

# Review of cardiac implantable electronic device related infection

Émile Saliba<sup>1</sup>  
Emmanuelle Massie<sup>2</sup>  
Ying Tung Sia<sup>3</sup>

<sup>1</sup>Cardiology Department, Hôtel-Dieu de Montréal, Montréal, QC, Canada;

<sup>2</sup>Internal Medicine Department, Hôpital Saint Luc, Montréal, QC, Canada; <sup>3</sup>Cardiology Department, Hôpital Pierre Boucher, Longueuil, QC, Canada

**Abstract:** Cardiac implantable electronic devices (CIEDs) are being used more and more often nowadays. Indications have grown, and access to implantation facilities has increased as well. These devices are often lifesaving, and they can be associated with many other benefits. However, as with any medical procedure, complications can occur. In fact, CIED infection is a prevalent complication that can cause high morbidity and can even lead to death. It is important that most clinicians be familiar with signs and symptoms associated with CIED infection as early diagnosis and treatment lead to better outcomes. Nonetheless, the prevention of such infections remains the cornerstone in the management of CIED-related infections. In this paper, we will review in detail the most significant risk factors that can lead to CIED infection. We will also explore the different available tools that can help decrease the incidence of this complication. In addition, we will summarize the different treatment modalities and the major prevention methods.

**Keywords:** cardiac implantable electronic device, infection, pacemaker, endocarditis

## Introduction

Ever since the first pacemaker was implanted in 1960, the use of cardiac implantable electronic devices (CIEDs) has increased exponentially.<sup>1</sup> Between 1997 and 2004, the use of permanent pacemaker and implanted cardiac defibrillator (ICD) has increased by 19% and 60%, respectively, in the USA. The arrival of the cardiac resynchronization therapy devices has also led to an increase in the use of CIED.<sup>1</sup> As indications for CIED have increased, patients with more comorbidities have also become eligible for these therapies, often requiring long and complex procedures. Although these procedures are safe, complications can occur and can be very morbid. CIED infection is associated with increased mortality and morbidity as well as increased health care-related expenses.<sup>2</sup> In fact, patients who develop CIED infection have increased long-term mortality even after successful treatment of the infection.<sup>3</sup> Some data have shown a tendency of increased rate of CIED infection, especially in the first few months after installation.

There are multiple CIED on the market nowadays. Pacemakers and defibrillators are the most commonly installed devices and are used in the management of symptomatic bradycardia and prevention or treatment of ventricular tachycardia. These devices are composed of two major components: the pocket (contains the generator) and the leads. The different components of the device can be infected individually or concomitantly. CIED infections can be divided into two main entities: isolated pocket infection or lead infection. Pocket infection is usually limited to the tissue surrounding the generator

Correspondence: Émile Saliba  
Institut de Cardiologie de Montréal, 5000  
Rue Bélanger, Montréal, QC H1T 1C8,  
Canada  
Tel +1 514 244 1473  
Email emile.saliba@umontreal.ca

and is usually not associated with any bacteremia. In contrast, lead infection can be associated with right-sided endocarditis and can cause bacteremia. In some cases, lead infection is not always associated with pocket infection, and it can occur in isolated manner. It is noteworthy to mention that some patients require lead changes and that old leads can remain in the patient if their removal is hard. This abandoned material can also get infected.

This paper reviews CIED infections and mainly focuses on risk factors and prevention of CIED infections. General therapeutic and diagnostic approaches are also outlined.

## Epidemiology

The true incidence of CIED infection is difficult to establish due to the lack of national mandatory registries and the lack of reporting. The incidence also varies according to the type of device being installed and depends on other risk factors. In the era of prophylactic antibiotic use before insertion, the incidence of CIED infection can be as high as 6%.<sup>4</sup> Implantable cardioverter defibrillator infection rate has recently been reported to be around 1.7%.<sup>5</sup> As previously mentioned, the incidence of infection can vary a lot according to registries and studies. However, in a recent systematic review by Persson et al,<sup>6</sup> CIED infection ranged between 0.2% and 3.7%, and it was the third leading cause of complication.

