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Infections of Cardiac Implantable Electronic Devices: Etiology, Prevention and Treatment

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1. Introduction

Since the initial use of prosthetic heart valves, the use of cardiac prosthesis and implantable devices has revolutionized the therapeutic options available to patients (de Oliveira et al.,2009). Cardiac Permanent PaceMakers (PPMs) have been implanted since the early 1960s. Over the past 50 years there have been tremendous advances in both the design of the device and the software employed. In the mid 1960s, transvenous leads were developed that could be inserted through a vein and thence into the heart, thus preventing the need for a thoracotomy. The development of 'active fixation' leads ensured a better contact with the endocardium and the presence of a steroid eluting tip helped to reduce any inflammation that might result. The introduction of the lithium iodine battery has dramatically increased the battery life to well over ten years. Radiofrequency programming became available in the 1970s, allowing simple adjustments to be made to pacemaker's settings without the need for surgery. Today, permanent pacemakers and ICD (Implantable Cardiac Defibrillator), together with any adjustments, can be completed within minutes using a portable computer. Information regarding events such as periods of bradycardia, tachycardia or ventricular fibrillation can be stored within the memory of the device and accessed by the specialist during the routine checkup. To maintain atrio-ventricular synchrony, dual chamber pacing was then introduced. Moreover, in the late 1990s, pacemaker technology had improved to the extent that it became possible to increase the pacing rate to match the patient's activity level (Allen et al., 2007).

A wide range of cardiac implantable electronic devices (CIEDs) are now available, including ICDs and cardiac resynchronization systems. PPMs are commonly used in patients with atrioventricular conduction block, sick sinus syndrome, and symptomatic sinus bradycardia, whereas ICDs target primarily patients at risk for life-threatening ventricular arrhythmias.

Since clinical trials have consistently demonstrated the ability of the ICD to reduce mortality in selected patients with moderate-to-severe left ventricular systolic

dysfunction, the indications for CIEDs have expanded dramatically and the rate of implantation has greatly rosen. A recent analysis showed that rate of implantation in US between 1997 and 2004 rose by 19% and 60% for PPMs and ICDs, respectively. Approximately 70% of device recipients were 65 years of age or older, and more than 75% of them had one or more coexisting illnesses. The rate of ICD implantation has increased in the elderly (70 to 79 years of age) and very elderly (80 years of age or older). The 2001 World Survey found that in developed countries, between 20% and 35% of CIED recipients were more than 80 years old. The National Hospital Discharge Survey found a 49% increase in the number of new CIED implantations, including both PPMs and ICDs. In 2003, although the absolute number of PPMs implantations was higher than that of ICDs (180284 versus 57436 implanted devices) most of the increase in CIED device implantation was due to ICD implantations (160% and 31% increases in ICD and PPM implantations, respectively) (Baddour et al., 2010).

Despite their unquestioned clinical importance and diffusion, CIEDs may be linked to several complications, including infections, and the consequences of them may be catastrophic. Therefore, development of strategies for the prevention of device associated infections is crucial (Borer et al., 2004).

The reported rate of infection after implantation of permanent endocardial devices ranges between 0.13% and 12.6%, depending on definition. The wide use of CIEDs and increasing age of patients set the stage for higher role of associated infections and related hospitalizations increased of about 3-fold (Baddour et al., 2010). Moreover, the cost of treating device-associated infections may be enormous, thus leading to increased healthcare expenses (Borer et al., 2004). Precise data regarding the actual healthcare burden of CIED infections are not available. The financial impact is due to multiple factors, including the costs of device removal, cost of new device (which would be required in the majority of patients) and costs related to cardiac and other medical evaluations, diagnostic procedures, surgical interventions for infected device removal, medical therapy, and increased length of stay in intensive care unit (Baddour et al., 2010).

2. Epidemiology of CIED associated infections

CIED infections have been recognized as a source of major comorbidity since the early 1970s. In earlier years, the rates of PPM infection ranged widely between 0.13% and 19.9%. Although most infections have been limited to the pocket, frank PPM endocarditis accounted for approximately 10% of PPM infections. The decreased size of ICDs allowed implantation without thoracotomy. Initially, abdominal implantation with tunneling was required. Subsequently, the entire device could be implanted prepectorally; with these less extensive operations the infection rate lowered to less than 7%. In a study on all ICD primary implantations, replacements, and revisions at a single center, there were 21 ICD-related infections (1.2%) among 1700 procedures. Among 959 patients with long-term follow-up, the infection rate was 3.2% with abdominal and 0.5% with pectoral systems respectively (Mela et al., 2001). However, globally, the rate of CIED infection has been increasing. Cabell et al. reported that the rate of cardiac device infections (PPMs, ICDs, valves, and ventricular assist devices) increased from 0.94 to 2.11 per 1000 patients between 1990 and 1999, a 124% increase during the study period. The rate of frank endocarditis was relatively unchanged (0.26 and 0.39 cases/1000 patients, respectively) (Cabell et al., 2004). These findings were similar to that analyzed in Olmsted County,

Minnesota, from 1975 to 2004. A total of 1524 patients were included with a total person-time follow-up of 7578 years. The incidence of CIED infection was 1.9/1000 device years (95% confidence interval [CI] 1.1 to 3.1), with an incidence of pocket infection alone of 1.37/1000 device-years (95% CI 0.62 to 0.75) and an incidence of pocket infection with bloodstream infection or device-related endocarditis of 1.14/1000 device-years (95% CI 0.47 to 2.74) (Uslan et al., 2007). Notably, the cumulative probability of CIED infection was higher among patients with ICDs than among those with PPMs. The National Hospital Discharge Survey similarly showed that between 1996 and 2003, the number of hospitalizations for CIED infections increased 3.1-fold (2.8-fold for PPMs and 6.0-fold for ICDs). The numbers of CIED infection–related hospitalizations increased out of proportion to rates of new device implantation. Moreover, CIED infection increased the risk of in-hospital death by more than 2-fold (Voigt et al., 2006).

