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Cardiac Implantable Electronic Device-Related Infections

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Abstract

The use of cardiac devices, that is, pacemakers and implantable cardioverter defibrillators, has increased, and the incidence will likely continue to increase due to an aging population with associated risk factors. Unfortunately, this implies an increasing number of complications, including infections. Cardiac device-related infection is a dreaded complication causing both increased morbidity and mortality, and considerable costs. Because of the presence of a foreign body in subcutaneous tissue, vasculature, and the heart, patients with cardiac device systems are at increased risk of endocarditis due to microbial agents. In general, an infected device system should be removed in its entirety. The timing of reimplantation varies due to indication and severity of the infection. Furthermore, the explant procedure may be complicated and should be performed by an experienced team including facilities to handle life-threatening complications. The subcutaneous implantable cardioverter defibrillator or leadless pacemaker can serve as an option in selected cases. This chapter will describe clinical aspects of cardiac device-related infections.

Keywords: cardiac device, endocarditis, infection, implantable cardioverter defibrillator, pacemaker

1. Introduction

Infective endocarditis (IE) is a potentially lethal disease. First described by Osler more than a century ago, it remains associated with a considerable burden of complications and death [1–3]. In fact, the incidence has increased over the years—in part reflecting a growing number of comorbidities in an aging population. Improvements in cardiovascular health care have not only contributed to increased life expectancy but also to a growing number of patients living with underlying cardiovascular pathologies that constitute risk factors for IE. Thus, endocarditis can be described as an adverse consequence of medical advances. This is certainly valid in the case of endocarditis affecting cardiac implantable electronic devices (CIEDs). Since the introduction of the pacemaker as a routine treatment for bradyarrhythmias in the 1960s, a rapid evolution of technology has resulted in several new implantable devices. CIEDs also include implantable cardioverter defibrillators (ICD) and cardiac resynchronization therapy (CRT). Today, device therapy is an essential therapeutic modality of cardiovascular care. It has extended the life span of patients and also improved health-related quality of life. Nowadays, approximately 1.2 million CIEDs are implanted each year worldwide [4].

This highly conventional and routine device treatment is however clouded by its potentially devastating complications. CIED infection is a severe complication associated with high mortality [5, 6]. The implantation rate is increasing globally and US data indicate that this is coupled with increased implantation in older patients with more co-morbidities. An increased use of more complex device systems also implies higher risks. All of this contributes to an end result of more CIED infections. As the disease panorama and indications are similar in large parts of the world, a similar increase outside the US seems inevitable.

A CIED infection can be challenging to diagnose and treat. It may involve the generator pocket, the leads, the endocardial structures, or a combination thereof. Involvement of endocardial structures including valves implies higher mortality. Diagnostic difficulties can be even greater than in IE because echocardiography is less accurate, blood cultures are less sensitive, and the diagnosis is sometimes not considered because of unspecific symptoms. Attempts to salvage infected devices are often unsuccessful. In this chapter, we present an outline of current recommendations regarding prevention, diagnostics, and management of CIED infections.

2. Technology and terminology

Cardiac device management involves many technical details. For those less familiar with these procedures, we recommend the supplementary appendix of a recent review [7]. In addition to an outline of the generators, leads, and materials used in CIEDs, it also describes the normal step-by-step procedures of implanting, revising, and removing CIEDs. Abbreviations are both abundant and inevitable in this field and are summarized at the end of this chapter.

3. Definition and categorization of CIED infection

There are no universally agreed definitions of CIED infection. Previously used definitions have varied, but common starting points have been the site or sites of infection on one hand and the signs of probable infection on the other [8, 9]. One common and theoretically simple distinction is between local device infection and infection also affecting the blood stream, leads, and/or cardiac valves. However, in clinical practice, it is sometimes difficult to differentiate between these categories [5]. The lack of a golden standard calls for a clear presentation of used criteria. Our proposed classification, summarized below, is a synthesis of earlier studies, recommendations, and guidelines [7, 10, 11].

In short, we suggest six different categories relevant when CIED infection is considered. These are presented in **Table 1**, besides basic strategies for device and antibiotic management. The first of three categories involving the generator pocket is not a definite infection but rather early post-implantation inflammation. These superficial signs of wound inflammation are expected to wear off shortly, when suspected causes such as sutures or dressing are removed. However, as they also can be an early sign of infection, close observation is recommended.

Actual infections can be categorized as complicated or uncomplicated pocket infection based on whether they also involve blood stream infection. Echocardiography and the modified Duke criteria can be used to classify more extensive infections: suspected or definite lead infection (CIED-LI), and CIED-associated infective endocarditis affecting the heart valves (CIED-IE) [12]. A large proportion of patients end up as "possible CIED-LI". Diagnosing a definite and isolated CIED-LI

Diagnostic classifications	Device an antibiotic strategy	Treatment duration[***]
Early post-implantation inflammation Erythema near the incision site within 30 days of implantation WITHOUT any of the following: - purulent exudate, - dehiscence, - fluctuance, - systemic signs of infection[*] A small area (<1 cm) of erythema and purulence next to a stich, (*stich abscess*), is also included in this category.	- No need for device extraction. - Remove suspected cause (stitches or local dressing/skin preparation) - Consider observation only or short oral empiric antibiotic therapy and expect clinical resolution within 2 weeks. Close observation as this can be early signs of pocket infection.	Consider 7–10 days of flucloxacillin. For penicillin-allergic or MRSA-colonized patients, consider clindamycin.
Pocket infection—uncomplicated One or more of the following: - spreading cellulitis around the pocket, or - incision site purulent exudate (excluding stitch abscess), or - wound dehiscence, or - erosion through skin with exposure of generator or leads,[**] or - fluctuance (abscess) or fistula formation AND: negative blood cultures AND: no signs of systemic infection	- Device removal recommended - Commence intravenous empiric antibiotic therapy targeting Gram-positive (including MRSA) bacteria. (Treatment for Gram-negative bacteria will depend on susceptibility testing after blood cultures for this group). - Start targeted treatment after results from blood cultures.	10–14 days iv (if no complications occur)
Pocket infection—complicated As uncomplicated pocket infection, but WITH: - positive blood cultures, or - evidence of lead or endocardial infection, or - symptoms/signs of systemic infection.	- Device removal recommended - Commence intravenous empiric antibiotic therapy targeting both Gram-positive (including MRSA) and Gram-negative bacteria. - Start targeted treatment after results from blood cultures.	Treat as CIED-IE or CIED-LI depending on the nature of complication.
Definite CIED lead infection (CIED-LI) Symptoms/signs of systemic infection NO signs of generator pocket infection AND: echocardiography consistent with lead vegetations AND: presence of major Duke microbiological criteria [12] OR: Symptoms/signs of systemic infection NO signs of generator pocket infection AND culture, histology, or molecular evidence of infection on explanted lead	- Device removal recommended - Commence intravenous empiric antibiotic therapy targeting both Gram-positive (including MRSA) and Gram-negative bacteria. - Start targeted treatment after results from blood cultures.	For isolated CIED-LI consider short course, 2 weeks of treatment after device removal. If any uncertainty (as when tricuspid valve is not normal or "ghost lesions" remain after device removal): treat as CIED-IE.

