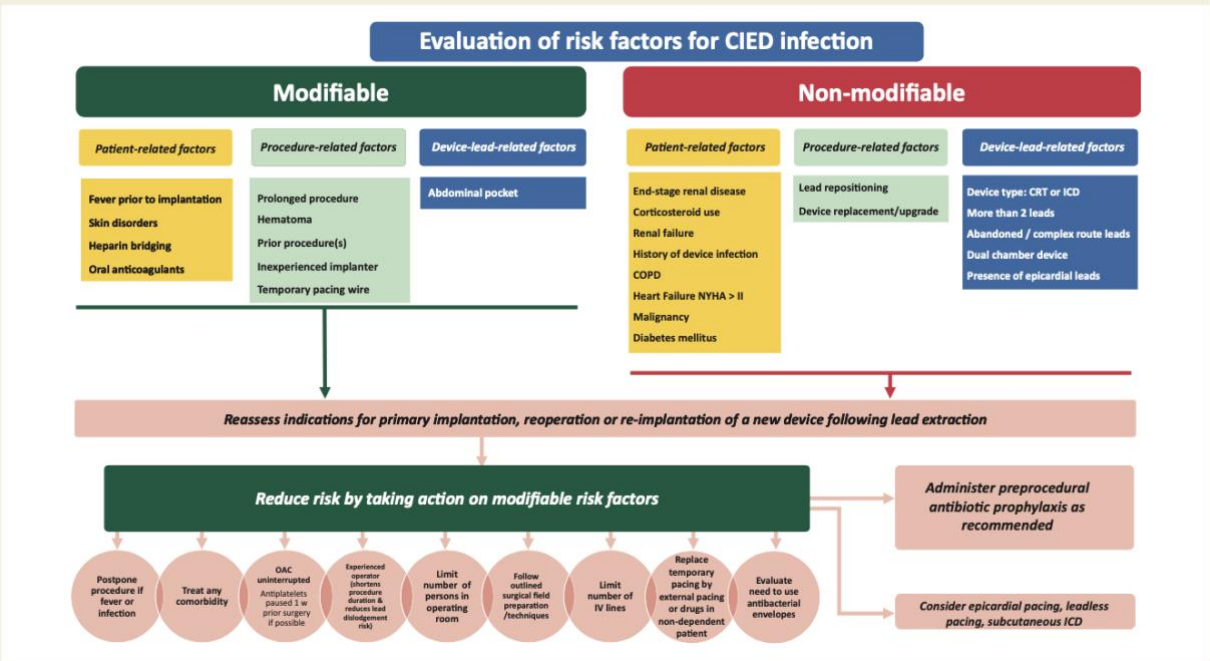
Table 2. Risk factors of CIEDI

Risk factors associated with increased CIEDI rates	
Patient related factors	• DM • Renal disease (dialysis dependent and independent) • COPD • Malignancies • Heart failure • Corticosteroid use • OAG • Age • Systemic infection (fever, leucocytosis, etc.) • Temporal pacing

Procedure related factors	• Revision surgery • Replacement surgery • Change of leads and/or device • Lack of experience (surgeon) • Low volume hospital • Lack of antibiotic prophylaxis • Long surgery time
Device related factors	• Lead numbers • Device type

DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; OAG oral anticoagulation

Figure 3. Risk factors and CIEDI prophylaxis (15)



CIED, cardiac implantable electronic device; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; ICD, implantable cardiac defibrillator; NYHA, New York Heart Association; OAG, oral anticoagulation; w, week; IV, intravenous