3. Definition and clinical presentation

CIED pocket infection is defined on the ground of signs and symptoms of local infection associated with microbiological confirmation based on results of cultures of intraoperatively collected fluid samples, explanted CIED, or purulent discharge from the pocket site. CIED infection can present as acute or chronic syndromes that can be both early or tardive. In the early, acute form, the short time elapsed between device implantation and occurrence of infection may prompt the diagnosis. In chronic and tardive infections there is often a delay between the onset of symptoms and the diagnosis. This may be due to the fact that CIED-related infections are not routinely considered in the differential diagnosis. In other cases, possible clues to the diagnosis are ignored. Clinical manifestations of pacemaker infection are linked to the portion of the device involved. Moreover, signs and symptoms may be limited to the insertion pocket or be systemic or absent altogether (Cacoub et al,. 1998).

A CIED-related infection is considered nosocomial when occurs 48 hours after admission and is not incubating at the time of admission. Infection of CIED is regarded as health care associated if patient received intravenous therapy at home, attended an outpatient hemodialysis center in the previous 30 days, was hospitalized in an acute care hospital for 2 days in the 90 days before admission, or resided in a nursing home or long-term care facility. In contrast, CIED-related infection is recognized as community acquired if it does not fit the above definitions (Tablan et al., 2003).

3.1 Clinical presentation

In the vast majority of cases, local inflammation of the generator-pocket site is present, including erythema (34%), pain (32%), swelling (21%), warmth (11.5%), and drainage through a fistulous or poorly healed incision (25%). In most severe cases cutaneous erosion (23%) with percutaneous exposure of the generator and/or leads may be seen. All these signs can be associated or not with bacteremia (Cacoub et al,. 1998). These local changes usually prompt medical attention. Some patients present with systemic symptoms that include malaise, fatigue, anorexia, or decreased functional capacity. Sometimes isolated local symptoms occurr without fever. Chua et al. reported the presence of localized signs without systemic involvement in 69% (88 of 123) of patients, a combination of local and systemic signs and symptoms in 20% (25 of 123), and systemic signs and symptoms alone in

11% (13 of 123) of patients (Chua et al., 2000). In implanted patients with unexplained fever CIED associated endocarditis should be ruled out. In CIED recipient isolated bacteremia pro,t medical investigation to rolu out endocarditis. Pacemaker endocarditis should be considered in all patients with cardiac pacemakers and chronic fever, recurrent bronchitis, pulmonary infection, and recurrent or persistent pocket infection (Cacoub et al., 1998; Klug et al., 1997). In some patients, involvement of lungs may be evident, including pleural effusions, pneumonia, pulmonary abscess, recurrent pulmonary embolism. Recurrent bronchitis is evident in 32% to 43% of patients with pacemaker endocarditis. A serious complication of pacemaker infection is generator or lead erosion through the skin. This can be the consequence of primary infection or can be the result of pressure on the overlying tissue, resulting in erosion and subsequent contamination. Erosion has been noted to be more common after elective pacemaker replacement than initial implantation (Harcombe et al., 1998). Other rare conditions associated to CIED infections are thrombosis of a vein where leads were in place (subclavian vein or superior vena cava), symptomatic pulmonary embolism, septic arthritis, vertebral, sternal or femoral osteomyelitis, splenic, brain, liver and perinephric abscess (Sohail et al., 2007a).

4. Pathophysiology

4.1 Etiology

In patients with pacemaker infection bacterial pathogens can be found in blood or pacemaker pockets. Pacemaker's hardware can be colonized as well. The most common pathogens in pocket infections are skin flora, and, specifically, Staphylococcus aureus and coagulase-negative staphylococci, including Staphylococcus epidermidis. Rarely, enteric Gram-negative bacilli can be found. Repeated cultures and percutaneous aspirates should help make the distinction between normal skin flora and pathogenic culture isolates (Gandelman at al., 2007).

Staphylococcal species cause most of CIED infections and account for 60%-80% of cases in most reported series (Fig.1). A variety of coagulase-negative Staphylococcus (CoNS) species have been described a causative agents of CIED infections. CoNS are a common cause of microbiological specimen contamination, and thus, repeated isolation of the same species of CoNS with an identical antibiotic susceptibility pattern is advisable to be diagnostic. Polymicrobial infection sometimes involves more than one species of CoNS. The prevalence of oxacillin resistance among staphylococcal strains has varied among studies ranging from 4 to 22% (Sohail et al., 2007a; Viola et al., 2010).