Diagnostic classifications	Device an antibiotic strategy	Treatment duration[***]
Possible CIED-LI: Symptoms/signs of systemic infection AND: echocardiography consistent with lead vegetations NO major Duke microbiological criteria present OR: symptoms/signs of systemic infection AND: major Duke criteria present NO echocardiographic evidence of lead vegetations	- Consider device removal during continued observation with repeated echography and repeated blood cultures. (For details about patient evaluation, see 8. Diagnosis) - Commence intravenous empiric antibiotic therapy targeting both Gram-positive (including MRSA) and Gram-negative bacteria. - Start targeted treatment after results from blood cultures.	Continue initial iv treatment until diagnosis is established or ruled out.
CIED-associated endocarditis, CIED-IE Duke criteria for definite endocarditis satisfied, with echocardiographic evidence of valve involvement	- Device removal recommended - Commence intravenous empiric antibiotic therapy (**Table 5**) targeting both Gram-positive (including MRSA) and Gram-negative bacteria. - Start targeted treatment after results from blood cultures.	Native cardiac structures involved: 4 weeks iv Extracardiac foci (e.g. skeleton): 6 weeks iv
Probable CIED infection Occult bacteremia, neither proof of CIED infection nor alternative sources of infection but resolving after CIED extraction.	- Device removal after thorough evaluation and exclusion of alternative sources of bacteremia. - Antimicrobial treatment, as CIED-LI.	Treat as CIED-LI.

*Clinical systemic signs of infection include rigors, fever, embolic phenomena, and improvement after treatment.
**In some guidelines, device erosion is described as an entity of its own, as this always means that the system will be infected, regardless of symptoms.
***Consider day 1 as the first day of appropriate antimicrobials unless persistently bacteremic on therapy.

Table 1.
Adopted from Sanoe et al. [7].

is difficult, but possible and would require a structurally normal tricuspid valve that remains normal after device extraction and no findings suspicious of pocket infection. Cases with occult bacteremia and neither proof of CIED infection nor alternative sources of infection, resolving after CIED extraction, are reasonable to title probable CIED infection. It may take time and sometimes also device removal before a definite diagnosis is established. However, the proposed categories may be relevant before that, as a way to structure early management. Clinical systemic signs of infection include rigors, fever, embolic phenomena, and improvement after treatment.

4. Epidemiology

The last decades have seen a steady increase in the number of patients with CIEDs [13–15]. Originally made up mostly of pacemaker implants, the continuing increase today is largely due to rising implantation rates of ICD and CRT devices [16]. Using current evidence to determine the true incidence of CIED infection is hard, as there is no uniform or mandatory reporting, no universal definition of how to classify the disease and many differences between studies regarding the time frame for measured incidence. Reviews of the literature suggest an overall incidence of CIED infection of 0.5–2.2%, based on different follow up periods from 6 weeks to 11 years [7]. Some studies instead report incidence per 1000 device years. Three large registry studies of pacemaker and ICD patients report 1.8-3.1 per 1000 device years [17–19].

As new surgical procedures mature, implantation volumes increase, and the operating staff becomes more skilled, it is often reasonable to expect that the incidence of complications will decrease [20]. For CIED infections however, the opposite has been the case. Despite the variations in reported incidence and technique of reporting incidence, there are consistent results from several long-term registry studies showing increasing infection rates over time [9, 13, 18, 20–22]. These studies display not only the well-known trend of increasing implantation rate, accentuated by wider indications for ICD treatment, but also an unproportional increase in CIED infections. Furthermore, they report higher incidence of infection for ICDs and CRT compared to pacemakers and for device revisions (such as upgrades or replacements) compared to *de novo* implantations [23, 24].

A clarifying example is a study of US discharge registries 1993–2008; during the 16-year study, implantation of pacemakers increased by 45% and ICDs by 504% and the total increase in all CIED implantation was 96%. The incidence of CIED infection increased by 210% to 2.41% between 1993 and 2008. The rate of infection was fairly constant up to 2004 when a marked increase occurred. The study revealed a parallel increase in four comorbidities (renal failure, heart failure, diabetes, and respiratory failure) among the patients starting in 2004 [13]. This shift also coincided fairly close in time with the introduction of new, broader indications for ICD treatment.

This resulted in speculations about comorbidities, together with the risks of more complex devices, explaining the increase in CIED infections [13]. As neither the aging population with more comorbidities nor the wider indications for ICDs are temporary phenomena, a conclusion has been that this has set the stage for further increases in CIED infection rates, making the study of risk factors more relevant than ever [14].

5. Predictors for CIED infection

Device-related infections are the result of an interaction between different types of risk factors—related to the patient, the implantation procedure, the microbe, or the device itself [11]. These factors predispose to device infection by either increasing the risk of generator or lead contamination at the time of implantation or increasing the risk of bacteremia from a distant source with hematogenous seeding of device leads [25]. Establishing risk factors is central for prevention and numerous risk factors have been identified (**Table 2**). The evidence supporting these factors varies and their combined effect is not easily quantifiable.

5.1 Risk factors related to patient, device, and procedure

A systematic review concluded that the three most consistently identified risk factors were the number of prior procedures, their complexity, and lack of antimicrobial prophylaxis [7]. The importance of antibiotic prophylaxis has also been showed in randomized controlled trials [11].