Treatment and extraction

Once the diagnosis of CIED infection has been made, there should not be any delay to start with an appropriate treatment. Regardless of the type of CIED infection diagnosed, the first line therapy currently is a combination of extraction surgery, which could be transvenous lead extraction (TLE) or an open surgical extraction, where the complete device with all accessories are removed, and antibiotic therapy (16,15,32). The first line therapy for superficial incisional infection, differs in the way, that no extraction surgery of the device is

required, it is solely treated by antibiotic therapy (32). While a retrospective review has shown that the mortality within 30 day is seven-fold higher in patients with a CIED infection (superficial incisional infection excluded), who were exclusively treated with antibiotic and did receive the surgery, alternative treatments have been explored. The need for alternative treatments is rising, because as with any other surgery TLE as well as open surgeries come with risks, which could make this treatment option inappropriate for some patients. Additionally patients may wish not to undergo yet another surgery, and would prefer a conservative treatment (33). New treatment options have been explored in the past few years; negative pressure wound therapy (NPWT) is one of the newer treatment option that has been successfully applied in selected patients with cardiac pacemaker pocket infection (34). In different patients where the risk of TLE surgery exceeds the benefits other treatment options have been explored, which includes pocket revision, closed-loop irrigation systems and partial removal. In one case series with 5 selected patients with CIED infections a conservative treatment was chosen, the treatment consisted of two parts, sterilization of the device and removal of the infected and damaged tissue and other foreign materials that are not essential. There were no relapses of CIED infections one year after the procedure (35). A different approach showed similar success in selected patients with a local CIED infection, the patients received a vacuum-assisted closure (VAC) treatment, after the device was removed, the lead however were only shortened and not fully removed, in contrast to TLE surgery. These patients were observed for up to 4 years, during this period only one patient developed a new local CIED infection, while the others were still in remission (36).

Coming back to the patient presented here, after the accident, the patient had a first revision surgery, the old ICD device was removed and simultaneously a new device was placed in a slightly different place, the patient was placed under antibiotic therapy for a period of 4 weeks. Due to the different risk factors the patient is now presenting, the chance for a CIED infection relapse is higher, which was proven to be true, just one year after the revision surgery, the patient developed a new CIED infection. As the standard treatment protocol for CIED infections shown in Figure 4, the patient was scheduled for a TLE surgery with a combination of antibiotic therapy, and the follow up surgery for a new device is delayed ensuring a complete remission of the CIED infections to reduce the risk for a new relapse in the future. Figure 5 indicates the appropriate timing for a new implantation surgery, which depends on the type of CIEDI the patient was suffering from.

Figure 4. Treatment algorithm for CIED infection (37)