Several factors are responsible for the higher propensity of Staphylococci to cause CIED infections. Staphylococci are frequent colonizer of human skin and contamination of CIED generator, electrode leads or pocket tissue at the time of implantation is the predominant mechanism for the majority of the pocket infections. Staphylococci express on their membranes several adherence factors that enable them to bind the foreign materials and establish chronic infection. In addition, these organisms are capable of producing biofilm on the device surface which helps them to evade host defences and limit antimicrobial penetration. Finally, Staphylococci are the predominant pathogens responsible for secondary catheter-related bloodstream infections as they can seed the intravenous leads during an episode of bacteremia.

Corynebacterium species, Propionibacterium acnes, Gram-negative bacilli, including Pseudomonas aeruginosa, and Candida species account for a minority of CIED infections. Fungi other than Candida and nontuberculosis mycobacteria are rarely responsible for CIED infection (Sohail et al., 2010).

The microorganisms that cause CIED infections may be acquired either endogenously from the skin of patients or exogenously from the hospital environment. An association has been found between the presence of preaxillary skin flora and the pathogens isolated from pacemaker infection. Although low concentrations of methicillin-resistant CoNS have been detected in patients with no previous healthcare contact and no recent antibiotic exposure, a CIED infection due to multidrug-resistant staphylococci suggests that a healthcare environment is the site where infection was acquired (Da Costa et al., 1998a).

Pacemaker endocarditis usually presents with bacterial growth in both blood and hardware cultures. Although there is no uniform agreement regarding the rate of positive blood cultures in pacemaker endocarditis, S. epidermidis and S. aureus occur most frequently. Other pathogens include Corynebacterium sp., Pseudomonas aeruginosa, and Aspergillus niger. In one study, polymicrobial infections were found in 18.1% (Cacoub et al., 1998).

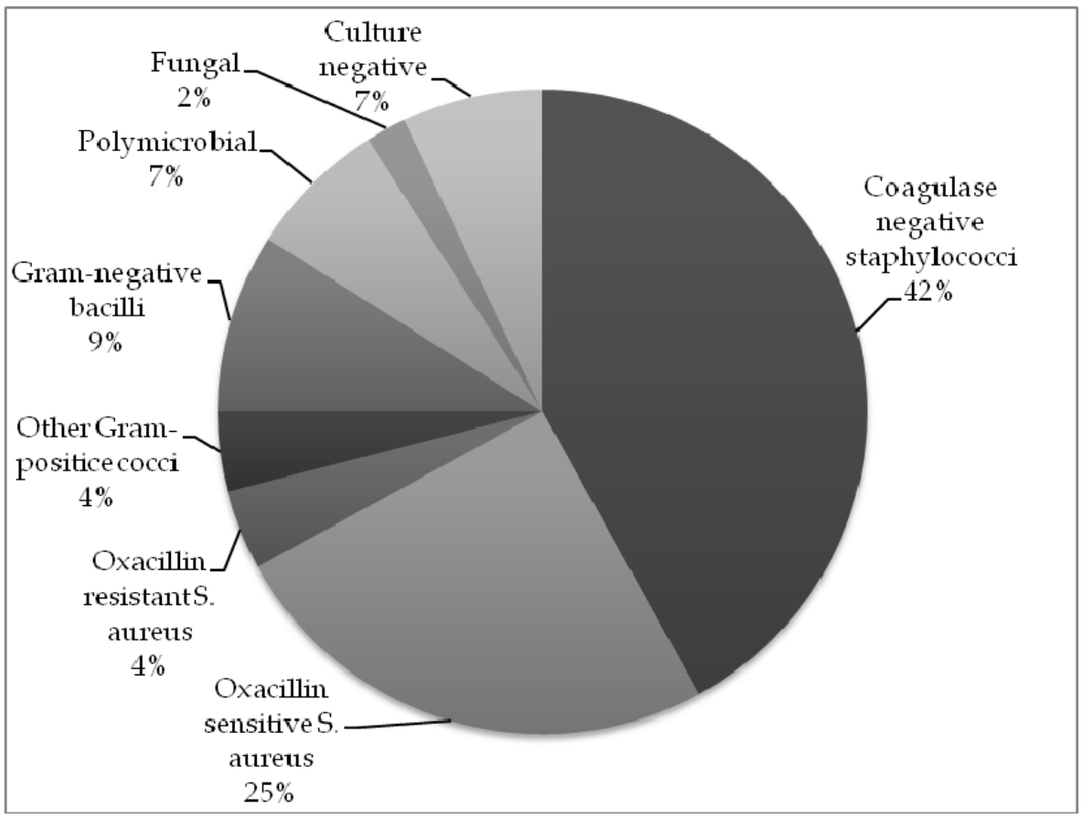

Fig. 1. Microbiology of CIED infection. Modified from Baddour et al., 2010.

4.2 Pathogenesis

The generator is placed within a surgically created space known as pocket. Electrode leads are attached to the generator and travel within the venous system to the right heart.

