Advances in Arrhythmia and Electrophysiology

Microbiology and Pathogenesis of Cardiovascular Implantable Electronic Device Infections

Avish Nagpal, MD; Larry M. Baddour, MD; Muhammad R. Sohail, MD

Advancements in our understanding of cardiac conduction abnormalities and pathophysiology of congestive heart failure coupled with innovations in device manufacturing and programming have helped to create a demand for a plethora of newer cardiovascular devices over the past 3 decades. Appropriate use of cardiovascular implantable electronic devices (CIEDs) in carefully selected patients is associated with better survival and significant improvements in quality of life. Cardiac resynchronization therapy devices are the newest “breed” to join an existing and growing family of permanent pacemakers (PPMs) and implantable cardioverter-defibrillators (ICDs). The number of cardiac devices implanted each year continues to grow exponentially. Unfortunately, because of the invasive nature of the implantation procedures required for placement of these devices and multiple comorbid conditions in device recipients, the benefits of these devices can be eclipsed by infectious complications. Infection is a very serious and dreadful complication requiring complete removal of the infected device and systemic antimicrobial therapy. Moreover, the financial cost of managing device infections is enormous. In this article, we review the latest developments pertaining to CIED infections, with a special emphasis on pathogenesis and microbiology.

Epidemiology

Since their first conceptualization and use in the late 1950s, CIEDs have undergone significant enhancements in design and function, and their use continues to rise, with a growing number of indications for placement, improvements in implantation techniques, and enhancements in device programming and monitoring. Earlier investigations reported a highly variable CIED infection rate, ranging from 0.13% to 19.9%. However, a more recent review of case records from the Massachusetts General Hospital reported 21 (1.2%) ICD-related infections among 1700 patients who underwent device implantation procedures. In a study by Mela et al., CIED infection occurred in 1.8% of 1170 patients who underwent a primary implant, a generator change, or a revision of their systems. In a population-based study from Olmstead County, Minnesota, the estimated rate of CIED infections was 1.9 per 1000 device-years. Interestingly, the cumulative probability of device infection in this study was higher among patients with ICDs than in those with PPMs, an observation that has also been reported by other investigators.

Contrary to expectations that increasing sophistication in device manufacturing and implantation techniques, coupled with higher volumes of implantation and more experience, will lead to a reduction in the CIED infection rate, recent data from large database surveys suggest that the rate of infectious complications has been rising out of proportion with the rate of CIED implantations. According to National Hospital Discharge Survey data from 1996 to 2003, 180 284 PPMs and 57 436 ICDs were placed in 2003, representing a 49% increase in the number of implants during the study period. More specifically, there was a 160% increase in the rate of ICD implantations compared to a 31% increase in the rate of PPM implantations. However, the same study noted that there was a 3.1-fold (PPM, 2.8-fold; ICD, 6-fold) increase in the rate of hospitalizations related to CIED infections. In a more recently published update to these data, the ongoing disproportionate increase in CIED infections was reaffirmed.

Similar trends were noted in an earlier review of CIED infection rates among Medicare beneficiaries. This particular study reported a 42% increase in the CIED implantation rate from 1990 to 1999, and this hike was accompanied by an alarming 124% increase in the rate of device infections. Although precise reasons for this trend are not yet understood, the disproportionate increase in the rate of CIED infections compared with the rate of CIED implantations has been attributed to increasing use of these devices in older individuals with multiple comorbid conditions.