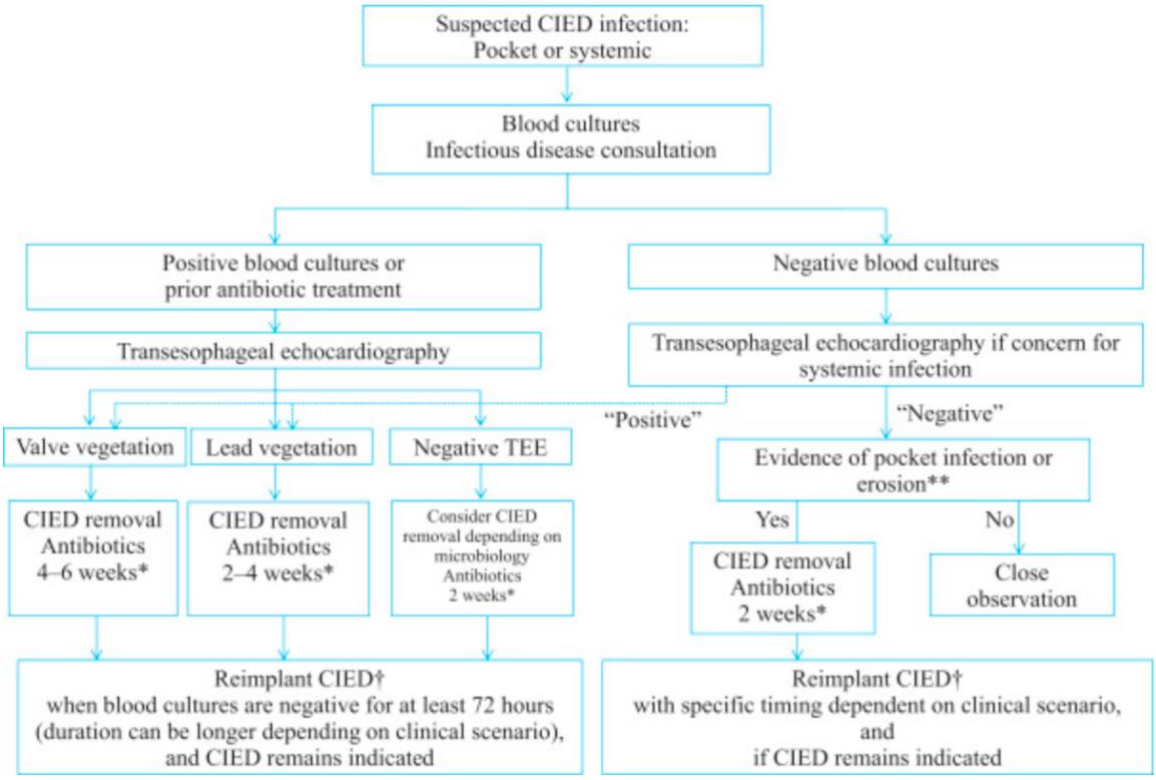
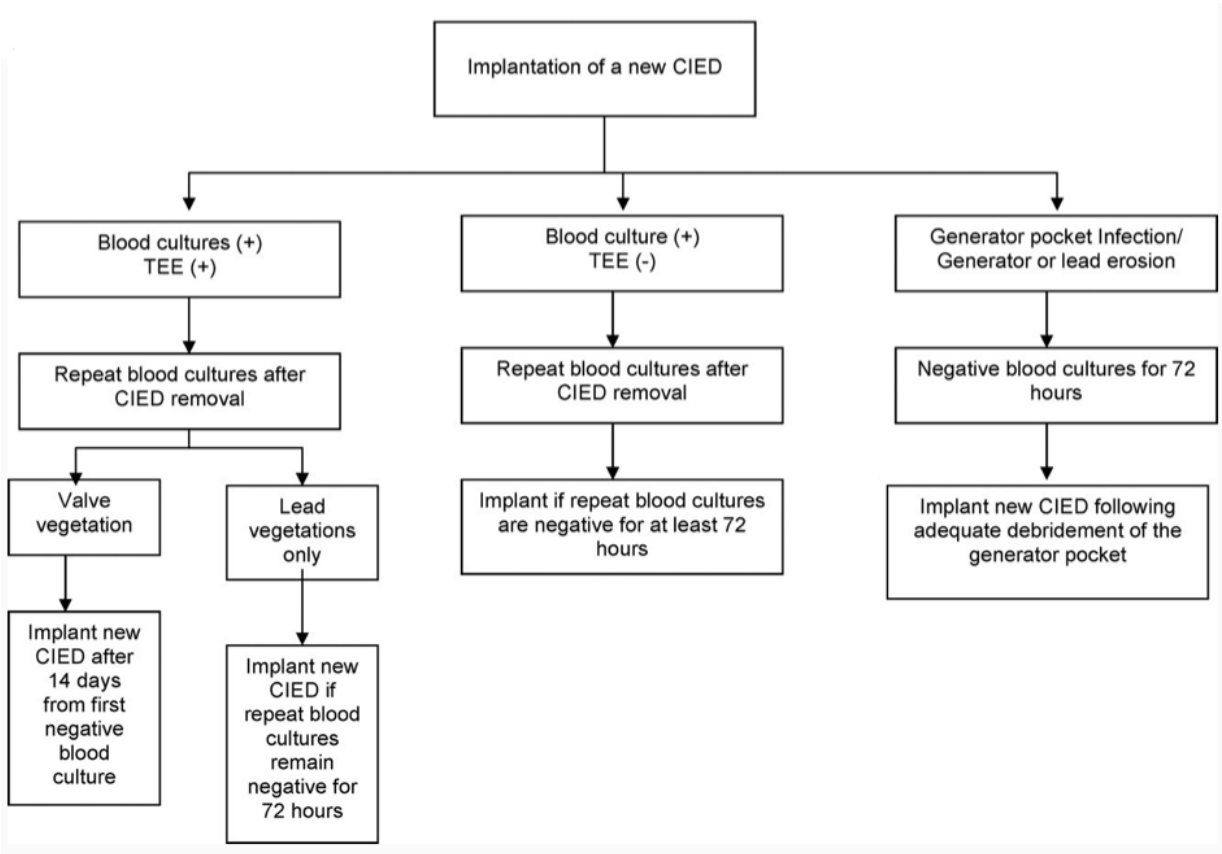