Pacemaker infection can be limited to the superficial portion of the pocket and leads or involve deeper intravascular and intracardiac components. The latter is known as pacemaker endocarditis. Among patients with pacemaker endocarditis, vegetations can occur on the tricuspid valve, the electrodes, and the right atrial or ventricular endocardium.
The pocket may become infected at the time of implantation, during subsequent surgical manipulation, or if the generator or subcutaneous electrodes erode the overlying skin. In this latter case, erosion can also occur as a secondary event due to underlying infection. Pacemaker endocarditis can be linked to several factors, including pacemaker lead contamination during placement, spread of the organisms along the wires from the superficial component, or hematogenous seeding of the intravascular electrodes and wires during a bacteriemic episode. While Gram-posivie bacteriamias can cause CIED infections, hematogenous seeding of a CIED is unlikely to occur in cases of Gram-negative bacteremia. The disruption of the physiologic blood flow through the tricuspid valve often caused by a pacing lead passing through the valve and associated regurgitation may contribute to pacemaker infection. Microbial adherence to endothelium has been shown to increase in areas of high shear turbulence (Baddour et al., 2010).
CIED infection is the result of the interaction between the device, the microbe, and the host.

4.2.1 Devices factors

Initial adhesion of bacteria to the device is mediated by physico-chemical properties of the plastic surface, such as hydrophobicity, surface tension, and electrostatic charge.
Factors like the nature of plastic polymer, irregularity of its surface, and its shape, can all affect bacterial adherence to the device. Plastic polymers that encase medical devices, as well as the pathogens that adhere to them, are hydrophobic. An irregularly surfaced device favours microbial adherence more than a smoothed surfaced one. When this physiochemical interaction exists, the risk of CEID infection is related to subsequent invasive manipulation of the device and may be linked to a limited experience of the physician performing the procedure (Darouiche, 2001).

4.2.2 Microbial factors

Bacteria, particularly Gram-positive cocci, can adhere to and be engulfed by endothelial cells that lie on endothelialized lead after a certain period of time. This is thought to be an important mechanism of device infection by the hematogenous route.
Microbial adherence may be linked also to interactions of bacterial surface with proteins on device's surface. CoNS may adhere directly to plastic polymers of the surface of the device via fimbria-like surface protein structures or via a capsular polysaccharide (Veenstra et al., 1996). Bacteria may also adhere to host matrix proteins that coat the surface of an implanted device. Host extracellular matrix proteins include fibrinogen, fibronectin, and collagen that are layered on implanted biomaterials. None of the major virulence factors or toxins of S Aureus have been found in CoNS, and it seems clear that the development and persistence of CoNS infections, which are so often associated with foreign materials, are due to different mechanisms, such as microbiological adherence. On the contrary, Staphylococci have a variety of surface adhesins that allow the pathogen to establish a focus of infection. Subsequent accumulation of bacteria on the device's surface requires the production of polysaccharide intercellular adhesin, which is strongly linked to with the staphylococcal cell

surface and mediates cell-to-cell adhesion. The layers of bacteria on the surface of an implanted device are encased in this extracellular slime and constitute a biofilm. Biofilm is defined as a surface-associated community of one or more microbial species that are firmly attached to each other and the solid surface and are encased in an extracellular polymeric matrix that holds the biofilm together. Bacteria in a biofilm are more resistant to antibiotics and host defences, perhaps as a result of the dense extracellular matrix that protects the microbes included in the interior of the community (Lazăr & Chifiriuc, 2010). When a free-floating bacterial cell enters the biofilm, it undergoes a phenotypic shift, in which expression of large groups of genes is up-regulated. Phenotypic variation is thought to support the persistence of infection due to staphylococci in a biofilm that coats the surface of a CIED. Small colony variants are phenotypes that have caused CIED infections and harbor several characteristics that are thought to enhance the survival of staphylococci either in a biofilm or in endothelial cells covering the device, including resistance to certain antibiotics (Baddour et al., 1990; Boelens et al., 2000).

4.3 Risk factors

Several studies have identified host or procedural factors that may be associated with CIED infections.

Among the host factors, the strongest association is between renal failure and risk of CIED infection. Risk of device infection appears to be particularly high in patient with end-stage renal failure who are undergoing chronic hemodialysis via an implanted central catheter. These patients are at risk of recurrent bacteremia from their dialysis catheter and subsequent secondary seeding of the tranvenous device leads or pulse generator. Renal failure is also associated with immune dysfunction that further increases the odd of CIED infections in these patients (Bloom et al.,2006).

Anticoagulant therapy with warfarin has also been linked to a higher risk of CIED infection. Precise reasons for this association are unclear but are likely related to the increased risk of pocket hematoma, which may lead to delayed wound healing or need for surgical drainage in some cases. Reopening the pocket to drain a large hematoma increases the risk of pocket contamination with skin flora and subsequent CIED infection (Lekkerkerker et al., 2009).

Use of immunosuppressive medications, especially long term corticosteroids therapy, has also been identified as a risk factor for CIED infections (Sohail et al., 2007b).

Procedure-related factors may also play an important role in the development of CIED infections. In a prospective cohort of 6319 patients receiving CIED implantation in 44 medical centers, Klug et al. identified 42 patients who developed CIED infection during 1 year of follow-up. Factors associated with an increased risk of infection included fever within 24 hours before implantation, use of preprocedural temporary pacing, and early reintervention. Implantation of a new system compared with partial or complete system replacement and use of periprocedural antimicrobial prophylaxis were both associated with a lower risk of infection (Klug et al., 2007). There is evidence that perioperative antimicrobial prophylaxis is associated with a reduction in CIED infections (Bertaglia et al., 2006; Da Costa et al., 1998b; de Oliveira et al., 2009).