Infection is a major complication of CIED implantation and is associated with significant morbidity and mortality. In 1 study of 33 cases of definite pacemaker endocarditis, the mortality rate was ~24%, with one half of the deaths occurring in the early postoperative period. The study authors reviewed the previously published data on CIED infections and estimated an overall mortality rate of 41% in patients with CIED-related endocarditis who were managed medically (with antibiotics alone) versus 18% in those managed by combined medical and surgical therapy. According to...
the most recent estimates based on 2007 Medicare data, the adjusted mortality rate during an admission where patients underwent a CIED procedure to treat infection was found to be 4.8- to 7.7-fold higher than that for an admission related to CIED implantation in the absence of infection. The disproportionate increase in mortality rate was observed throughout a follow-up period of 1 year. During this time, the mortality rate remained 1.6- to 2.1-fold higher, depending on the type of device. Additionally, the length of stay in CIED infection-related admissions was increased by 2.5 to 4.0 days compared to CIED implantation admissions without infection. Interestingly, length of hospital stay was variable depending on the type of device, with it being smaller for PPMs (2.5 days) than for ICDs (3.1 days) and cardiac resynchronization therapy devices without a defibrillator (4.0 days).

The cost of care for managing CIED infections remains substantially high. According to one estimate, the average cost of combined medical and surgical treatment of CIED infection in the United States was $35 000 (PPM, $25 000; ICD, $50 000).

A more precise cost estimate, adjusted for comorbid conditions, was reported in the aforementioned 2007 Medicare Standard Analytic File study. Investigators estimated that adjusted incremental cost of admission for an episode of CIED infection was $15 893 for ICDs, $16 208 for PPMs, $14 360 for cardiac resynchronization devices without a defibrillator, and $16 498 for cardiac resynchronization devices with a defibrillator. Most of the incremental cost of care in infection cases compared to the device implantation cost in cases without infection was attributed to the necessity of monitoring such patients in a critical care setting and medications, including parenteral antibiotics.

**Risk Factors**

Risk factors for CIED infection can be broadly categorized as host related, device related, and procedure related. Multiple investigators have evaluated an association of purported risk factors with increased odds of CIED infection. In a large single-center study, patients with CIED infections were more likely to have congestive heart failure, diabetes mellitus, a history of generator replacement, and ongoing anticoagulation therapy with warfarin. Moderate to severe renal insufficiency was identified as the most potent risk factor for device infection in the study, with an odds ratio (OR) of 4.8. Besides increasing the risk of device infection, renal insufficiency was also noted as an independent risk factor associated with increased risk of death in CIED recipients (hazard ratio, 2.98; 95% CI, 1.17–7.59).

In a retrospective review of our institutional database, previous history of device infection, malignancy, long-term corticosteroid therapy, history of multiple device revisions, presence of a permanent central venous catheter, use of >2 pacing leads, and a lack of antibiotic prophylaxis at the time of device placement were identified as risk factors for PPM infections in univariate analysis. In a multivariable logistic regression model, long-term corticosteroid use (OR, 13.90; 95% CI, 1.27–151.7) and the presence of >2 pacing leads (OR, 5.41; 95% CI, 1.44–20.29) were identified as independent risk factors for PPM infection. In contrast, use of antibiotic prophylaxis before device implantation had a protective effect (OR, 0.087; 95% CI, 0.016–0.48).

### Table 1. Evidence for Efficacy of Perioperative Antibiotic Administration in the Prevention of CIED Infection

<table>
<thead>
<tr>
<th>Risk factor analyses</th>
<th>Retrospective analysis (PPM only)</th>
<th>Prospective analysis (PPM only)</th>
<th>Prospective analysis (PPM and ICD)</th>
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<td></td>
<td>Antibiotic prophylaxis had a protective effect (OR, 0.087; 95% CI, 0.016–0.48; P&lt;0.005).</td>
<td>Lack of antibiotic prophylaxis was associated with an increased risk of infection (HR, 2.23; 95% CI, 1.81–2.98; P&lt;0.001).</td>
<td>Antibiotic prophylaxis was negatively correlated with risk of infection (adjusted OR, 0.4; 95% CI, 0.18–0.86; P&lt;0.02).</td>
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### Meta-analysis

Seven prospective clinical trials included (PPM)

- Antibiotic prophylaxis had a protective effect (OR, 0.256; 95% CI, 0.10–0.656; P<0.0046).

### Clinical trial

- Double-blind, randomized, placebo-controlled clinical trial (PPM and ICD)
  - Patient enrollment was stopped prematurely because of a significant difference in favor of the antibiotic arm (RR, 0.19; 95% CI, 0.04–0.86; P=0.016).