Over the last 16 years, ICD implantation increased by a staggering 504% compared to a 45% increase for pacemakers. In addition, the financial burden associated with those infections has also increased.<sup>7</sup> According to Sohail et al,<sup>2</sup> a CIED infection-related hospital admission could cost as much as \$53,349. Infection of complex devices is usually associated with higher costs. Moreover, with the increasing prevalence of heart failure and with the aging of the population, it is expected that CIED implantations keep increasing. Thus, it is probable that CIED infection rate would also increase.

Most CIED infections only involve the pocket, and deeper infection such as endocarditis only occurs in around 10% of cases. However, some studies have reported the prevalence of lead vegetation to be as high as 40%.<sup>8,9</sup> In addition, the risk of infection can increase up to tenfold if the patient is undergoing a lead replacement or a device upgrade.<sup>10</sup> Early infection refers to cases occurring the first month following the procedure. Late infections occur between 1 and 12 months after implantation, and delayed infections occur after 12 months. In a study by Lekkerkerker et al,<sup>11</sup> 28% of patients had an early infection, 35% had a late infection, and 37% of patients presented with a delayed infection. Up to 24% of infections occurred 2 years after device installation.

CIED infections have been on the rise for the last few years. According to Voigt et al,<sup>12</sup> CIED infections in the USA have risen by 12% between 2004 and 2006. As a consequence, hospitalization rates have increased by a staggering 57% and mortality rates doubled. This surge in CIED infection is secondary to increased patient comorbidities and to increased awareness and better diagnosis of this condition.<sup>1,12</sup> Mortality associated with CIED varies greatly as it depends on the rapidity of diagnosis and on appropriate management. Mortality can be as high as 36% in patients admitted with a diagnosis of CIED infection.<sup>2</sup> According to Sohail et al,<sup>2</sup> mortality tends to be higher for many years even after the acute CIED infection was properly managed (absolute risk increase of 15% at 1 year and at 3 years).<sup>3</sup>

## Risk factors

### Device related

The risk of infection increases depending on which type of device is being installed and on the amount of leads. According to Durante-Mangoni et al,<sup>13</sup> the presence of two leads or more is one of the most important risk factors of CIED infection. Early data did not support the fact that biventricular devices were associated with higher infection rates.<sup>11</sup> However, a recent meta-analysis demonstrated that abdominal pockets, epicardial leads, presence of two or more leads, and dual-chamber systems are the main device-related risk factors for infection.<sup>14</sup>

### Patient related

Patients with increased comorbidities are at increased risk of infection. Predisposing factors are immunosuppression, advanced age, cancer therapy, chronic kidney disease, diabetes mellitus, cirrhosis, active infection, and reintervention.<sup>13,15</sup> A recent meta-analysis suggested that chronic obstructive pulmonary disease and male sex increased the risk of CIED infection.<sup>14</sup> Altered defense mechanisms and increased procedure complexity accounted for this risk increase. In addition, these patients often required more frequent hospitalizations and could undergo invasive investigations, all which increase the risk of CIED infection.<sup>12</sup>

Chronic kidney disease patients requiring hemodialysis are particularly at increased risk of CIED infection, especially in the presence of a temporary dialysis catheter.<sup>16</sup> Heart failure and other cardiac structural anomalies increase the complexity of the implantation procedure, and this is also associated with an increased rate of infection.<sup>15</sup> CIED infection in patients requiring dialysis is associated with high short-term mortality and is more often accompanied by endocarditis.<sup>17</sup>

The use of anticoagulant increases the risk of pocket hematoma. This often leads to extra wound dressing changes and can sometimes require percutaneous drainage. Increased manipulation of the wound can lead to colonization by skin flora and increases healing time.<sup>11,13</sup> Accordingly, higher infection rates are observed in anticoagulated patients. In the case of warfarin, its discontinuation is not recommended because bridging therapy with low-molecular-weight heparin increases pocket hematoma formation.<sup>18</sup> Most other anticoagulants are stopped prior to the procedure.