In a meta-analysis of 60 studies (180,000 patients), the most significant patient-related risk factors were diabetes mellitus, end-stage renal disease, chronic obstructive pulmonary disease, corticosteroid use, previous device infection, renal insufficiency, malignancy, and congestive heart failure. Other significant risk factors were symptomatic heart failure, preprocedural fever, anticoagulant drug use, heparin bridging, and chronic skin disorders. Procedural risk factors identified were postoperative hematoma, reintervention for lead dislodgement, device revision/replacement, lack of antibiotic prophylaxis, temporary pacing before the procedure, generator exchange, and inexperienced operator (<100 procedures). Significant

Patient-related risk factors:	Procedure-related risk factors:
Age and comorbidities	Pocket hematoma
Renal failure	Device replacement versus *de novo* implant
End stage renal disease/hemodialysis	Extended procedure
Diabetes mellitus	Inexperienced surgeon
Heart failure	Lack of prophylactic antibiotics
Chronic obstructive pulmonary disease	
Temporary pacing	**Device-related risk factors:**
Periprocedural fever (within 24 h)	History of multiple device-related procedures
Malignancy	≥2 leads
Skin disorder	ICD/CRT (compared to pacemaker)
Prior CIED infection	Epicardial lead(s)
Anticoagulation	Abandoned lead(s)
Immunosuppressive drug/stat	Recent device manipulation

Microbe-related risk factors:
S. aureus and other gram-positive cocci
Existence of central venous catheter
Postoperative wound infection

Table 2.
Risk factors for CIED infection [7, 11, 14, 25].

device-related risk factors were abdominal generator pocket, presence of epicardial leads, and positioning of two or more leads [26].

Although this meta-analysis did not show higher infection risks for ICDs compared to pacemakers, there are numerous other studies indicating such a risk, and a generally higher risk with more complex devices including CRT [18, 27–29]. Even though it is hard to exactly quantify the difference in risk of infection with an ICD or CRT compared to a pacemaker, it is clear that more complex devices should be regarded as a risk factor [11].

Several risk factors are linked to the reopening of the device pocket, for example during upgrades, which increases the risk of introducing bacteria—highlighting problems with today's frequent upgrades and recalls.

Several summaries of known risk factors attribute age as a risk factor [11, 25, 30]. However, it is not certain that it is a fully independent factor and some studies show contradicting results, for example, the meta-analysis mentioned above [17, 26]. As old age has been consistently associated to more co-morbidities and more complex devices, we have chosen to list "old age and comorbidities" as a risk factor [11]. There are also uncertainties regarding male sex that has been listed as a risk factor of infection in a few studies [7]. Reopening of the pocket is linked to several risk factors.

5.2 Microbe-related risk factors

Studies point to a risk of CIED infection as high as 35–45% when *Staphylococcus aureus* (*S. aureus*) is found in blood cultures [8, 29], 30% with other Gram-positive cocci [31], and 6% with blood cultures with Gram-negative bacteria [32]. Hence, the finding of either *S. aureus* or other Gram-positive cocci in blood cultures is in itself a substantial risk factor for CIED infection [7].

5.3 Risk factors associated with early versus late onset infections

Studies on infections of ICD systems suggest that there are differences between risk factors as to whether they increase the risk of early onset infections (within 6 months of implantation) or later infection. In one study, epicardial leads and postoperative wound complications, such as pocket hematoma, were associated with early infection while the length of hospitalization and chronic obstructive pulmonary disease was associated with later infection. A more general interpretation of this has been suggested; circumstances that increase the probability of pocket contamination in the postoperative period are more likely to be associated with early onset infection, while overall poor health of the patient increases the risk of late onset infection [33]. Attempts have also been made to find useful differences between pathogens related to early versus late onset infections, yet without clinically significant findings [34]. Although these efforts to describe patterns, typical of early versus late infections, can increase the understanding of the pathogenesis and prevention, there are yet no simple implications for management or other obvious clinical benefits of making such a division.

6. Mortality

Reviews of current evidence have found all-cause mortality to be substantial, ranging from 0% to 35%, with big variation probably due to different proportions of patient comorbidities between the studies and differences related to devices or the definition of CIED infection [7]. The high mortality figures do not only reflect the acute effects of the infection; a high proportion of the reported deaths are related to cardiac and other noninfection causes. This is also coherent with the observation that mortality is up to threefold higher when longer follow-up periods are compared to in-hospital or 30-day mortality [7]. Another observation has been

Patient-related risk factors	Procedure-related risk factors
Abnormal renal function	CRT device
Older age	Complicated device removal
Abnormal right ventricular function	De novo implant
Corticosteroid therapy	Epicardial right ventricular pacing system in those undergoing reimplantation
Endocarditis	Late removal (versus immediate)
Heart failure	System upgrade/revision
Length of time lead in-situ	
Medical therapy	
Metastatic malignancy	
Moderate/severe tricuspid regurgitation	
Pathogen other than a coagulase negative Staphylococcus	
Pre-reimplantation elevation of C-reactive protein	
Systemic embolization	
Thrombocytopenia on admission	

Adapted from Sandoe et al [7].

Table 3.
Risk factors for mortality in CIED infections.

that studies including only CIED endocarditis report higher mortality (25–29%) than studies of infections localized to the device pocket [7].

Studies of mortality often focus on finding risk factors of mortality, and the most frequently reported appear to be abnormal renal function, endocarditis, and old age [35–37]. Conditions often associated with endocarditis (systemic embolization, tricuspid regurgitation) have also been noted as risk factors of mortality. Another risk factor is the identified microbe, where *S. aureus* is associated with an increased mortality [38, 39].

Table 3 shows risk factors for mortality in CIED infection as presented by Sandoe et al. [7]. Included are also factors related to device types and whether the device is extracted or if the patient receives medical therapy alone. This is discussed further under "Management", but in short, device removal is clearly associated to lower mortality [40]. Although there are possible fatal complications from device removal, the mortality associated with delaying this procedure is even higher [41]. Therefore, there is no indication for extraction as strong as infection [11, 42].

7. Pathogenesis

There are two basic mechanisms of infection, either bacterial contamination at the time of implant or hematogenous seeding of the device during bacteremia from a distant focus of infection [5].

Excluding rare cases of contamination during manufacturing, it can occur perioperatively by anyone handling the device or via the air of the operation theater. Without ventilation with laminar flow, it is likely that coagulase-negative staphylococci on skin squamae, either from the patient or any of the operating staff, are present in the air. An example of this is the *en passant* finding in one study where 14 unused sterile leads were placed on the operation table during a CIED implantation. One of the leads was positive for *Staphylococcus epidermidis* after culturing [7, 43]. During implantation and possible later manipulations or revisions, skin incisions always carry the risk of skin flora contaminating the wound and eventually the device [7, 20]. It is a common notion that most CIED infections are the result of contamination at the time of implantation, which is supported by the proven effect of surgical site prophylaxis [16].