CID indicates cardiovascular implantable electronic device; PPM, permanent pacemaker; OR, odds ratio; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; RR, risk ratio.

Indeed, benefit of prophylactic antimicrobial therapy in reducing the risk of CIED infection has been demonstrated in multiple studies (Table 1), including a recent double-blind, randomized clinical trial. Because of the striking difference in infection rates between the 2 groups, favoring the antibiotic arm (risk ratio, 0.19), this clinical trial was interrupted before completion by the safety review board.

An association between patient age and sex and the risk of device infection was evaluated in one study that used the National Danish Pacemaker Registry. In this study, male sex, younger age at device implantation, and lack of antibiotic prophylaxis were associated with a higher rate of PPM infection (P<0.001). The authors attributed increased rates of infection among younger patients to the presence of nontransvenous systems, a well-known risk factor for device infection. Besides implantation technique, the experience of the operator also has an impact on the risk of CIED infection. In an analysis of device infection rates among Medicare beneficiaries, the risk of ICD infection was significantly higher in patients who had their device implanted by physicians with the lowest volume of procedures (OR, 2.47; 95% CI, 1.18–5.17). Other procedure-related factors associated with increased odds of device infection include fever within 24 hours before the implantation procedure, use of temporary pacing wires before permanent device implantation, early reintervention, abdominal generator placement, and development of a postoperative hematoma at the pocket site. An association of multiple comorbid conditions, such as renal failure, respiratory failure, heart failure, and diabetes mellitus with increased odds of CIED infection should be an important consideration in the decision-making process re-
garding the potential benefit of CIED therapy, especially among patients with a limited expected overall survival.

Pathogenesis
CIEDs can become infected through at least 2 distinct mechanisms. First, contamination of the pulse generator or leads during the time of initial implantation or subsequent manipulation can occur, resulting in colonization of subsequent bacterial growth on the device and development of clinical infection. Erosion of the device through intact skin that is due to mechanical factors can lead to a similar pathway to infection.

Second, a less common mechanism involves hematogenous seeding of the device from a distant focus of infection. The risk of hematogenous seeding depends on the causative pathogen and timing of onset of bacteremia from the date of device implantation. In a population-based study from Olmsted County, Minnesota,\(^9\) the rate of CIED infection in the setting of Staphylococcus aureus bacteremia was as high as 54.6%. This high rate of underlying CIED infection in the setting of S aureus bacteremia has been consistently observed in several other studies as well.\(^{26,27}\) Interestingly, a review of our institutional database suggested that 30% of the patients with bacteremia caused by gram-positive cocci other than S aureus also had evidence of underlying CIED infection.\(^{28}\) In this particular study, the rate of CIED infection in patients with coagulase-negative staphylococcus (CoNS) bacteremia was almost 2-fold that of non-CoNS gram-positive coci bacteremia (36% versus 20%, \(P=0.13\)). In contrast, the risk of hematogenous seeding of the device in the setting of gram-negative bacteremia from a distant focus appears to be extremely low.\(^{29}\)

In addition to these factors, it is intuitive that there are a number of device factors that may play a role in the pathogenesis of CIED infections. These may include size and type of the pulse generator material, surface features, and material used for coating the leads. For example, polyvinyl chloride favors bacterial adherence more than Teflon, polyethylene more than polyurethane, latex more than silicone, silicone more than polytetrafluoroethylene, and stainless steel more than titanium. Similarly, irregular, textured, and hydrophobic surfaces favor bacterial adherence as do synthetic materials used for manufacturing the device compared with biomaterials. Polymeric tubing is also known to favor bacterial adherence more than wire mesh.\(^{30,31}\) However, the role and importance of these factors with regard to risk of CIED infection is undefined at present, and this area is in crucial need of investigation.

Microbial Virulence Factors
Several virulence factors enable and contribute to the ability of microorganisms to cause of CIED infections (Table 2). These can be broadly categorized into 3 distinct groups: (1) adherence factors, (2) biofilm formation, and (3) microbial persistence.