Figure 5. Timing for new device implantation (20)



Prevention

The best treatment for any condition is prevention, not only can it decrease mortality and morbidity, but it will also help to relieve the health care system. When speaking about prevention of CIED infection, different measures should be considered. To ensure the best possible outcome, it is important to carefully evaluate all possible risk factors and eliminate all that are possible or adjust appropriately (16). The first and possibly most important step is to thoroughly evaluate if the indication for a CIED implantation is of no doubt, by preventing unnecessary device implantations, the patient will be protected from any possible complication that can arise from this surgery. In early years of CIED implantation, the indications were rather few, over the time the devices were modified and the indications for those devices continued to expand. Due to the demographical changes, that have happened there are now much more older patients that are eligible for a CIED, while this development has saved many lives, new challenges have arisen. Many of the older patients come with multiple comorbidities, which has been proven to be a risk factor for development of CIED infections. Especially in those patients all possible preventive measurements should be applied to reduce the development of complications, including CIED infections. It is crucial to treat the pre-existing comorbidities optimally and reach a stable status of the patient prior to the implantation surgery. Also, an extensive anamnesis and physical examination can help to reveal pre-existing conditions and possible current infections. When preparing the patient for the surgery an evaluation of all foreign bodies that are intruding the body should be made and everything that is not absolutely needed should be removed prior to the surgery (8). If the patient presents with fever or leucocytosis 24 h prior to the surgery, it not recommended to proceed with the surgical plan, until the patient has successfully recovered from the systemic infection, and only then perform the surgery to implant a device (38). Many studies concluded that temporary pacing in fact can double the risk for CIEDI, therefore it is desirable to avoid using temporary pacing and if required offer more favourable options (39). Once all patient related risk factors have been addressed and accordingly adjusted, an appropriate device should be chosen for the patient, keeping in mind the patient's status and history. A device with two or more leads is known to increase the CIEDI risk, similar is the situation with CRT compared to ICD implantation, therefore a device with less leads and if suitable ICD should be used. (40) Other preventive strategies include avoiding 'bridging' with heparin, since it enhances the risk for haematomas and those ultimately lead to a higher infection rate. If patients require anticoagulants due to different reasons, the use of warfarin is advised (15).

Administering antibiotic as a prophylaxis to all patients prior to the surgery is known to reduce the risk for CIEDI significantly and is therefore part of the preparation procedure. The choice of antibiotic is dependent on the property of the drug, which must be appropriate for the coverage of S. aureus species since they are known to cause most of those infections. In high-risk patients a consideration is to use an 'antibiotic-impregnated envelope', which was used in a study, and almost halved the CIEDI rate in the first-year post-surgery. The antibiotic-impregnated envelope is a mesh that is covered with minocycline and rifampin and is evolving the device and dissolves after some time. (15,19,38,39,40,41). The complete surgical team should be trained to ensure sterile operating settings at all time, additionally it is recommended to keep the surgery time as short as possible and to have an experienced surgeon performing the procedure, precautions like wearing two layers of gloves can be added (39). The post-surgical care is also crucial for the prevention of the CIEDIs, when taking care of the surgical wound special instructions should be maintained, making sure that the entire wound is covered and also keeping the wound dry, educating the patient about special behaviour after the surgery, and making sure the patient understands the instructions, can prevent avoidable complications like CIEDIs (39). In Table 3 are recommendation on how to adjust different situation to prevent CIEDI. All necessary precautions were followed for the patient in this case report, the patient received the antibiotic prophylaxis prior to the surgery as is recommended, there were no risk factors that the patient presented, that were not addressed. No errors were identified prior-, during, and post-surgically, in this case there was an accident were the patient got a direct injury to the spot of device placement, and this incident exacerbated, leading to his CIEDI. There is no hint suggesting that additional precautions could have prevented the CIEDI from developing.