Other small studies suggest that pectoral transvenous device placement is associated with significantly lower rates of CIED infection than those implanted abdominally or by

thoracotomy. Thus, the use of a pectoral approach is not only less invasive but also appears to confer an ancillary benefit of lower infection risk (Mela et al., 2001).
Physician experience in CIED implantation may also play a role in the rate of subsequent CIED infection. In a study of Medicare administrative data, Al-Khatib et al. found a significantly higher risk of ICD infection within 90 days of device implantation in patients whose device was placed by physicians in the lowest quartile of implantation volume. Rates of mechanical complications at 90 days were also higher for lower-volume physicians (Al-Khatib et al., 2005).

5. Diagnosis

5.1 Clinical and microbiological diagnosis

In all patients with suspected CIED infection diagnosis is linked to both local and systemic signs of inflammation associated to positive microbiological culture of the skin pocket or other materials. Signs and symptoms of systemic inflammation include malaise, fever with or without chill, leucocytosis and, in most severe cases, hypotension. A new onset valvular murmur suggests CIED endocarditis. Local signs of infection include redness and oedema and pain of the skin pocket.
Definitive diagnosis of CIED infection is linked to microbiological cultures. Usually, samples are taken from the generator pocket. Alternatively, once the device has been removed, samples from lead tips may be cultured to identify the causative organism and support a diagnosis of CIED infection. Gram staining, anaerobic and aerobic bacterial cultures, should all be performed. If the initial Gram stain is negative, both tissue and the lead tip should be cultured for fungi and mycobacteria. Percutaneous aspiration of the device pocket is not recommended because of its low diagnostic accuracy and the theoretical risk of introducing microorganisms into the pocket site or spreading germ into the blood stream. Contamination of leads may also occur at the time of their extraction throught a contamined skin pocket; this may explain some of the positive lead-tip cultures found in patients without systemic manifestation and with negative blood cultures. If a CIED-related endocarditis is suspected, at least two sets of blood cultures should be obtained before starting any antimicrobial therapy. Positive blood cultures, particularly due to staphylococcal species, provide a strong clue that the clinical syndrome is due to CIED infection (Baddour et al., 2010).

5.2 Instrumental diagnosis

5.2.1 Transthoracic and transesophageal echocardiography

Endocarditis is clinically confirmed when valvular or lead neostructures consistent with vegetations are detected on echocardiography, or if the Duke criteria for infective endocarditis are met (Table 1)(Klug et al., 1997, Durak et al. 1994). Vegetation is defined as an oscillating intracardiac mass which can be seen on the electrodes, the leads or the cardiac valve leaflets. To be diagnostic, vegetation should be noted in more than one echocardiographic plane (Klug et al., 1997; Sanfilippo et al., 1991; Victor et al., 1999). Both transtoracic echocardiography (TTE) and transesophageal echocardiography (TEE) may be employed, even though TEE is more accurate and is the actual gold standard.

Definite infective endocarditis	
Pathological criteria	
Microorganisms: demonstrated by culture or histology in vegetation, in a vegetation that has embolized, or in intracardiac abscess, or demonstrated by culture of the lead	
Clinical criteria	
Two major criteria, or one major and three minor criteria, or five minor criteria	
Major criteria	
	Positive blood culture for infective endocarditis
	Typical microorganisms for infective endocarditis from two separate blood cultures
	Streptococcus viridans, *Streptococcus bovis*, HACEK group, or
	Community-acquired *Staphylococcus aureus* or enterococci, in the absence of a primary focus, or
	Persistently positive blood culture, defined as microorganism consistent with infective endocarditis from
	Blood cultures drawn >12 hours apart, or
	All of three or a majority of four or more separate blood cultures, with first and last drawn at least 1 hour apart
	Evidence of endocardial involvement:
	Positive echocardiogram for infective endocarditis:
	Oscillating intracardiac mass on PM leads or on the endocardial structure in contact with PM leads
	Abscess in contact with PM leads
Minor criteria	
	Fever >38°C
	Vascular phenomena: arterial embolism, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, Janeway lesions
	Immunologic phenomena: glomerulonephritis, Osler nodes, Roth spots
	Echocardiogram: consistent with infective endocarditis but not meeting major criterion as noted previously (sleevelike appearance)
	Microbiological evidence: positive blood culture but not meeting major criterion as noted previously

Table 1. Diagnostic criteria for infective endocarditis. Modified from Durak et al., 1994.

TTE is not helpful in ruling out a diagnosis of lead-related endocarditis, particularly in adults, due to its poor sensitivity. Moreover, patients can develop both right-sided (lead-related) and left-sided endocarditis. Actually, sensitivity of TTE for left-sided and for perivalvular extension of infection is lower than TEE. On the contrary several indirect echocardiographic features of endocarditis may be better seen with TEE. They include pericardial effusion, ventricular dysfunction or dyssynchrony, and pulmonary vascular pressure estimations. TEE may be not always available and can be discomfortable for the patients. For these reasons, even if TEE rapresents the gold standard for the diagnosis of CIED infections, and is recommended for the initial diagnosis, TTE can be used during the course of patient's illness for additional studies or follow-up. It is important to underlyine that an echocardiographyc image of a mass adherent to the lead may be a sterile thrombus

or infected vegetation and it is impossible to distinguish between the two with echocardiography. Masses that are detected in patients without positive blood cultures or other signs of infection are likely to sterile vegetation (thrombus). In addition, the failure to visualize a mass adherent to a lead with TEE does not exclude lead infection. Thus, even when vegetation is demonstrated, differential diagnosis may be difficult if microbiological culture are not positive. Clear guidelines for CIED infection diagnosis are lacking. Based on clinical practice and expert opinion, a summary of recommendations for diagnosis of CIED infections is provided in Table 2.