Microbial Adherence
Attachment to the device surface and surrounding tissues is a key initial step in the pathogenesis of CIED infection. Although the initial adherence of microbes to a prosthetic device is nonspecific and driven by physicochemical factors, it is followed by more-specific interactions among the microorganism, prosthetic devices, and host proteins. Microorganisms carry multiple surface adhesins that facilitate their binding to host matrix proteins. These are collectively termed microbial surface components reacting with adherence matrix molecules (MSCRAMMs).\(^{32}\) These molecules bind to various host extracellular matrix components, including fibrinectin, fibrinogen, and collagen, that coat the outer surface of an implanted device.\(^{33}\) Multiple MSCRAMMs have been hypothesized and tested in in vitro models. The S aureus genome, a major causative pathogen for CIED infection, is believed to contain a number of MSCRAMM genes compared to relatively fewer ones in the genomes of CoNS species.\(^{34}\) Relevant S aureus MSCRAMMs implicated in the pathogenesis of cardiovascular infections include clumping factor A (ClfA) and fibronecit-binding proteins A and B (FnBPA and FnBPB).\(^{35}\)

CoNS do not possess the major virulent factors or toxins produced by S aureus, and there has been significant interest over the past several years in the virulence characteristics of these bacteria, especially in infections related to foreign devices. Biofilm formation generally is believed to be the most significant virulence factor in these organisms. In fact, the presence of biofilms in CoNS suggests an ancestral mode colonization used by poorly pathogenic bacteria.\(^{34}\) However, other models of adherence, including direct attachment to plastic polymers on device surfaces through fimbiae-like surface protein structures (staphylococcal surface proteins) or through capsular polysaccharides, have also been proposed.\(^{36–38}\) Staphylococcus lugdunensis, a species of CoNS, has attracted attention recently because of its more-aggressive clinical course resembling that of S aureus.\(^{39}\) However, S lugdunensis does not produce the adherence factors and toxins produced by S aureus. Therefore, other adherence

## Table 2. Microbial Virulence Factors

<table>
<thead>
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<th>1. Microbial adherence</th>
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<tr>
<td>MSCRAMMs: Clumping factor A (ClfA) and fibronecit-binding proteins A and B (FnBPA and FnBPB)</td>
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<tr>
<td>Staphylococcal surface proteins</td>
</tr>
<tr>
<td>Capsular polysaccharides</td>
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<tr>
<td>vWF-binding protein</td>
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<tr>
<td>Fibrinogen-binding protein (FnB)</td>
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<tr>
<td>Autolysins</td>
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<td>2. Biofilm formation</td>
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<tr>
<td>Polysaccharide intercellular adhesion (PA), a β-1,6-linked N-acetylglucosamine</td>
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<td>Accumulation-associated protein (AAP)</td>
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<td>3. Microbial persistence</td>
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<td>Small colony variant formation by Staphylococcus aureus and coagulase-negative staphylococci</td>
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<tr>
<td>4. Other factors</td>
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<tr>
<td>Lantibiotics: epidermin, Pep5, epilancin K7, and epidicin 280</td>
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<tr>
<td>Poly-γ-D-glutamic acid (PGA)</td>
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MSCRAMMs indicates microbial surface components reacting with adherence matrix molecules; vWF, von Willebrand factor.
proteins have been investigated and identified. These include von Willebrand factor-binding protein and the fibrinogen-binding protein Fbl. Additional virulence factors associated with CoNS have been described. These include poly-γ-DL-glutamic acid (PGA), which appears to shelter Staphylococcus epidermidis from innate host defense as well as facilitates colonization of human skin by enabling survival in high-salt environments. Lantibiotics such as epidermin, Pep5, epilancin K7, and epicidin 280 have also been implicated in the pathogenesis of infections caused by CoNS. These are antibiotic peptides containing the rare thioether amino acids lanthionine, methyl lanthionine, or both and are active against gram-positive bacteria. Their antimicrobial properties provide them with a survival advantage by excluding competing organisms that are sensitive to their bactericidal activities.