The alternative, and less common, pathway involves hematogenous seeding from a distant focus. In this case, the type of pathogen is critical to the risk of infection with *S. aureus* conferring the highest risk, whereas the risk of CIED infection from gram-negative bacteremia is low [20].

The common conceptual separation of local device pocket infection from infection involving leads and bacteremia serves a purpose for describing pathogenesis or planning preventive strategies. In practice, it is however often hard to differentiate between the two [5]. Once the generator pocket is infected, bacteria can migrate along the leads to finally reach intracardiac structures. And although pocket infection most often is due to perioperative contamination, hematogenous seeding to the pocket is also a possibility [14]. The eventual consequence of CIED infection can be the forming of vegetations anywhere on the lead and on the tricuspid valve as well as the right atrial or ventricular endocardium. Septic pulmonary embolism is a frequent complication of device endocarditis [5].

However, pathogenesis cannot be reduced to blood stream or wound contamination. It is the result of specific interactions between the device, the microbe, and the host [14]. Risk factors related to the patient (host) and device have been discussed in earlier sections. Additionally, there are specific device factors related to surface features and chemical interactions between pathogens and devices affecting pathogen adherence. The development of devices with better surface properties in this regard

is an important topic under current exploration, although not currently relevant in clinical practice, and therefore beyond the scope of this chapter [7, 11, 16, 20]. Finally, there are specific virulence factors, all related to microbial ability to adhere to device surfaces that are crucial for establishing CIED infection. The most important of these is the ability to form biofilm [20, 25, 44]. This reduces the effectiveness of the normal immune system response to infection, supplies a barrier against antibiotic penetration, and (by metabolic downregulation) makes bacteria less susceptible to antibiotics.

8. Diagnosis

The signs and symptoms of CIED infection depend on the location of the infected part of the device, but establishing the diagnosis can sometimes be challenging with a variety of manifestations. Fever is present in most cases. It is reasonable to always consider device infection for patients with CIEDs and unexplained fever, keeping in mind that a blunted fever response is common among the elderly [5]. In some cases, with typical symptoms of localized generator pocket infection, diagnosing CIED infection is simple. In other cases, the symptoms can be extremely vague despite extensive infection, often resulting in diagnostic delays. As with other types of endocarditis, diagnosis is not built on a single test, but rather evaluation of a pattern of signs and investigations where echocardiography and blood cultures play a fundamental role. Sometimes, *S. aureus* bacteremia can be the only sign of device infection [5]. A central recommendation in guidelines is also that the patient with suspected CIED infection should be evaluated by a multidisciplinary team [14].

8.1 Clinical presentation

The most common type of CIED infection (~60%) is a generator pocket infection with symptoms of localized inflammation including erythema, pain, swelling, warmth, erosion, and purulent drainage or skin dehiscence [45]. In less than half of these cases, there are also systemic signs of infection or positive blood cultures [25, 45]. Often, these signs are easily identified, motivating the patient to seek medical attention. But sometimes, the symptoms are more subtle, presenting soon after implantation and thereby hard to differentiate from pure postoperative inflammation, skin reactions to dressings, disinfection agents, and sutures or a restricted and superficial infection [7, 11].

A second major manifestation is that of infection affecting either cardiac valves, device leads, or a combination of these two (CIED-IE or CIED-LI). This accounts for 10–23% of all CIED infections [25, 46]. Many of these patients have typical signs of systemic infection, presenting with fever, rigors, malaise, fatigue, or anorexia. Most, but not all, show positive blood cultures [11, 45]. Parallel symptoms of device pocket infection make the diagnosis easier, but this is not always the case. Instead, the presence of a CIED is often disregarded by the first doctor seeing the patient [24]. Major diagnostic tools recommended by guidelines are cardiac imaging, repeated blood cultures and use of the modified Duke criteria (**Table 4**) [7, 12].

In the case of cardiac vegetations, the tricuspid valve is the most common site, but vegetations may also appear on both the pulmonic and left-sided valves. *S. aureus* is the most common pathogen. In this patient group, it is common with symptoms or radiographic findings indicating septic embolism to the lungs (~40%) as well as other organs (18%), and occasionally distant abscess formation [46–48]. Possible embolic phenomena are important to keep in mind, as secondary foci of infection, such as vertebral osteomyelitis or discitis, can be the main symptom presented by the patient [7, 47]. Other possible sites of metastatic abscesses are brain, liver, kidney, and spleen. In some cases, it will be hard to distinguish if a distal site of infection is the result of

Duke criteria	
Major	**Definite endocarditis**
Blood culture positive for IE	- 2 major criteria; or
Evidence of endocardial involvement	- 1 major criterion and 3 minor criteria; or
Echocardiogram positive for IE	- 5 minor criteria
New valvular regurgitation (worsening of pre-existent murmur not sufficient)	
	Possible endocarditis:
Minor	- 1 major and 1 minor criterion
Predisposition (predisposing heart condition, iv drug use)	-3 minor criteria
Fever (>38°C)	
Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhage, and Janeway lesions	
Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth´s spots, and rheumatoid factor	
Microbiological evidence: positive blood culture but does not meet a major criterion or serological evidence of active infection with organism consistent with IE	
Microorganisms consistent with IE: (positive results from 2 separate blood cultures required)	
- Streptococcus viridans	
- Streptococcus bovis	
- HACEK group (*Haemophilus* spp., *Aggregatibacter*, *Cardiobacterium*, *Eikenella*, *Kingella*)	
- Staphylococcus aureus	
- Community-acquired enterococci, in the absence of a primary focus	
Or:	
Microorganisms consistent with IE from persistently positive blood cultures, defined as follows: at least two positive cultures of blood samples drawn >12 h apart, or	
all of three or a majority of ≥4 separate cultures (with first and last sample drawn at least 1 h apart)	
Single positive blood culture for *Coxiella burnetii* or antiphase 1 IgG antibody titer >1:800	

Table 4.
The Duke criteria, adapted from Li et al. [12].

hematogenous seeding from a cardiac device or if the opposite is true [25]. Less than 10% present with septic shock, usually caused by virulent pathogens such as *S. aureus* or *Pseudomonas aeruginosa* [7, 44]. Less virulent pathogens are generally associated with a more subacute or chronic presentation. In rare cases, this can be coupled with immune-complex mediated conditions such as nephritis or vasculitis [44].