Class I
1. All patients should have at least 2 sets of blood cultures drawn at the initial evaluation before initiation of antimicrobial therapy. (Level of Evidence: C)
2. Generator-pocket tissue Gram's stain and culture and lead-tip culture should be obtained when the CIED is explanted. (Level of Evidence: C)
3. Patients with suspected CIED infection who either have positive blood cultures or who have negative blood cultures but have had recent antimicrobial therapy before blood cultures were obtained should undergo TEE for CIED infection or valvular endocarditis. (Level of Evidence: C)
4. All adults suspected of having CIED-related endocarditis should undergo TEE to evaluate the left-sided heart valves, even if transthoracic views have demonstrated lead-adherent masses. In pediatric patients with good views, transthoracic echocardiography may be sufficient. (Level of Evidence: B)
Class IIa
Patients should seek evaluation for CIED infection by cardiologists or infectious disease specialists if they develop fever or bloodstream infection for which there is no initial explanation. (Level of Evidence: C)
Class III
Percutaneous aspiration of the generator pocket should not be performed as part of the diagnostic evaluation of CIED infection. (Level of Evidence: C)

Table 2. Recommendations for Diagnosis of CIED Infection and Associated Complications. Modified from Baddour et al., 2010.

5.2.2 Positive Emission Tomography (PET)

Infection staging and identification of other septic locations may be very important in order to monitor treatment efficacy before any re-implantation. It might be useful to assess the extension of infectious disease (staging) in these patients by non-invasive whole-body imaging, and Fluoro-18 desoxyglucose (18F-FDG) PET is a potential candidate for this purpose. The use of 18F-FDG PET imaging in inflammatory processes is related to the high affinity of inflammatory cells such as neutrophils, lymphocytes and macrophage for 18F-FDG. 18F-FDG PET shows high diagnostic accuracy when infection affects the box of generator but is slightly less reliable when the leads are involved. Globally, sensitivity and specificity are optimal for box infection even if mild physiological uptake may be seen in normal cases. Physiologically, a slight 18F-FDG uptake may be observed around the box even in not infected patients, particularly in the area of the muscle interface. However,

uptake around the box is much higher in case of infection. Leads infection represents a different challenge. The size of the leads and the size of the vegetation are both very small and may easily be below the theoretical resolution of the PET system. For leads, sensitivity and specificity are lower, and diagnosis is based upon visualization of mild focal uptake along the leads. Interpretation of negative cases should be cautious, particularly if patients have received prolonged antibiotherapy (Bensimhon et al., 2010).

6. Prevention

The significant morbidity and mortality associated with device infections and the need for device removal make prevention of infections extremely important. Prevention of CIED infection can be addressed before, during, and after device implantation. Before implanting intravascular devices, it is important to ensure that patients do not have clinical signs of infection. In this case definitive implantation should be posponed after the resolution of infection. Once CIEDs are implanted, both pharmacological and non pharmacological strategies can be adopted in order to reduce risk of infection.

6.1 Pharmacological strategies

A meta-analysis of 7 randomized studies on 2023 patients examining the impact of systemic antibiotics on the risk of pacemaker-related infections suggested that systemic antibiotic prophylaxis significantly reduces the incidence of serious infective complications after pacemaker implantation (Da Costa et al., 1998b). A following observational study was performed to assess the safety and long-term efficacy of a simple scheme of antibiotic prophylaxis, and to identify the predictors of long-term infective complications in patients undergoing pacemaker implantation or replacement. This study showed the efficacy of a single dose of cefazolin in preventing infective complications (Bertaglia et al., 2006). Finally a prospective, randomized, double-blinded, placebo-controlled trial was developed to determine whether prophylactic antibiotic administration reduces the incidence of infection related to device implantation was. This double blinded study included 1000 consecutive patients who presented for primary device implantation or generator replacement randomized in a 1:1 fashion to prophylactic antibiotics or placebo. Intravenous administration of 1 g of cefazolin or placebo was done immediately before the procedure. Follow-up was performed at 10 days and 1, 3, and 6 months after discharge. The primary end point was any evidence of infection at the surgical incision (pulse generator pocket), or systemic infection related to the procedure. The safety committee interrupted the trial after 649 patients were enrolled because of a significant difference in favor of the antibiotic arm and concluded that antibiotic prophylaxis significantly reduces infectious complications in patients undergoing implantation of pacemakers or cardioverter-defibrillators (de Oliveira et al., 2009). Most experts continue to advocate a first-generation cephalosporin, such as cefazolin, as prophylaxis agent. Although not generally recommended, some authors advocate the use of vancomycin, particularly in centers where oxacillin resistance among staphylococci is high. If vancomycin is used, then it should be administered 90 to 120 minutes before the procedure. Vancomycin also represents an alternative to a first-generation cephalosporin in patients who are allergic to cephalosporins (Sohail et al., 2007b). In patients who are allergic to both cephalosporins and vancomycin, daptomycin and linezolid are alternative agents for prophylaxis. Antibiotic prophylaxis is also recommended if subsequent invasive manipulation of the CIED is required. Currently, there are no data to

support the administration of postoperative antibiotic therapy, and this is not recommended because of the risk of drug adverse events, selection of drug-resistant organisms, and costs (Baddour et al., 2010).