Biofilm Formation

The ability of staphylococci to colonize a prosthetic device, including a CIED, and form a thick, multilayered biofilm is probably the most important virulence factor of these organisms. A similar phenomenon is noted among Candida infections; however, specific characteristics of their respective biofilms may be different. Biofilm formation is believed to occur in 2 distinct stages: (1) adherence and (2) accumulation. As described previously, the initial adherence mechanisms appear to be nonspecific and include physicochemical reactions, including van der Waal forces, hydrophobic interactions, and polarity. Thereafter, adherence proteins, including staphylococcal surface proteins and capsular polysaccharide/adhesin, facilitate further binding to the prosthetic device surface. Attachment to the polymer surface of a prosthetic device is also facilitated by interaction of adherence proteins with extracellular host matrix proteins, such as fibronectin, fibrinogen, and von Willebrand factor coating the polymer surface. Some investigators have also suggested a role for S epidermidis autolysins in direct binding to plastic and plasma protein-coated polymer surfaces.

During the second stage of biofilm formation, intercellular adherence occurs by production of polysaccharide intercellular adhesin (PIA), which is a β-1,6-linked N-acetyl glucosamine. The synthesis of PIA is mediated by the ica operon, which consists of 4 genes: icaA, icaD, icaB, and icaC. Other proteins, such as accumulation-associated protein (AAP), may be a significant contributor to biofilm formation.

Once formed, biofilms mechanically trap bacteria, leading to their existence in a dormant state (Figure 1), which makes them resistant to the killing action of antimicrobial agents. The precise mechanism of antimicrobial resistance is unclear but seems to be multifactorial and may vary among different organisms. The purported mechanisms of antimicrobial resistance include physical restriction of antimicrobial penetration into the biofilm by extracellular matrix, existence of microbes in a dormant state where they are less susceptible to growth-dependent killing of antimicrobial agents, and expression of biofilm-specific antimicrobial-resistant genes that are not required for biofilm formation. Although a number of investigators have characterized the mechanisms of resistance in Pseudomonas aeruginosa biofilms, similar studies of staphylococcal biofilms are lacking. A better understanding of the resistance mechanisms, along with tools to specifically address biofilm susceptibility, may help us in targeted antimicrobial therapy. Various strategies for control of biofilms have been proposed for orthopedic device infections, and these principles could potentially be applied to CIED infections. Proposed strategies include targeting pathways involved in microbial adherence and inhibition of cell-to-cell signaling, degradation of extracellular matrix, and use of bioacoustic and bioelectric effect.

Microbial Persistence

Small colony variants (SCV) of S aureus (Figure 2) represent subpopulations of naturally occurring phenotypes with distinctive characteristics and pathogenic traits. These are characterized by retardation in growth rate; reduced or absent β-hemolysis; delayed coagulase reaction; decreased susceptibility to aminoglycosides; and an auxotrophic requirement for hemin, menadione, thiamine, and CO2. Although generally described in the context of persistent or recurring S aureus infections, SCV are not required for biofilm formation. Although a number of investigators have characterized the mechanisms of resistance in Pseudomonas aeruginosa biofilms, similar studies of staphylococcal biofilms are lacking. A better understanding of the resistance mechanisms, along with tools to specifically address biofilm susceptibility, may help us in targeted antimicrobial therapy. Various strategies for control of biofilms have been proposed for orthopedic device infections, and these principles could potentially be applied to CIED infections. Proposed strategies include targeting pathways involved in microbial adherence and inhibition of cell-to-cell signaling, degradation of extracellular matrix, and use of bioacoustic and bioelectric effect.
infections, these phenotypic variants have also been reported in CoNS responsible for CIED infection.64–66