Table 3 Prevention of CIEDIs

Preventive measurements	
Patient related factors	• Thorough patient selection • Evaluating patients' status • Eliminating all modifiable risk factors • Stabilize all non-modifiable risk factors • Remove all unnecessary foreign bodies (catheters etc.)

	• Delay surgery if patient presents with infection signs (fever, leucocytosis, etc.) • Patient education
Device related factors	• Use a device with less leads or leadless • Use ICD if suitable
Procedure related factors	• Ensure a sterile operating field • Follow proper hand hygiene etiquette • Have an experienced surgeon • Perform surgery in a hospital with high volume CIED surgeries
Post-surgical care	• Adequate wound care • Patient education
ICD, implantable cardioverter defibrillator	

Prognosis

The outcome of CIEDI can be devastating, according to different studies, mortality is way higher (up to 3-fold) in patients who suffer from CIEDI than in those without any infection. The mortality rate varies between 10% to 35%, it increases with time, from up to 12% at admission to 17% after one year to 35% for long-term mortality (42–44). The timing of the extraction surgery is a factor that has impact on the prognosis, it can be divided into early and late extraction surgery, where early extraction surgery is defined as the removal of the device within 7 days after admission for CIEDI, and late as the procedure after 7 days. The delay of the extraction surgery can influence the outcome negatively, some of the possible consequence are, a longer hospitalization, post-surgical complications and a significant higher mortality rate (45). Another significant problem that arises from an CIEDI are the financial burden for the patient and the health care system. Although the medicine is constantly

improving, until today there is no better approach, than trying to prevent CIEDI from happening.

Conclusion

Since the introduction of cardiac implantable electronic devices, the indications have been extended, allowing more patients to be treated for otherwise fatal diseases. Following the patient's post-surgically, a significant increase of device infections has been noticed. This is particularly problematic because those infections are leading to higher morbidity and mortality. Physicians and researchers are trying to evaluate the reason for the higher infection rate and simultaneously looking into treatment options. Different risk factors have been identified, the lack of antibiotic prophylaxis before the procedure has been particularly linked to higher infection rates. Pre-existing comorbidities as well as surgeons' ability and the device itself seem to impact the result, by identifying all possible risk factors a targeted prevention strategy can be applied. As for the treatment options extraction of the system with antibiotics therapy are known to be the most effective one, but new therapies have been tried and showed promising results, but before those strategies can be introduced as standard procedures further investigations need to be performed. A very important step before implanting any device according to all experts is to minimize the risk factors or if possible, eliminate those. The preventive measurements depend on multiple factors, such as the patients, device, and procedure characteristics, but initially should evaluate if a device is indeed beneficial for the patient. During this literature review some uncertainties were noticed, such as identifying all risk factors, young age of the patient particularly needs further insight, as different results have been shown by experts.