Preprocedural fever (24 hours) and local skin disorders have also been associated with increased infection rates. In addition, a history of CIED infection also increases the rate of device infection.<sup>14</sup> Withdrawal of indwelling central venous lines 24 hours preprocedure will also decrease the rate of infection.

## Procedure related

Postoperative hematoma, reintervention for lead dislodgement, device replacement or revision, lack of temporary antibiotics prophylaxis, temporary pacing, operator inexperience, and procedure length all increase the risk of CIED infection.<sup>14</sup> Generator replacement increases the risk of infection by 4% approximately, and lead replacement can increase the risk by around 15%.<sup>19</sup> The higher infection rate in reintervention procedures is probably related to the altered defense mechanisms of scar tissue and to the increased healing time.<sup>11</sup> In addition, increased tension in the pocket may lead to local tissue ischemia and necrosis, which can compromise the incision line and lead to wound dehiscence.<sup>20</sup> These factors can lead to the growth of local bacteria and can increase the risk of infection. The implantation of biventricular resynchronization therapy seems to be the procedure at most risk of infection.<sup>21</sup> CIED infection is significantly higher when they were installed by operators with low volume of implants.<sup>22</sup>

The use of prophylactic intravenous antibiotics should be routine before all CIED procedures. A large double-blinded placebo-controlled study by de Oliveira et al<sup>23</sup> demonstrated the superiority of a single intravenous dose of 1 g of cefazolin when compared to placebo. The study was terminated prematurely by the ethics committee due to the benefits of prophylactic antibiotics. In patients at high risk of infection, the use of an antibiotic (minocycline and rifampin)-coated membrane during implantation greatly reduces the risk of infection.<sup>24,25</sup> Several observational trials as well as a randomized placebo-controlled trial have shown that the use of various topical antibiotics after the procedure showed no benefit on the rate of CIED infection.<sup>26,27</sup>

The REPLACE registry, has demonstrated that at 6-month follow-up, hospitals with high CIED infection rates had sicker patients and lower overall procedural volume.<sup>19</sup>

## Clinical manifestations

Most CIED infections usually manifest in the first 6 months after implantation.<sup>28</sup> In total, 28% of those patients developed the infection in the first month after implantation, 35% between 1 and 12 months, and 24% of patients developed the infection 24 months after the implantation.<sup>11</sup>

In general, pocket infections are much more common than lead infection and endocarditis. They typically develop in the first month following implantation, but late infections can also be seen. Early infections are usually associated with local symptoms such as pocket erythema, swelling, pain, and warmth. In contrast, skin erosion is more frequent with late infection, and it can be the only manifestation. When skin erosion is present, infection is certain. Systemic symptoms such as fever and chills can be seen in early and late infections, but they are not a common manifestation. The infection can also extend to the leads, and vegetations can develop on the tricuspid valve.<sup>29–31</sup>

Even though lead infection is not easily diagnosed based on clinical evidence, it can be seen in up to 40% of patients who present with pocket infection. In general, the intracardiac portion of the lead is more often infected than the transvenous portion.<sup>32</sup> Symptoms vary according to the extent of the disease. Fever and chills are usually present, and some patients can present with sepsis and can even be in septic shock.<sup>1</sup> Vegetations can also invade the tricuspid valve and cause tricuspid regurgitation. Pulmonary complications such as pneumonia, emboli, and abscesses can be secondary to septic emboli.<sup>33</sup> In rare cases, left-sided vegetations can also develop.

Occult bacteremia can also be an infrequent presentation of CIED infection. This can occur without any other manifestations around the pocket. For example, in patients with a non-*Staphylococcus aureus* Gram-positive cocci bacteremia, the CIED infection rate was 30%. Less frequently, patients can present with relapsing bacteremia even when initial investigations showed no signs of pocket or lead infection.<sup>34</sup> The use of additional imaging modalities, especially a functional one, can help identify the exact location of infection.