The unique characteristics of SCV enable them to persist within phagocytes for up to 5 days without being killed.67 Because they are slow growing and often mixed with a normal phenotypic population, antimicrobial susceptibility testing of these organisms can be quite challenging. Moreover, alterations in bacterial membrane properties make these organisms relatively resistant to aminoglycosides. Absence of specific growth factors, such as menadione (a precursor of menaquinone that acts as an acceptor of electrons from NADH in the electron transport chain) and hemin (required for the synthesis of cytochromes that accept electrons from menaquinone), leads to a disruption of the electron transport chain and, consequently, a reduced electrochemical gradient across the bacterial membrane. As a result, certain antibiotics, like aminoglycosides, which require a charge differential for uptake, are rendered virtually ineffective.68

On the basis of these characteristics, various therapeutic interventions have been suggested that specifically target SCV. One such intervention is the use of rifampin to target the intracellularly persistent S aureus SCV. However, monotherapy with rifampin is not recommended because of its low threshold for emergence of drug resistance. Therefore, it is usually combined with either a β-lactam agent or vancomycin. It has also been suggested that the addition of vitamin K, the isoprenylated form of menadione, could be added to the standard antibiotic regimen to revert SCV forms to normal phenotypes as a short-term measure in selected situations to rapidly turn off toxin production and thereby reduce the severity of an infection.69

Microbiology
Considering the pathogenic mechanisms just described, it is no surprise that staphylococcal species are responsible for the bulk of CIED infections. In a retrospective review of 189 cases of CIED infections from 1991 to 2003 at our institution,3 42% of all infections were caused by CoNS, whereas S aureus was responsible for another 29% of the infections (Figure 3). Only 9% of the infections were caused by gram-negative bacilli, which included the standard antibiotic regimen to revert SCV forms to normal phenotypes as a short-term measure in selected situations to rapidly turn off toxin production and thereby reduce the severity of an infection.69

CIED-related endocarditis is usually caused by staphylococcal species. In a study of 52 patients with endocarditis related to pacemaker lead infection, cultures were positive in 88.4% of patients, and of these, >90% were staphylococcal species, including S epidermidis and S aureus.71 However, unusual organisms such as mycobacteria and Aspergillus species have also been described in isolated case reports.72–75

The role of local skin flora at the time of device implantation were explored in a study by Da Costa et al,76 who collected culture specimens from the site of implantation before and after device insertion in 103 consecutive patients who underwent elective PPM implantation. During a mean follow-up of 16.5 months, infection occurred in 4 (3.9%) patients. In 2 of these patients, an isolate of Staphylococcus schleiferi was recognized by molecular method as identical to the one previously found in the pacemaker pocket before device implantation. In another patient, S aureus was isolated at the time of infection but was absent at the time of pacemaker insertion. In the last patient, S epidermidis was identified both at the time of pacemaker insertion and at the time of device erosion from the generator pocket; however, antibiotic resistance profiles of the 2 isolates were different.

Several factors could be responsible for a culture-negative rate of up to 14% in various studies of CIED infection. These include prior antimicrobial use,77 organisms trapped in biofilms, or the existence of SCV. Use of newer techniques to disrupt biofilms, such as vortexing and sonication successfully applied in orthopedic practices,78 may be helpful in increasing culture yields in CIED infection and would allow targeted antimicrobial therapy.

Clinical Manifestations
CIED infections can present in a variety of ways. By far, the most common clinical presentation is that of a generator pocket infection. Findings suggestive of a pocket infection include erythema, pain, swelling, tenderness, discharge, or ulceration. Intraoperative purulence may be encountered in some cases, even in the absence of any external purulent drainage. Pocket infection can be associated with a bloodstream infection in some cases. Alternatively, positive blood cultures may be the sole manifestation of CIED infection without any evidence of pocket infection or vegetations on transthoracic echocardiography or transesophageal echocar-
diography (TEE). Finally, a device infection may present with CIED-related infective endocarditis. In a retrospective review of 189 patients with CIED infection treated at the Mayo Clinic in Rochester, Minnesota, from 1991 to 2003, 52% of the patients presented with pocket infection, and 17% had a bloodstream infection associated with pocket involvement. CIED-related endocarditis was identified in 23% of the cases by echocardiography, whereas 11% of patients had a bloodstream infection as the sole manifestation of underlying device infection. The remaining 5% of the cases presented with generator or lead erosion without any gross inflammatory changes at the pocket site. Whether device erosion is a manifestation of an underlying low-grade infection or occurs because of mechanical reasons remains a matter of debate. Nevertheless, once exposed to the outside environment, pulse generator and electrode leads inevitably become contaminated or infected with skin flora. Therefore, all eroded devices should be deemed infected and treated accordingly.