In contrast to the diversity of symptoms mentioned above, occult bacteremia (or in rare cases fungemia) without localized symptoms at the generator pocket represents a diagnostic challenge primarily by the absence of findings [11, 25]. Studies indicate that laboratory abnormalities are present in less than half of the cases of CIED infection, hence normal laboratory results should not rule out CIED infection [9, 25]. Distant foci of infection could result in hematogenous seeding of the device but should not always be interpreted as evidence of actual CIED infection. To avoid misdiagnosis and unnecessary and riskful extractions, an algorithm for managing bacteremia among CIED patients has been presented by DeSimone and Sohail [49].

Except for these three main presentations, there are occasional cases of device erosion through the skin with neither positive blood cultures nor any other local inflammatory changes. Usually, erosion is a slow process of fat necrosis and migration from deeper layers of the skin and seldom presents shortly after implantation.

The exact cause often remains unclear but can be low grade device infection, other local infections or mechanical factors alone [11]. Whenever a generator or lead has eroded through the skin, the whole device system should be regarded as infected [7].

8.2 Diagnostic challenges

Beyond the typical and distinct clinical manifestations, there are also many cases with scarce or misleading symptoms. One study reports that many diagnostic delays are related to the fact that CIED infection was not considered in the original differential diagnosis, for instance, when device patients present with mainly respiratory or rheumatic symptoms that are interpreted as bronchitis [5, 47]. Other reasons for delay could be that possible hints about the diagnosis were disregarded, for instance positive blood cultures for *Staphylococcus epidermidis* first considered to represent contamination. Sometimes, the diagnosis was taken into consideration, but wrongly excluded without adequate investigations, such as a negative transthoracic echocardiography (TTE) being interpreted as sufficient for excluding the diagnosis [47].

8.3 Microbiology and adequate sampling

A series of studies consistently show that staphylococci and Gram-positive bacteria in general are responsible for most CIED infections. Methicillin resistance among *S. aureus* has been reported to various extents, depending on geographic and individual factors [5]. We found the figures of the prevalence of respective pathogens fairly consistent with the results of prior studies and systematic reviews [7, 9, 11, 25, 45, 47, 50–52]. Consistent are also reports of negative cultures despite clinical infection. A reason for this may be previous antibiotic treatment and fastidious microbes [25]. Negative blood cultures should be interpreted with caution and exclusion of infection should not rely exclusively on cultures.

At least two sets of blood cultures (including aerobic and anaerobic cultures) are recommended before starting antibiotic therapy. For patients presenting with acute symptoms, ideally the two sets should be taken at different times within 1 h from peripheral sites. If the clinical presentation is chronic/subacute, guidelines recommend three sets of cultures to be taken from peripheral sites with >6 h between each sample, before antibiotic therapy is started [7]. The point of taking multiple cultures with certain waiting periods is hopes of improved sensitivity and the ability to differentiate between transient and persistent bacteremia. Consistently positive blood cultures with the same pathogen are highly indicative of CIED infection. If purulent drainage is present from the device pocket, a culture can be very useful and more sensitive than other pocket cultures. Percutaneous aspiration of the pocket should, however, not be done because of the risk of introducing microorganisms and possibly causing device infection [14]. When a device is removed, device pocket swabs and tissue culture as well as both proximal and distal lead cultures should be obtained [11]. The lead-tip cultures should be interpreted with caution if extracted through an infected device pocket because of the risk of contamination. Possible femoral extraction would reduce this risk. The clinical situation when lead tip cultures interpreted as unequivocally significant is when there is no sign of pocket infection [25, 50]. After device removal, the recommendation is to obtain new blood cultures after 48–72 h.

8.4 Cardiac imaging

Echocardiography is a cornerstone for diagnosing CIED infection, visualizing lead or endocardial vegetations, and estimating valve regurgitation and vegetation size. TTE is superior for pericardial effusion and estimations of ventricular

function and pulmonary pressure. TTE is also convenient for repeated monitoring of vegetations and cardiac function before or after extraction. Transesophageal echocardiography (TEE) is however superior for diagnosing lead and endocardial infection (CIED-LI, CIED-IE), visualizing vegetations, valves and parts of the lead that are difficult to see by TTE. It is also superior for visualizing left-sided endocarditis and perivalvular abscesses. For the diagnosis of CIED-IE, the sensitivity of TEE is >90%, compared to 22–43% for TTE [7]. Hence, both modalities should be used, but in this complimentary manner. Despite the high sensitivity of TEE, it is important keeping in mind that a normal echocardiography does not completely rule out the possibility of CIED infection [5, 7, 10, 11, 14, 30].

It has been demonstrated that TEE cannot distinguish vegetations from sterile thrombi [14, 30]. In studies validating TEE, 5–10% of identified lead masses, first described as vegetations, were concluded to represent incidentally found thrombi [53, 54]. This underlines the importance of a thorough multidisciplinary evaluation using the sum of all findings to assess the patient; masses found on leads in patients without symptoms of infection or positive blood cultures should consequently not be treated with device extraction and antibiotics, but possibly anticoagulants [10].

New imaging modalities (^{18}F-FDG positron emission tomography/computerized tomography, ^{99m}TcHMPAO-WBC) have been studied in a few early reports suggesting slightly increased sensitivity compared to TEE and possibly a high negative predictive value. Limited evidence of their possible added clinical value, high costs, and limited availability so far has not resulted in recommended routine use and guidelines describe them as a possibility to consider in selected and complicated cases. The same approach is recommended for intracardiac echocardiography that possibly may enhance diagnostic accuracy, but just like TEE, is unable to distinguish thrombi from infective vegetations [7, 11, 30].

The role of ordinary chest X-ray has not been studied specifically. Guidelines recommend chest X-ray for patients presenting with acute symptoms as a baseline image during circumstances when full medical records may not be available [7]. Chest computerized tomography or pulmonary angiography can contribute in complicated diagnostic processes by finding septic emboli that constitute a minor Duke criterion.

9. Management

Successful management of CIED infection is dependent on complete and prompt device removal, long antimicrobial treatment, and reimplantation if the device is still indicated. In a few cases, device removal may not be possible, which substantially reduces the probability of curing the infection. There is a lack of randomized controlled trials to guide management of CIED infection. Most of today's practice is based on the results of observational studies or clinical expertise [25, 55].

In the case of suspected CIED infection, initially two or three blood cultures (depending on urgency) should be taken, followed by the initiation of empiric antibiotic treatment. After that, it is important to determine whether the device should be removed or not [7].