Some authors have tried to create risk scores and to find which factors allow better determination of CIED infection. For example, in the PREDICT-SAB study, the findings suggest that the presence of a permanent pacemaker, more than one device-related procedure, and duration of *S. aureus* bacteremia  $\geq 4$  days are independent predictors of CIED

infection in patients presenting with *S. aureus* bacteremia. In contrast, patients who did not have any of those risk factors and who did not have signs of pocket infection had a low risk of CIED infection.<sup>35</sup>

## Diagnosis

The diagnosis of a CIED infection can be challenging in some cases. Pocket infections are diagnosed based on the clinical presentation, but lead involvement requires additional diagnostic exams to rule out. Given that lead involvement is associated with higher mortality and morbidity, the use of imaging modalities such as echocardiography is essential in the evaluation of those patients.<sup>36</sup>

Echocardiography is of utmost value to rule out lead infection or endocarditis. Transthoracic echocardiography is a good initial test to screen for lead involvement but is not sensitive enough to rule it out. Thus, most experts recommend the use of transesophageal echocardiography (TEE) as the gold standard exam to detect vegetations.<sup>1</sup> Some authors even recommend the use of intracardiac echocardiography, which has a sensitivity of 100% and a specificity of 82%.<sup>37</sup> TEE will help better identify masses or vegetations on the leads; however, blood cultures and inflammatory markers should be closely followed to make sure that the nature of such masses is infectious.<sup>13</sup>

DUKE criteria are sometimes used to diagnose CIED-related endocarditis, but their sensitivity and specificity are relatively low in this context.<sup>38</sup> Acute inflammatory markers such as sedimentation rate and C-reactive protein can be elevated, and they can be associated with leukocytosis. If white blood cell count is high, it can be followed to assess appropriateness of therapy.<sup>30</sup> Surrogate markers for bacterial infections such as procalcitonin have not been evaluated in the diagnosis of CIED infection.

When doubt persists, nuclear medicine imaging modalities can help increase the diagnostic yield. Radiotraced white blood cell scintigraphy can detect CIED infection and has a sensitivity of 94%.<sup>38</sup> Fluorine-18 marked fluoro-deoxyglucose positron emission tomography has an even better diagnostic yield, but it is not widely available,<sup>39</sup> and its combined use with the DUKE criteria can produce an even higher yield.<sup>40</sup> It has also been shown to detect infection related to left ventricular assist devices.<sup>41</sup>

According to the latest American guidelines, two sets of blood cultures should always be drawn before antibiotics administration.<sup>1</sup> If antibiotics have already been started, two to four sets of blood cultures should be drawn after an adequate washout interval. When endocarditis is present, all

blood cultures drawn before antibiotic therapy usually show growth of the same pathogen. Although unusual, only one set of blood cultures can be positive, and the use of additional diagnostic exams is essential to distinguish between infection and contaminants. If the device is removed, the generator and the leads should be cultured to confirm the diagnosis.<sup>30</sup> Percutaneous aspiration of the infected site is not recommended as colonizing pathogens and skin flora could contaminate this specimen.

In some cases, a definite diagnosis is still hard to obtain. Some authors suggest sonication of the extracted device and of blood cultures. In fact, sonication has been shown to be more sensitive than swab cultures in identifying the culprit pathogen. This usually implies the placement of the extracted device in a Ringer's solution, which is then vortexed and cultivated. In one study, sonication permitted the identification of significant bacterial growth in 54% of cases compared to 20% for device swabs.<sup>42</sup>

## Microbiology

As shown in Table S1, the majority of CIED infections are caused by *S. aureus* and *Staphylococcus epidermidis* infections.<sup>43</sup> Methicillin-resistant staphylococci can also infect CIED, but the prevalence of such infections is quite variable. Up to 20% of patients present with non-staphylococci-related CIED infections such as *Corynebacterium*, *Propionibacterium*, *Peptococcus*, Gram-negative rods (especially *Pseudomonas aeruginosa*), enterococci, and fungi.<sup>43</sup> In addition, 10% of infections can be polymicrobial, and 10% can remain without having a clear pathogen identified.<sup>13</sup> Early infections are typically associated with staphylococci species.<sup>11</sup>