6.2 Non pharmacological strategies

Several preventive measures are recommended in combination with prophylactic antibiotics. Using a strictly aseptic technique during implantation is of paramount importance, including surgical scrubbing, use of standard operating room, facemasks, caps, and sterile gowns and gloves, and the use of sterile, dry gauze pads to cover surgical incisions (Voet et al., 1999). Other preventive strategies include to limit the duration of temporary pacing to the shortest time and to limit the number of people in the room during the procedure to those absolutely necessary. Prevention of hematoma during the procedure is important, and several interventions have been used, although there are no data to support their use (Lekkerkerker et al., 2009). This can be achieved by meticulous cauterization of bleeding sites and packing the pocket with antibiotic-soaked sponges to provide tamponade while leads are being placed. The application of topical thrombin may be helpful, particularly in anticoagulated patients. Irrigation of the pocket is useful to remove debris and may reveal persistent bleeding that could lead to a pocket hematoma. In addition, irrigation with an antimicrobial-containing solution for pocket cleansing has been used. Use of monofilament suture for closure of the subcuticular layer may avoid superficial postoperative cellulitis. A compressive dressing applied 12-24 hours after skin closure may further decrease the risk of hematoma formation. In the immediate postoperative period, recent data indicate that low-molecular-weight heparin predisposes to hematoma formation and should be avoided (Robinson et al., 2009). A hematoma should be evacuated only when there is increased tension on the skin. Needle aspiration should otherwise be avoided because of the risk of introducing skin flora into the pocket and subsequent development of infection. Finally, routine ambulatory care follow-up after CIED placement to detect early infectious complications has been performed in many centers and this is actively recommended (Deuling et al., 2009).

7. Therapy

7.1 Conservative treatment

Optimal management of CIED infection depends on the clinical presentation and causative pathogen. Conservative treatment with antibiotics alone without removal of the device may be sufficient in patients with local signs without sepsis, endocarditis or skin erosion. Seven to ten days of antibiotic therapy with an oral agent with activity against staphylococci is reasonable (Gandelman et al., 2007).

7.2 Device removal

Complete removal of all hardware is the recommended treatment for patients with established CIED infection or sepsis (Chua et al., 2000; Sohail et al., 2007a). This includes cases in which a localized pocket infection occurs in the absence of signs of systemic infection. Complete removal of hardware is needed because infection relapse rates due to retained hardware are high (Field et al., 2007). Erosion of any part of the CIED should imply contamination of the entire system, including the intravascular portion of leads, and complete device removal should be performed. Complete CIED removal should be

performed when patients undergo valve replacement or repair for infective endocarditis, because the CIED could serve as a nidus for relapsing infection and subsequent seeding of the surgically treated heart valve. An epicardial system should be considered if a new CIED is required after valve surgery with initial CIED removal. Device removal is also recommended in those patients with S. aureus bacteremia with clinical or echocardiographic evidence of CEID infection, un-explained bacteremia, or relapsing bacteremia after antibiotic treatment (Chamis et al., 2001).

7.2.1 Approach to hardware removal

Two techniques for removing pacemaker systems are currently available: invasive thoracotomy and percutaneous extraction. The choice of the less invasive percutaneous technique is usually based on time elapsed from implantation, vegetation size, absence of vegetation on the tricuspid valve, and the general conditions of the patient. Percutaneous lead extraction has become the preferred method for removal of CIED hardware. However, these procedures involve significant risks, including cardiac tamponade, hemothorax, pulmonary embolism, lead migration, and death, even in experienced hands. Thus, the performance of these procedures should be limited to centers with the appropriate facilities and training, including the presence of immediate availability of cardiothoracic surgery to provide backup in the event of complications. In high-volume centers, percutaneous lead removal can be accomplished relatively safely with a high rate of success (Jones et al., 2008). A primary surgical approach to lead removal in patients with CIED infection should be limited to patients who have significant retained hardware after one attempt at percutaneous removal. Another scenario in which a preference for surgical lead removal has been advocated is in patients with lead vegetations >2 cm in diameter, because of concerns about the risk of pulmonary embolism with percutaneous lead extraction. Experience suggests, however, that percutaneous removal in patients with large vegetations can be done without precipitating a clinically apparent pulmonary embolism. Until additional data are available, decisions regarding percutaneous versus surgical removal of leads with vegetations larger than 2 cm in diameter should be individualized and based on a patient's clinical parameters and the extractor's evaluation (Field et al., 2007; Gandelman et al., 2007; Sohail et al., 2007a).

Antimicrobial therapy is adjunctive in patients with CIED infection, and complete device removal should not be delayed, regardless of timing of initiation of antimicrobial therapy. Selection of the appropriate antimicrobial agent should be based on identification and in vitro susceptibility testing results. Because most infections are due to staphylococcal species, treatment agent should be effective against those germs. In case of oxacillin resistant infections is suspected, vancomycin should be administered initially as empirical antibiotic coverage until microbiological results are known. Patients with infections due to oxacillin-susceptible staphylococcal strains can be given cefazolin or nafcillin alone with discontinuation of vancomycin. Vancomycin should be continued in patients who are not candidates for betalactam antibiotic therapy and those with infections due to oxacillin-resistant staphylococci. Compared with Gram-positive infections, Gram-negative and fungi are less frequently isolated and empiric coverage against those microorganisms is not routinely indicated; it should be started after microbiological identification has been performed.