9.1 Device removal

Results from several retrospective studies have shown that complete and early device removal (despite its rare but potentially fatal complications) together with antibiotics is more effective than medical therapy alone with dramatically lower figures for mortality and infection relapse [9, 41, 56]. A multivariate analysis of a large CIED infection cohort showed a sevenfold increase in 30-day mortality for patients treated

with medical therapy alone compared to the combination with device removal [41]. In a large retrospective study of patients in Cleveland, 97% (pocket infection and CIED-IE) were cured by extraction combined with antibiotics [45]. Therefore, complete device removal is the general recommendation for established CIED infection [7, 11].

What is the implication of this for our previous presented clinical categories? The most benign case is that of post-implantation inflammation, where the device should not be removed. However, a close follow-up is important: what is first perceived as inflammation can later be interpreted as early symptoms of infection [7]. If symptoms instead are accordant with device pocket infection (complicated or uncomplicated), device removal is inevitable. That is also the case for the more extensive infections, definite CIED-LI and CIED-IE.

Remaining are two diagnostically more difficult categories: "possible CIED-LI" and "probable CIED infection" (occult bacteremia) for which guidelines recommend that device removal is considered while the patient is under continued observation with repeated echocardiography and blood cultures. Evaluation by physicians with specific expertise in CIED infection is always recommended when a diagnosis is established, but is also an option for *suspected* infection if the investigation is complicated [11]. Additional radiology could strengthen a diagnosis in the case of complications of CIED infection such as septic arthritis, spine infection, pulmonary embolism, vein thrombosis, or metastatic abscess [7, 25]. If available, new modalities such as FDG-positron emission tomography/computerized tomography might play a role by adding information in complex cases. In the case of bacteremia of an unknown source, all removable non-CIED sources of infection (such as intravenous lines) should be taken out [11]. A single positive blood culture without other symptoms is not sufficient for immediate device removal but the identified pathogen can give vital information. As mentioned in previous sections, CIED infection is more likely with Gram-positive bacteremia. *S. aureus* should not be neglected and instead always regarded as a possible pathogen, requiring further investigations in search of a source [11]. In the case of *S. aureus* bacteremia where there are no clinical or echocardiographic findings supporting CIED infection, earlier American Heart Association guidelines have mentioned six parameters associated with CIED infection [14]:

- Relapsing bacteremia after finished antibiotic course.

- No other source of bacteremia is identified.

- Bacteremia persisting >24 h.

- The CIED is an ICD.

- The patient has a prosthetic valve.

- Bacteremia occurs within three months of device implantation.

A scientific statement from the Heart Rhythm Society stresses that early diagnosis and lead extraction Within three days of diagnosis were associated with lower mortality in a small study [11, 40]. British guidelines recommend extraction as early as possible, but not later than within two weeks of diagnosis [7]. CIED infection can also occur for surgically implanted devices with epicardial leads. Basically, what has been stated for ordinary leads is also valid for epicardial leads. Complete device removal is recommended, after analyzing the risk of surgery for the individual patient compared to the risk from CIED infection. For localized pocket infection though, a practice of cutting the epicardial leads, only extracting the portion close to the pocket is used [11].

9.2 Antibiotic treatment

For patients with suspected post-operative inflammation, the use of antibiotics is controversial. It is reasonable to first consider if continued observation is sufficient. If needed, guidelines recommend a short oral course [7]. For all other clinical categories, some antimicrobial treatment is recommended. A multidisciplinary approach involving infectious disease specialists and individual adaptations depending on the patient's risk factors and comorbidities is essential.

A basic principle is to start with broad empirical treatment, if systemic infection is suspected. At this stage, treatment should target both Gram-positive, including methicillin-resistant *S. aureus* (MRSA), and Gram-negative bacteria [11]. The duration of antibiotic treatment is counted from the first negative culture after device removal and depends on a number of factors including the specific pathogen, extent of device infection, and existence of complications, if the device has been successfully removed or not. As with other parts of management, there is a lack of solid evidence and the choice of antibiotics and treatment durations are primarily based on expert opinion and experience [11]. Examples of regimens from current guidelines are provided in **Tables 1** and **5**, but it is also important to always consider local resistance patterns. The category "uncomplicated device pocket infection" by definition does not include systemic infection. However, some of these patients will eventually develop sepsis and therefore it is reasonable to start empiric therapy. Once a pathogen is identified through cultures, treatment should be modified accordingly.

9.3 Reimplantation

After removal of infected devices, it is crucial to always thoroughly reassess the need for a new CIED. Some patients no longer meet an original indication because of improvements in heart rhythm or function. Others have a strong personal opinion and do not accept a new implantation [11]. For some patients, another type of device can reduce possible risks of infection relapse (device downgrade and alternative devices are further described under prevention). The percentage of patients with CIED infection not requiring a replacement device has ranged from 13 to 52% in different studies [25].

Diagnosis/scenario	Suggested antibiotics	Dose[*]	
Pocket infection, uncomplicated	Vancomycin or daptomycin or teicoplanin	1 g q12h iv 4 mg/kg q24h iv 6 mg/kg to a maximum of 1 g given at 0.12 an 24 h and then q24h	
CIED-LI, CIED-IE, or complicated pocket infection, pending blood cultures, e.g. in sepsis	Vancomycin AND meropenem or daptomycin AND meropenem	1 g q12 iv 1 g q8h 8–10 mg/kg q24h 1 g q8h iv	(appropriate spectrum, but risk of nephrotoxicity) (gentamicin in high dose, according to local guidelines, may be appropriate depending on local epidemiology) (less risk of nephrotoxicity than vancomycin)
CIED-LI or CIED-IE or complicated pocket infection with negative blood cultures	Vancomycin AND gentamicin or daptomycin AND gentamicin	1 g q12h iv 1 mg/kg q12h iv 8–10 mg/kg q24h 1 mg/kg q12h iv	(appropriate spectrum but risk of nephrotoxicity)

iv: intravenously, q8h: every 8 hours, q12h: every 12 hours, and q24h: every 24 hours. [*]All doses may require adjustment due to impaired renal function.

Table 5.
Examples of guideline regimens for empiric antibiotic treatment.

Clearance of infection is a prerequisite before hardware can be reimplanted. The optimal timing of reimplantation is however not known as no prospective trials have been done. According to recommendations from the Heart Rhythm Society, it is reasonable to await a 72 h period of negative blood cultures before reimplantation, also mentioning that there are single center studies indicating that reimplantation the same day as device extraction is possible for isolated pocket infections [11]. The existence of undrained abscesses or other sources of infection would demand further postponing of these suggested waiting times. It is also recommended that a new device is placed on the contralateral side, an attempt to reduce the risk of seeding the new device from a prior tissue infection [9]. If remains of valvular infection are suspected, the waiting period should be extended to at least 14 days according to the European Society of Cardiology guidelines [5]. British guidelines, illustrating that there is no unanimity here, recommends reimplantation to whenever possible be delayed until signs of infection have resolved suggesting 7–10 days [7].