References

1. Zipes DP, Wellens HJJ. Sudden Cardiac Death. Circulation. 1998 Nov 24;98(21):2334–51.
2. Srinivasan NT, Barts Heart Centre, St Bartholomew's Hospital, London, UK, Schilling RJ, Barts Heart Centre, St Bartholomew's Hospital, London, UK. Sudden Cardiac Death and Arrhythmias. Arrhythmia Electrophysiol Rev. 2018;7(2):111.
3. Wong CX, Brown A, Lau DH, Chugh SS, Albert CM, Kalman JM, et al. Epidemiology of Sudden Cardiac Death: Global and Regional Perspectives. Heart Lung Circ. 2019 Jan;28(1):6–14.
4. Santini M, Lavalle C, Ricci RP. Primary and secondary prevention of sudden cardiac death: who should get an ICD? Heart. 2007 Nov 1;93(11):1478–83.
5. Seidl K, Strauss M, Kleemann T. ICD-Therapie zur Sekundärprävention. Herzschrittmachertherapie Elektrophysiologie. 2010 Jun;21(2):96–101.
6. Matchett M, Sears SF, Hazelton G, Kirian K, Wilson E, Nekkanti R. The implantable cardioverter defibrillator: its history, current psychological impact and future. Expert Rev

Med Devices. 2009 Jan;6(1):43–50.
7. Jeffrey K, Parsonnet V. Cardiac Pacing, 1960–1985: A Quarter Century of Medical and Industrial Innovation. Circulation. 1998 May 19;97(19):1978–91.
8. Fazelifar AF. CIED complications. In: Radiographic Atlas of Cardiac Implantable Electronic Devices [Internet]. Elsevier; 2022 [cited 2022 Mar 10]. p. 53–64. Available from: https://linkinghub.elsevier.com/retrieve/pii/B9780323847537000054
9. Sławiński G, Lewicka E, Kempa M, Budrejko S, Raczak G. Infections of cardiac implantable electronic devices:Epidemiology, classification, treatment, and prognosis. Adv Clin Exp Med. 2019 Feb 28;28(2):263–70.
10. Gupta N, Kiley ML, Anthony F, Young C, Brar S, Kwaku K. Multi-Center, Community-Based Cardiac Implantable Electronic Devices Registry: Population, Device Utilization, and Outcomes. J Am Heart Assoc [Internet]. 2016 Mar 9 [cited 2022 Jan 16];5(3). Available from: https://www.ahajournals.org/doi/10.1161/JAHA.115.002798
11. Moore K, Ganesan A, Labrosciano C, Heddle W, McGavigan A, Hossain S, et al. Sex Differences in Acute Complications of Cardiac Implantable Electronic Devices: Implications for Patient Safety. J Am Heart Assoc [Internet]. 2019 Jan 22 [cited 2022 Mar 10];8(2). Available from: https://www.ahajournals.org/doi/10.1161/JAHA.118.010869
12. Hussein AA, Wilkoff BL. Cardiac Implantable Electronic Device Therapy in Heart Failure. Circ Res. 2019 May 24;124(11):1584–97.
13. Sohail MR, Uslan DZ, Khan AH, Friedman PA, Hayes DL, Wilson WR, et al. Management and Outcome of Permanent Pacemaker and Implantable Cardioverter-Defibrillator Infections. J Am Coll Cardiol. 2007 May;49(18):1851–9.
14. DeSimone DC, Sohail MR. Approach to Diagnosis of Cardiovascular Implantable-Electronic-Device Infection. Kraft CS, editor. J Clin Microbiol [Internet]. 2018 Jul [cited 2022 Jan 16];56(7). Available from: https://journals.asm.org/doi/10.1128/JCM.01683-17
15. Blomström-Lundqvist C, Traykov V, Erba PA, Burri H, Nielsen JC, Bongiorni MG, et al. European Heart Rhythm Association (EHRA) international consensus document on how to prevent, diagnose, and treat cardiac implantable electronic device infections—endorsed by the Heart Rhythm Society (HRS), the Asia Pacific Heart Rhythm Society (APHRS), the Latin American Heart Rhythm Society (LAHRS), International Society for Cardiovascular Infectious Diseases (ISCVID) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). EP Eur. 2020 Apr 1;22(4):515–49.
16. Nielsen JC, Gerdes JC, Varma N. Infected cardiac-implantable electronic devices: prevention, diagnosis, and treatment. Eur Heart J. 2015 Oct 1;36(37):2484–90.
17. Bongiorni MG, Burri H, Deharo JC, Starck C, Kennergren C, Saghy L, et al. 2018 EHRA expert consensus statement on lead extraction: recommendations on definitions, endpoints, research trial design, and data collection requirements for clinical scientific studies and registries: endorsed by APHRS/HRS/LAHRS. EP Eur. 2018 Jul 1;20(7):1217–1217.
18. Mahmood M, Kendi AT, Farid S, Ajmal S, Johnson GB, Baddour LM, et al. Role of 18F-FDG PET/CT in the diagnosis of cardiovascular implantable electronic device infections: A meta-analysis. J Nucl Cardiol. 2019 Jun;26(3):958–70.
19. Kirkfeldt RE, Department of Cardiology, Aarhus University Hospital, Skejby, Denmark, Johansen JB, Department of Cardiology, Odense University Hospital, Odense, Denmark, Nielsen JC, Department of Cardiology, Aarhus University Hospital, Skejby, Denmark. Management of Cardiac Electronic Device Infections: Challenges and Outcomes. Arrhythmia Electrophysiol Rev. 2016;5(3):183.
20. Baddour LM, Epstein AE, Erickson CC, Knight BP, Levison ME, Lockhart PB, et al. Update on Cardiovascular Implantable Electronic Device Infections and Their Management: A Scientific Statement From the American Heart Association. Circulation. 2010 Jan 26;121(3):458–77.