## Management

Empirical antibiotic therapy should have an appropriate bio-film penetration rate, a good bactericidal activity, and should be suitable for bacteremia as well. At all times, antibiotics should be tailored according to local bacteria resistance and sensitivity patterns. In general, empirical antibiotics should have adequate coverage of Gram-positive cocci as well as Gram-negative bacteria.<sup>43</sup> The duration of appropriate therapy is outlined in Table S1. Antibiotic therapy should always be individualized and should be given according to the latest guidelines. The Infectious Diseases Society of America provide additional information on this topic.<sup>1</sup>

In most cases, complete device retrieval is necessary in addition to intravenous antibiotics. Most guidelines recommend removal of the generator and all leads even if the infection is only limited to the pocket. This recommendation

also includes abandoned leads and all foreign material. In one study, 71.4% of patients with retained material showed recurrence.<sup>44</sup> Devices should be removed as soon as possible especially if the patient is displaying signs of sepsis or shock. Attention should be given to patients who are permanently paced to avoid potentially disastrous consequences of removing chronotropic input. Installation of temporary pacemakers should be avoided if possible, since it could get infected, especially if bacteremia is present. However, optimal timing of device removal is quite controversial. It is usually recommended that the patient receives a few days of intravenous antibiotics before removal. This reduces the risk of complications such as septic emboli, and it also reduces the risk of recurrence of infection. Given that some patients might require temporary pacemakers, the administration of antibiotics will reduce the risk of persistent infection.

Newly installed leads are easier to remove than older ones due to the lack of endothelialization. In some patients, complete device extraction can be hazardous because of advanced age and increased comorbidities. Risk of device extraction increases with older leads and with complex systems. According to heart rhythm society, vegetations larger than 2 cm indicate surgical removal of the leads, thus it is required to have a TEE before device removal.<sup>45</sup> Lead extraction-associated risk decreases when the extraction is performed in a high volume center.<sup>46</sup>

In select rare cases, such as limited infection and high patient comorbidities, the generator should be removed and replaced as long as the pathogen is of low virulence and aggressive debridement is performed.<sup>13</sup> Lopez et al<sup>47</sup> reported the case of five patients in whom complete device extraction was not possible, and so conservative therapy was chosen. All patients received a new generator (soaked in a gentamycin and vancomycin solution) and had oral antibiotics on discharge. At 2 years follow-up, none of the patients had recurrence of the infection. Thus, it is possible to consider a conservative approach in some selected patients.

In general, if the infection is limited to the pocket, antibiotics should be given for at least 2 weeks and at least 7 days after device extraction.<sup>1</sup> Therapy should be extended for 3 weeks if there is bacteremia and for 6 weeks if endocarditis is present.<sup>1</sup> For left-sided endocarditis, treatment should be administered according to local guidelines.

## Device reimplantation

Once the CIED is removed, it is always judicious to review the indication for the implantation of a new one since a significant portion of patients might no longer meet the indication for a CIED. As previously mentioned, the administration of anti-

biotics will reduce the risk of infection of the new device. In all cases, two separate sets of blood cultures have to be negative before implanting the new device. Optimal timing of this reimplantation is controversial. Some authors suggest waiting 7 days in the case of pocket infections and 14 days in the case of bacteremia. However, this depends on many factors, since some patients are pacemaker dependent for example.<sup>30</sup> Most experts recommend waiting at least 2 weeks before installing any permanent devices.<sup>30</sup>

In patients who only need defibrillators and in whom no pacing is needed, the use of a subcutaneous implanted defibrillator should be considered as it reduces the risk of subsequent infection.<sup>48</sup> Subcutaneous ICD is effective in treating ventricular tachycardia and has been studied in many trials.<sup>49</sup> As a matter of fact, this type of device is associated with very low rates of infection, and if infection was to occur, the extraction of this device is much easier than the extraction of transvenous devices.<sup>49</sup> Subcutaneous ICDs have been shown to have lower rates of infection even in patients in whom a previous transvenous CIED was explanted for infection.<sup>48</sup> In patients with high risk of infection, the use of epicardial leads can also be considered to reduce the risk of systemic infection.<sup>30</sup> Leadless pacemakers could also eventually be one of the options.<sup>50</sup>