The pacemaker-dependent patient poses a special challenge. Some form of temporary pacing is needed as a bridge to reimplantation. Common problems of traditional temporary pacing are frequent loss of capture, undersensing, and that the systems in general are large and inconvenient, all this confining the patent to stay immobilized in a hospital bed during antibiotic treatment before reimplantation. Studies of "semi-permanent" systems with active fixation leads and an external reusable pacemaker have shown that this practice is safe, reduces hospital stays, and makes the patient more mobile [11, 57]. However, these studies have so far only included a smaller number of patients and therefore are not able to rule out that the risks for relapsing infection earlier observed with temporary pacing still holds [58]. Therefore, all sorts of temporary pacing should still be regarded as a risk factor and avoided if possible, even though this semi-permanent technique probably is a way to reduce adverse events [5]. For ICD-patients with high risk of sudden cardiac death, the wearable cardioverter defibrillator can be a promising option. This noninvasive device is worn under normal clothing safely and effectively treats ventricular tachyarrhythmias, thus offering bridging to ICD reimplantation, (if the indication still holds) without increasing the risk of CIED infection relapse [59].

9.4 Management when device removal is not possible

Despite all known benefits of device removal, there are a small proportion of the patients that either decline device removal or are considered medically unfit for device removal. For many of these patients, it is likely that extraction will require surgical intervention and often they may be more or less dependent on a device (for instance CRT) that is not considered possible to reimplant. They may also have other, permanent, sources of infection or a short life expectancy [11]. There is not much evidence to guide the management of these patients, but various smaller reports have described very varied outcomes. Some describe patients being cured with medical therapy alone. Others describe the strategy of partial device removal (only generator), which is possible for nonpacemaker-dependent patients, with cure rates in a wide range from 13 to 71%. There are also reports of ICD patients with 100% failure [7].

British guidelines include regimens for attempts to salvage devices with medical therapy alone [7]. These consist of different combinations of antibiotics (for instance daptomycin and vancomycin), aiming to break through biofilm and are based on combinations that have salvaged infected non-CIED prosthetic materials and other devices. The duration of therapy is often 6 weeks. There is no known test to evaluate this therapy besides observation and blood cultures after the end of a course. Infection relapse is equivalent to a failure to salvage the device. In that case (unless the decision about device removal does not change), the only option is a palliative strategy of life-long suppressive antibiotic treatment. Patients in this

group are usually cardiovascularly stable and have responded well to antibiotics with clinical improvement and cleared bloodstream infection. This strategy can obviously only be applied to a few selected patients and the outcome is also unclear. Compared to curative strategies, this should be regarded as a last resort [11].

9.5 Risks associated with device removal

Device removal should be performed in specialized centers with expertise in the procedure and acute cardiac surgery backup available [30]. Percutaneous procedures have become the most used method as procedural risks are lower compared to open surgery. In case of failures with a percutaneous technique, a conversion to open surgery is common. Removal of leads engrafted in cardiac tissue can be dangerous. Over time, fibrous anchoring tends to develop between leads and vascular and cardiac structures. Inter-lead anchoring is also common. The major procedural complications are related to these anchorings and accidental tears or perforations of either the superior vena cava or parts of the myocardial wall with resulting dramatic bleeding and tamponade. Lead fracture often requires shifts to open surgery and can cause life threatening arrhythmias. To reduce risks, new techniques with locking stylets, photoablation of fibrous attachments, and less invasive methods aided by thoracoscopy have been developed [30, 60, 61]. In experienced centers, procedure mortality is low, between 0.1 and 0.6% [5]. If removal employs this type of special equipment, or concerns a lead implanted more than a year ago, the procedure is referred to as *extraction* as compared to *explantation* [11].

A number of procedural risk factors have been identified one of the more evident being elapsed time since lead implantation, which is related to the fibrous anchorings. Other risk factors are female sex, multiple leads (lead-lead anchoring), operator inexperience, and radiological findings of calcification involving leads. ICD is a risk factor as the device is bigger and more complex. In particular, the coils are suspected of stimulating fibrotic growth between device and myocardium and some extracting operators choose to only implant single coils for this reason [60].

In the case of very large vegetations, there is risk of pulmonary embolism. For very large vegetation, a shift to open surgery is common. There is uncertainty about how large vegetations should be for this shift to benefit the patient. Guidelines state that additional data are needed and recommend individualized decisions for vegetations >2 cm in diameter [5].

10. Prevention

As CIED infection results in substantial morbidity and mortality as well as high and rising costs for health care systems, good prevention is essential. The first subsection here is valid for all device patients. The following, covering secondary prevention, is specific for CIED infection patients. Being an essential and integrated part of all CIED infection management, it is not always specifically referred to as prevention. Finally, we give an outline of new therapies and devices with possible implications for all potential devices.

10.1 Primary prevention

Before implantation, the patient must be evaluated for clinical signs of infection. Fever during the last 24 h before implantation is a risk marker for later CIED infection. Signs of systemic infection should always result in elective implantations being postponed and acute procedures should be avoided until the infectious episode is resolved [7]. Perioperative antibiotics reduce the risk of infection. A randomized controlled

study was interrupted after having enrolled 649 patients, showing an infection rate of 3.4% for the placebo group versus 0.6% in the antibiotics group [11]. When risk markers are studied, neglected perioperative antibiotics are one of the more consistent predictors of infection risk. Intravenous administration of a cephalosporin or penicillinase resistant penicillin 1 h before procedural start or vancomycin 2 h before start are commonly used [11]. Repeated dosing after skin closure or general postoperative antibiotic use is not recommended. Except for TYRX™ (see Section 10.3), there is so far no support in evidence for local installation of antibiotics or antiseptics into the device pocket [7, 62].

Implantation should ideally take place in a designated CIED laboratory fulfilling requirements for ventilation suitable for device surgery. This is underlined by the fact that it is not unusual with perioperative CIED contamination today and many CIEDs are implanted in catheterization laboratories with lower ventilation requirements than operation theaters [7]. Implantation should be carried out with an aseptic technique, in an environment observing operating theater discipline. Alcoholic chlorhexidine (2%) should be used to prepare the skin over the operative site. Devices and surgical equipment should be left uncovered for the minimum possible time [7].