In cases where CIED infection is complicated by infective endocarditis, the tricuspid valve is the most frequently involved structure followed by the aortic and mitral valves. Therefore, all eroded generator and electrode leads inevitably become contaminated or infected with skin flora. Therefore, all eroded devices should be deemed infected and treated accordingly. Nevertheless, once exposed to the outside environment, pulse generator and electrode leads inevitably become contaminated or infected with skin flora. Therefore, all eroded devices should be deemed infected and treated accordingly.

Laboratory abnormalities are frequent but quite nonspecific in CIED infections. Most commonly encountered abnormal laboratory values include peripheral leukocytosis and anemia. Inflammatory markers like erythrocyte sedimentation rate and C-reactive protein may be elevated in cases of systemic infection but are neither sensitive nor specific and, thus, are not recommended to establish or refute the diagnosis of CIED infection.

**Diagnostic Evaluation**

CIED pocket infection can be readily established based on inflammatory signs and symptoms at the generator pocket. However, a pocket hematoma in the early postoperative period can mimic a pocket infection, and differentiation between the two can be challenging. Blood and pocket swab (if any drainage in present) cultures should be obtained in all cases at admission or outpatient encounter. Although laboratory findings of leukocytosis, thrombocytosis, or elevated inflammatory markers can supplement the clinical impression, they should not be relied on solely to establish or refute the diagnosis of CIED infection because these laboratory values can be normal in a significant number of patients.

Cardiac imaging with TEE is strongly recommended in all cases of suspected CIED infection where blood cultures are positive. TEE should also be considered in patients who present with systemic signs and symptoms of infection but where blood cultures may be negative because of prior antibiotic therapy. Transesophageal echocardiography has a poor sensitivity for use in the diagnosis of CIED-related infective endocarditis and is not the imaging modality of choice in this situation.

After the decision is made to remove the device, pocket tissue and lead tip cultures should be performed at the time of device removal and are more sensitive in leading to a microbiological diagnosis than are pocket swab cultures. However, it is also important to avoid certain pitfalls in interpreting culture and imaging data in this setting. Pocket swab, tissue, and lead cultures should only be obtained when there is a clinical suspicion of device infection. Routine swab culture of devices removed for reasons other than infection can be positive in up to one third of patients. Positive cultures in this setting indicate either device colonization or results from contamination of specimens during transport or in the laboratory rather than reflect infection. Whether colonization of the devices is a risk factor for subsequent development of clinical infection is an undefined, but a keen area of interest. Therefore, device culture should not be done unless suspicion for infection is present.

Interpretation of TEE results also requires clinical judgment. It is important to recognize that not all masses or tissue strands observed during the imaging procedure are infective vegetations. All abnormalities detected on TEE should be interpreted in the clinical context. In cases where there is no clinical evidence of underlying device infection and where blood cultures remain negative, antimicrobial therapy should not be prescribed, and repeat surveillance blood cultures may be performed in 2 to 4 weeks. It is equally important to recognize that a negative TEE does not exclude the possibility of underlying CIED infection. As described in aforementioned passages, persistent *S. aureus* or CoNS bacteremia can be associated with underlying CIED infection in a significant number of patients, and this possibility should always be considered when no alternative focus of infection, responsible for bloodstream infection, is evident after an extensive diagnostic evaluation.