## CIED infection prevention

To reduce the incidence of CIED infections, prevention is of utmost importance. CIED installation or upgrade should only be done in patients with a clear indication for it. Ideally, a pacemaker or a defibrillator should be installed once patients are in a stable condition and in those who do not show any signs of local or systemic infection. Elective procedures should be rescheduled if the patient has a central catheter installed.

CIED implantation should always be done in a sterile environment and according to usual surgical sterilization guidelines. New sterilization techniques have been shown to reduce infection rates. For example, the “bundled skin antiseptic preparation” showed superiority compared to standard sterilization techniques, but it requires more time and more resources.<sup>51</sup> Good hemostasis throughout the procedure is also beneficial as the risk of hematoma formation will be reduced, and consequently the risk of infection.<sup>30</sup> In contrast, other sterilization techniques have been associated with increased risk of infection. In the REPLACE registry, there was some doubt on a possible increased rate of infection associated with povidone iodine compared to chlorhexidine alcohol. The difference between those two substances was especially significant in establishments



with high rates of infection.<sup>52</sup> However, another study found no statistically significant difference in the rate of CIED infection when either chlorhexidine alcohol or povidone iodine was used.<sup>52</sup>

The most frequently administered prophylactic antibiotics are second-generation cephalosporins. As previously mentioned, the use of prophylactic antibiotics has been clearly established and should be routinely done. This has been demonstrated in several trials<sup>53</sup> including a large randomized one.<sup>23</sup> However, the optimal timing of antibiotic use remains controversial. Most surgical references recommend that antibiotics be given 30–60 minutes before the procedure.<sup>54</sup> In a recent systematic review, the administration of a prophylactic antibiotic 1 hour before the CIED installation was shown to be effective at reducing surgical site infections.<sup>55</sup> It remains unclear if antibiotics effective against methicillin-resistant *S. aureus* (MRSA) should be administered to everyone, thus antibiotics should be chosen according to local bacterial prevalence.<sup>30</sup>

The latest advancement in CIED infection prevention is the use of antibiotic envelopes. TYRX™ (Medtronic, Dublin, Republic of Ireland) is a newly developed envelope that releases minocycline and rifampin in the generator pocket after the implantation of the device. This envelope has been shown to reduce the growth of several pathogens.<sup>56</sup> In addition, it has been shown to reduce biofilm production and to eliminate staphylococci growth.<sup>57</sup> This envelope is easily installed and does not render CIED implantation more difficult or cause more complications. In a study by Bloom et al,<sup>25</sup> the use of this antibacterial envelope was associated with an early infection incidence reduction of 0.5%, and these same results were reproduced in other trials.<sup>24</sup> The use of such envelopes in patients at high risk of infection seems to be beneficial and cost-effective. Some authors even suggest that the use of such envelopes becomes routine standard care.<sup>58</sup> Additional clinical trials are currently underway to evaluate the long-term infection risk reduction associated with antimicrobial envelopes.

Implementation of those recommendations will help reduce the global burden of CIED infections. For example, an infection control protocol was introduced at a tertiary referral central in the UK, and it was associated with a 54% reduction of CIED infection.<sup>59</sup> This protocol consisted of thirteen different steps. All patients were screened for MRSA, and if MRSA carriage was detected, topical skin eradication was performed with nasal mupirocin and 4% chlorhexidine. Signs of infection or sepsis 24 hours were an indication for procedure deferral. Intravenous antibiotic