21. Polyzos KA, Konstantelias AA, Falagas ME. Risk factors for cardiac implantable electronic device infection: a systematic review and meta-analysis. EP Eur. 2015 May;17(5):767–77.
22. Ishiguchi H, Ishikura M, Yoshida M, Imoto K, Sonoyama K, Kawabata T, et al. Incidence and risk factors for cardiac implantable electronic device infection in current clinical settings in a Japanese population: A 20-year single-center observational study. J Cardiol. 2020 Jul;76(1):115–22.
23. Prutkin JM, Reynolds MR, Bao H, Curtis JP, Al-Khatib SM, Aggarwal S, et al. Rates of and Factors Associated With Infection in 200 909 Medicare Implantable Cardioverter-Defibrillator Implants: Results From the National Cardiovascular Data Registry. Circulation. 2014 Sep 23;130(13):1037–43.
24. Klug D, Balde M, Pavin D, Hidden-Lucet F, Clementy J, Sadoul N, et al. Risk Factors Related to Infections of Implanted Pacemakers and Cardioverter-Defibrillators: Results of a Large Prospective Study. Circulation. 2007 Sep 18;116(12):1349–55.
25. Bluhm Gös, Jacobson B, Julander I, Levander-Lindgren M, Olin C. Antibiotic Prophylaxis in Pacemaker Surgery—a Prospective Study. Scand J Thorac Cardiovasc Surg. 1984 Jan;18(3):227–34.
26. Mounsey JP, Griffith MJ, Tynan M, Gould FK, MacDermott AF, Gold RG, et al. Antibiotic prophylaxis in permanent pacemaker implantation: a prospective randomised trial. Heart. 1994 Oct 1;72(4):339–43.
27. de Oliveira JC, Martinelli M, Nishioka SAD, Varejão T, Uipe D, Pedrosa AAA, 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 Feb;2(1):29–34.
28. Aggarwal RK, Connelly DT, Ray SG, Ball J, Charles RG. Early complications of permanent pacemaker implantation: no difference between dual and single chamber systems. Heart. 1995 Jun 1;73(6):571–5.
29. Sohail MR, Uslan DZ, Khan AH, Friedman PA, Hayes DL, Wilson WR, et al. Risk Factor Analysis of Permanent Pacemaker Infection. Clin Infect Dis. 2007 Jul 15;45(2):166–73.
30. Herce B, Nazeyrollas P, Lesaffre F, Sandras R, Chabert J-P, Martin A, et al. Risk factors for infection of implantable cardiac devices: data from a registry of 2496 patients. Europace. 2013 Jan 1;15(1):66–70.
31. Palmisano P, Accogli M, Zaccaria M, Luzzi G, Nacci F, Anaclerio M, et al. Rate, causes, and impact on patient outcome of implantable device complications requiring surgical revision: large population survey from two centres in Italy. EP Eur. 2013 Apr;15(4):531–40.
32. Perrin T, Deharo J-C. Therapy and outcomes of cardiac implantable electronic devices infections. EP Eur. 2021 Jun 23;23(Supplement_4):iv20–7.
33. Llewellyn J, Meda G, Garner D, Wright DJ, Rao A. An Alternative to Transvenous Lead Extraction in Selected Patients with CIED Infections—A Retrospective Outcome Study. Hearts. 2022 Jan 20;3(1):6–13.
34. Zheng S, Huang X, Lin Y, Chen X, Lin G, Zhuang J. Negative-pressure wound therapy (NPWT) for the treatment of pacemaker pocket infection in patients unable or unwilling to undergo CIED extraction. J Interv Card Electrophysiol. 2021 Aug;61(2):245–51.
35. Lopez JA. Conservative management of infected pacemaker and implantable defibrillator sites with a closed antimicrobial irrigation system. EP Eur. 2013 Apr;15(4):541–5.
36. Poller WC, Schwerg M, Melzer C. Therapy of Cardiac Device Pocket Infections with Vacuum-Assisted Wound Closure-Long-Term Follow-Up: V.A.C. TREATMENT FOR LOCAL DEVICE INFECTION. Pacing Clin Electrophysiol. 2012 Oct;35(10):1217–21.
37. Kusumoto FM, Schoenfeld MH, Wilkoff BL, Berul CI, Birgersdotter-Green UM,