Risk of infection is also related to operator experience and the aggregated operation volumes of different centers—at least it has been shown that very small volumes are related to higher risk of complications: a study of Medicare recipients showed that physicians implanting 1–10 ICDs annually had higher complication rates than physicians implanting more than 29 devices [63]. A US registry study found a complication rate of 3.8% at centers performing fewer than 24 implants a year compared to 3.1% at centers implanting more than 110 devices a year [64]. British guidelines stress the importance of supervision of junior operators (with lower operation volumes) by senior operators. They also speculate about if a lack of supervision is more common for generator exchange procedures, which have a higher risk of infection than de novo implants, but often are viewed as simple and "straightforward procedures" [7].

Postoperative hematomas are a consistently found risk factor. If possible, antithrombotic treatment and anticoagulation should be discontinued prior to the procedure. If a pause in anticoagulation is not deemed possible, it is however better to continue with ordinary warfarin doses than discontinuing and trying to bridge with heparin as this is related to a significant increase in pocket hematomas [7]. As for new oral anticoagulants (NOACs), there are less data, but studies suggest that there is no difference in pocket hematoma between interrupted and continued NOAC regimens [65].

10.2 Secondary prevention

The most effective preventive measure against CIED infection is to avoid unnecessary CIED implants in the first place. For patients with CIED infection, a reassessment of the risks and benefits of the device before reimplantation is crucial, and a significant proportion of the patients do actually not meet indications for reimplantation. As the risk is also associated with various properties of the device, this reevaluation can also result in a device downgrade, for instance from a more complex to a simpler device, or from two defibrillator coils to one on an ICD. An option is also to change from transvenous leads to epicardial leads, or more commonly, to choose some of the newer devices described below.

A general principle of CIED infections is to remove all hardware, but if this is not possible, as much as possible should be removed. Examples of the latter is the isolated removal of the generator for nonpacemaker-dependent patients who refuse lead extraction or the practice of cutting the leads and removing the proximal part together with the generator when epicardial lead extraction is regarded too risky, all based on the presumption that the generator accounts for the biggest infection burden in a CIED and that its removal is a simple procedure compared to lead extraction.

The risk of infection is less with peripheral cannulae than cuffed central venous catheters and patients can be treated with peripheral cannulae for very long periods, as long as the cannulae are changed every 72 h [66]. In fact, the risk of infection for any vascular access increases with time in situ. A central venous catheter also increases the risk of venous thrombosis reducing access options for future CIED placement. For some patients, though, siting cannulae can become very complicated and alternative strategies are needed as oral administration during CIED infection is not a safe procedure. Peripherally installed catheters (PICC or "midline") may in that case be a better alternative than central venous catheters [7].

As mentioned in previous sections, temporary pacing with an intravenous pacing wire is associated with higher risk of infection relapse and should if possible be avoided for CIED infection patients. If central venous catheters are used, potential future access sites for CIEDs (contralateral prepectoral to existing CIED) should be avoided if possible. Semi-permanent pacing with screw-in leads is probably better than traditional temporary pacing, but both techniques should be avoided unless the patient is dependent on pacing. It seems that this is not only valid for CIED infection patients (and thereby also an example of primary prevention); for acute patients, it is becoming more common to directly implant a pacemaker, rather than using temporary pacing with higher risk of future CIED infection [7, 58, 67].

10.3 Alternative device systems

A leadless pacemaker suitable for VVI-pacing can be implanted in the right ventricle through femoral venous access. It is a means of avoiding the traditional complications associated with leads or generator pockets, and studies have shown promising results with lower complication rates compared to transvenous CIEDs [68, 69]. However, to our knowledge, no randomized controlled studies have yet compared leadless and transvenous pacemakers. Also, no long-term studies have yet been completed. In situations with limited venous access as well as reimplantation after CIED infection for high risk patients, leadless pacing should be considered.

A subcutaneous ICD is an alternative to transvenous systems that can be considered as an option for reimplantation in patients with high risk of CIED infection relapse. With this system, complications related to leads or vascular access are avoided. It has proved to be as effective as an ordinary ICD in treating life-threatening arrhythmias, but it is unsuitable for patients needing pacing, resynchronization therapy, or antitachycardia pacing [70–72].

Since 2001, the noninvasive wearable cardioverter defibrillator has been available to provide temporary protection against sudden cardiac death. It safely and effectively detects and terminates ventricular arrhythmias and should be considered as a bridging therapy to ICD reimplantation. As a reassessment of the indications should take place before every reimplantation, the wearable cardioverter defibrillator also has the potential of bridging to a device downgrade [59, 73, 74].

In addition to perioperative systemic antibiotics, an antibiotic envelope (TYRX™) has been developed, wrapping the device and slowly releasing antibiotics (minocycline and rifampin) in the device pocket. A meta-analysis of five prior studies including 4490 patients showed that use of the envelope is associated with significantly lowering the CIED infection rate, although the included studies were not randomized controlled trials [75]. Other studies have particularly showed benefits among patients categorized as high risk individuals for early CIED infection (risk factors, **Table 2**) [76]. As the envelope is costly and its use is not yet routine, this selected patient group is probably the most promising to start with, although there are cost-benefit studies indicating a role for this envelope as a standard of care for all patients, at least in the context of the US health care system [77].

Current evidence does not support the use of prophylactic antibiotics for dental procedures or other invasive procedures that do not involve direct device manipulation [11].

11. Conclusions

CIED infection is a rare but severe complication. As more complex devices are implanted in patients with more co-morbidities, the infection rate is on the rise. CIED infection should always be considered in device patients with unexplained fever—the presence of *S. aureus* bacteremia is equivalent to a risk of device infection of almost 50%. Once infection is established, renal impairment, old age, and endocarditis are some of the most consistently found predictors of mortality. Although not without lethal risks, device removal is the recommended treatment in all but a few cases and should be performed in designated centers. Combined with antibiotic treatment, this can enable cure rates as high as 97% according to some studies. Reassessment of the original indication should always precede device reimplantation. Intravenous lines and temporary pacing should be avoided if possible and technical alternatives such as leadless pacemakers, subcutaneous defibrillators, and antibiotic device envelopes should be considered as means of reducing risk of reinfection.

Abbreviations

CRT	cardiac resynchronization therapy
CIED	cardiac implantable electronic devices
CIED-IE	CIED-associated infective endocarditis
CIED-LI	lead infection
ICD	implantable cardioverter defibrillator
IE	infective endocarditis
NOAC	new oral anticoagulant
MRSA	methicillin-resistant *S. aureus*
TEE	transesophageal echocardiography
TTE	transthoracic echocardiography

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