prophylaxis was administered to everyone (flucloxacillin 1 g or clarithromycin 500 mg combined with gentamycin 1.5 mg/kg) 30 minutes before the procedure. Operators had a minimum scrubbing time of 2 minutes, and they were required to double glove during draping, and the outer glove was removed prior to skin incision. Sterilization was performed with a solution of 2% chlorhexidine gluconate with 70% isopropyl alcohol. Local hair was removed using an electric razor, and all diabetic patients had their glycemia lowered to <11.0 mmol/L. Cutting diathermy at 40 W was used after incision, and antibacterial-coated sutures were used for the wound. All intravenous accesses were closed systems, and they were installed in a sterile manner. Bair hugger was used to control the temperature in patients undergoing complex procedures. Finally, wound dressings were left intact for 3 days following installation. Implementation of such measures was found to be cost-effective and easy to put in place.<sup>59</sup> This strategy for infection control has also been proven to be safe and cost-effective in the context of other interventions.<sup>60</sup>

## Conclusion

The use of CIED is expected to increase in the next few years, and patients with more comorbidity will become eligible for them as well. Thus, precautions should be taken to avoid an increase of infections. To do so, it is very important to recognize the risk factors associated with them and to learn how to prevent them by working on the many factors that can influence the risk of infection.

## Disclosure

The authors report no conflicts of interest in this work.

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## Supplementary material

**Table S1** Pathogens associated with CIED infections

Study	N	Microbiology
Sandoe et al <sup>1</sup> (2015)	18 studies of at least 100 patients	Gram-positive (67.5%–92.5%) with CoNS being the most frequent one, followed by <i>Staphylococcus aureus</i> Gram-negative bacilli (1%–17%) Fungal infection (uncommon, no >2%) Polymicrobial (2%–24.5%) Negative culture (12%–49%)
Welch et al <sup>2</sup> (2014)	238	EARLY <sup>a</sup> : <i>S. aureus</i> (40.7%), CoNS (46.9%), and non-staphylococcal (15.4%) LATE <sup>b</sup> : <i>S. aureus</i> (25.9%), CoNS (52.9%), and non-staphylococcal (23.8%)
Durante-Mangoni et al <sup>3</sup> (2013)	82	Gram-positive cocci (84%) <ul style="list-style-type: none"> <li><i>Staphylococcus epidermidis</i> (41%)</li> <li><i>S. aureus</i> (21%)</li> <li>Streptococci/enterococci/peptococci (7.3%)</li> <li>Other CoNS (15%)</li> </ul> Gram-negatives (4.9%) Candida species (2.4%) <i>Propionibacterium acnes</i> (1.2%) Culture negative (7.2%)
Padeletti et al <sup>4</sup> (2011)	N/A	Staphylococcal (70%–90%): <i>S. aureus</i> , <i>S. epidermidis</i> Non-staphylococcal (10%–30%): <i>Enterococcus</i> spp., <i>Streptococcus</i> spp., <i>Proteus</i> , <i>Klebsiella</i> , <i>Escherichia coli</i> , <i>Pseudomonas aeruginosa</i> , <i>Salmonella</i> , <i>Mycobacteria</i> , <i>Mycetes</i> (rare) Polymicrobial (2%–7%) Culture negative (5%–20%) EARLY: <i>S. aureus</i> LATE: <i>S. epidermidis</i> , other Gram-positive bacteria, Gram-negative bacteria, or negative cultures
Sohail et al <sup>5</sup> (2011)	68	Methicillin-susceptible <i>S. aureus</i> (34%), methicillin-resistant <i>S. aureus</i> (13%) CoNS (25%) Polymicrobial (7%) <i>Serratia marcescens</i> , <i>Propionibacterium</i> spp., <i>Enterococcus</i> spp., <i>P. aeruginosa</i> (21%) Culture negative (7%)
Lekkerkerker et al <sup>6</sup> (2009)	75	CoNS (29%) <i>S. aureus</i> (25%) Polymicrobial (14%) Other (11%) Culture negative (15%) EARLY (1–12 months): <i>S. aureus</i> , CoNS LATE (>12 months): culture negative

**Notes:** <sup>a</sup>0–12 months after implantation; <sup>b</sup>>12 months after implantation.

**Abbreviations:** CIED, cardiac implantable electronic device; CoNS, coagulase-negative *Staphylococcus*; N/A, not available.

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