Pathogen identification and in vitro susceptibility testing can be used to guide treatment in patients with nonstaphylococcal CIED infections. When microbiological culture are

available, a de-escalation approach should be considered in order to minimize the development of antimicrobial resistances (De Gaudio et al., 2010). There are no clinical trial data to define the optimal duration of antimicrobial therapy for CIED infections, regardless of the extent of infection, or to determine when conversion to an oral agent is appropriate once complete device removal has been achieved. Factors that influence duration of therapy include the extent of device infection, the causative organism, the persistence of positive blood cultures, and associated complications such as valvular involvement, septic thrombophlebitis, or osteomyelitis. Blood cultures should be obtained from all patients after device removal. Therapy can be switched to an oral regimen once susceptibility results are known if there is an oral agent available that is active against the pathogen and the infected CIED has been removed. At least two weeks of parenteral therapy are recommended after removal of an infected device and for patients with bloodstream infection. Patients with sustained (>24 hours) positive blood cultures despite CIED removal and appropriate antimicrobial therapy should receive parenteral therapy for at least 4 weeks, even if TEE is negative for valvular vegetations.

7.2.2 Hardware reimplantation

It is important to assess the need for new device placement in any patient with an infected CIED. Based of available data, one third to one half of patients will not require new CIED placement. There are several factors, including reversal of the pathological processes that precipitated the need for CIED implantation and lack of appropriate clinical indications, that may obviate the need for new CIED placement (Sohail et al., 2007b). Adequate debridement and control of infection at all sites, both at the generator site and metastatic, if present, must be achieved before new device placement (Baddour et al., 2010). Removal of infected hardware should not be attempted until a careful assessment of a new implantation strategy has been performed, particularly in patients with pacemakers for complete heart block and resynchronization therapy devices. When implantation of a new device is necessary, it should be performed on the counterlateral side if possible to avoid relapsing device infection. If this is not possible, a transvenous lead can be tunneled to a device placed subcutaneously in the abdomen. Implantation is usually postponed to allow for resolution of infection, but patients who are CIED dependent represent a challenge, because they cannot be discharged with a temporary pacemaker. Active-fixation leads attached to pacing generators or defibrillators are now being used as a bridge until PPM implantation is deemed appropriate. Use of active-fixation leads connected to external devices permits earlier mobilization of patients dependant on cardiac stimulators and has been associated with a reduced risk of pacing-related adverse events, including lead dislocation, and local infection (Braun et al., 2006).

Optimal timing of device replacement is unknown. There have been no prospective trials that examined timing of new device replacement and risk of relapsing infection; however, several investigators recommend waiting for blood cultures to be negative before a new device is placed (Gandelman et al., 2007; Sohail et al., 2007a)

8. Conclusions

Currently, 3 million implanted cardiac pacing systems and 180000 implantable cardioverter-defibrillators exist worldwide. The rate of device implantations is increasing due to the aging of the general population and the development of new indications. Although

conferring obvious benefits, the use of these implantable devices is associated with some complications. Infections must be considered as a serious and potentially fatal complication.
The clinical presentation of device infection ranges from superficial wound infection to frank device-related endocarditis.
The incidence of infection related to pacemakers varies from 0.13% to 19.9% in prospective and retrospective studies. Serious complications, such as endocarditis and sepsis, may occur in 0.5% of patients. In addition, infectious complications have a significant economic impact to health care systems due to the high cost of treatment.
Data to guide treatment of patients with this condition are limited. However, the consensus from the published literature recommends prompt and complete device removal, combined with antimicrobial therapy of appropriate duration. Conservative treatment without explantation of all hardware is frequently unsuccessful. Given the progressive rise in antimicrobial-resistant bacteria in general, and gram-positive pathogens in particular, treatment of cardiovascular infections is likely to become more difficult in the future.
Finally, because a substantial number of patients may no longer require such devices, reimplantation should be done only after the continued need for such therapy has been reassessed.

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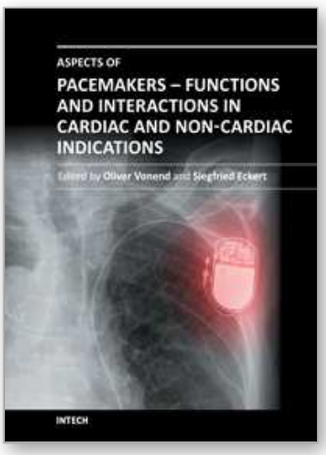

Aspects of Pacemakers - Functions and Interactions in Cardiac and Non-Cardiac Indications

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Outstanding steps forward were made in the last decades in terms of identification of endogenous pacemakers and the exploration of their controllability. New â€œartificialâ€ devices were developed and are now able to do much more than solely pacemaking of the heart. In this book different aspects of pacemaker â€“ functions and interactions, in various organ systems were examined. In addition, various areas of application and the potential side effects and complications of the devices were discussed.

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