Carrillo R, et al. 2017 HRS expert consensus statement on cardiovascular implantable electronic device lead management and extraction. Heart Rhythm. 2017 Dec;14(12):e503–51.
38. Rohacek M, Baddour L. Cardiovascular implantable electronic device infections: associated risk factors and prevention. Swiss Med Wkly [Internet]. 2015 Jul 31 [cited 2022 Mar 15]; Available from: http://doi.emh.ch/smw.2015.14157
39. Blomstrom-Lundqvist C, Ostrowska B. Prevention of cardiac implantable electronic device infections: guidelines and conventional prophylaxis. EP Eur. 2021 Jun 23;23(Supplement_4):iv11–9.
40. Barbar T, Patel R, Thomas G, Cheung J. Strategies to Prevent Cardiac Implantable Electronic Device Infection. J Innov Card Rhythm Manag. 2020 Jan 1;11(1):3949–56.
41. Asbeutah AAA, Salem MH, Asbeutah SA, Abu-Assi MA. The role of an antibiotic envelope in the prevention of major cardiac implantable electronic device infections: A systematic review and meta-analysis. Medicine (Baltimore). 2020 Jun 26;99(26):e20834.
42. Sohail MR. Mortality and Cost Associated With Cardiovascular Implantable Electronic Device Infections. Arch Intern Med. 2011 Nov 14;171(20):1821.
43. Goette A, Sommer P. Infections of cardiac implantable electronic devices: still a cause of high mortality. EP Eur. 2021 Jun 23;23(Supplement_4):iv1–2.
44. Sgreccia D, Vitolo M, Valenti AC, Manicardi M, Boriani G. Burden of disease and costs of infections associated with cardiac implantable electronic devices. Expert Rev Pharmacoecon Outcomes Res. 2022 Jan 2;22(1):7–16.
45. Lee JZ, Majmundar M, Kumar A, Thakkar S, Patel HP, Sorajja D, et al. Impact of timing of transvenous lead removal on outcomes in infected cardiac implantable electronic devices. Heart Rhythm. 2021 Dec;S1547527121025157.

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