The role of newer imaging techniques, such as PET and nuclide-tagged white blood cell scintigraphy in the diagnosis of CIED infection has not been fully established. Although there are anecdotal reports of their utility in the diagnosis of complicated and puzzling cases of CIED infection, especially device-related endocarditis, their routine use in the diagnosis of CIED infection cannot be recommended. Another possible use of nuclear medicine imaging is to exclude other occult foci of infection in patients with cardiac devices who present with unexplained fever and bacteremia.

**Principles of Management**

Management of CIED infection comprises of 3 key steps: (1) confirmation of diagnosis, (2) complete removal of all hardware (including all electrode leads, pulse generator, sutures, and sleeves), and (3) administration of systemic antibiotic therapy. Conservative medical management alone is ineffective and invariably leads to persistent or relapsing infection. Accurate identification of the causative pathogen is crucial in selecting targeted antimicrobial therapy; therefore, obtaining blood cultures in all patients with suspected CIED infection before starting empirical antimicrobial therapy is of utmost importance. Empirical therapy should be
guided by local antimicrobial resistance patterns. Considering that the majority of CIED infections are due to staphylococcal species, which frequently are oxacillin resistant, initial antibiotic therapy should include coverage for oxacillin-resistant staphylococci. We routinely use intravenous vancomycin for this purpose. Once culture results and antimicrobial susceptibility data are available, antibiotics should be adjusted accordingly. Although CIED pocket infections can be successfully treated with 10 to 14 days of therapy, the presence of a bloodstream infection warrants longer intravenous antibiotic therapy for at least 14 days after removal of the infected device and documentation of negative blood cultures. In cases of CIED-related infective endocarditis, we recommend 4 to 6 weeks of an intravenous antibiotic course based on American Heart Association guidelines for endocarditis treatment.86

Optimal management of *S* *aureus* bacteremia in the setting of an implanted cardiac device but with no clinical or echocardiographic evidence of device involvement is a subject of great controversy. In general, the device should be presumed infected in cases of high-grade *S* *aureus* bacteremia, especially when no alternative focus of infection can be identified, and it should be removed.

For patients who are deemed too high risk to be surgical candidates or who refuse device removal and, therefore, are managed conservatively, long-term suppressive antimicrobial therapy should be prescribed. Choice of antibiotic should be guided by antimicrobial susceptibility data in consultation with an infectious diseases specialist.

Future Directions

Over the past 15 years, significant progress has been made in understanding and managing CIED infections. However, there still remain areas of uncertainty where further research is needed. In particular, better characterization of mechanisms of antimicrobial resistance due to biofilm formation and SCV formation is required. This could be helpful in developing targeted adjunctive therapies. Additionally, the impact of device colonization on subsequent development of clinical infection remains poorly understood. Newer techniques, such as vortexing and sonication, which can facilitate growth of latent microorganisms contained in the biofilm, have been studied in some pilot investigations82 and should be further investigated. Moreover, long-term follow-up of the patients who are found to have device colonization, using the sonication technique to assess whether the presence of colonization would lead to an increased risk of subsequent infection, is needed. Another important area meriting further investigation is appropriate management of patients with CIED who develop *S* *aureus* bacteremia but who have no clinical or echocardiographic evidence of CIED infection. Could some of these patients be safely managed without device extraction? What criteria could be used to identify this subgroup of patients?

Appropriate timing of new device placement after removal of the infected device is also a subject of great controversy. In particular, larger prospective studies are needed to examine whether a single-stage explantation of an infected device and placement of new hardware may be appropriate in patients with infection limited to the generator pocket (without bloodstream infection). This strategy could shorten the duration of a patient’s critical care stay for rhythm monitoring, especially in those who are device dependent, and eliminate the need and risk for a second procedure requiring anesthesia. Ultimately, this could reduce the number of hospital days and lead to significant cost savings.

In the foreseeable future, gene and cell repair therapies may obviate the need for CIED placement. However, until then, we will continue our efforts at improving patient outcomes by defining and applying optimal management strategies. This will require ongoing cooperation and understanding among various subspecialties and organizations that represent academic, industrial, and political interests. Most importantly, patients and their families should be engaged in the decision-making for these strategies.

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