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Infections of Cardiac Implantable Electronic Devices: Diagnosis and Approach

Rose Mary Ferreira Lisboa da Silva[1*] and Alessandra de Souza Maciel[2]

[1]Department of Internal Medicine, Faculty of Medicine, Federal University of Minas Gerais, Brazil.
[2]Hospital das Clínicas, Federal University of Minas Gerais, Brazil.

Authors' contributions

This work was carried out in collaboration between both authors. Author RMFLS wrote the first draft of the manuscript. Author ASM managed the literature searches. Both authors read and approved the final manuscript

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ABSTRACT

With the expansion of the indications for implantation of cardiac electronic devices, there was an increase in these procedures and, consequently, there was an increase of the infection rate. The risk of infection depends on many factors, including device type and the number of implantation procedures. In addition to significant morbidity, one-year mortality is approximately 20%. Knowledge of the factors associated with this unfavorable outcome, clinical manifestations, diagnosis and treatment are very important for proper approach. This review presents all these aspects and strategies for the prevention of infection related to implantable electronic cardiac devices.

Keywords: Pacemaker; cardiovascular implantable electronic device; infection; mortality; review.

**Corresponding author: Email: roselisboa@uol.com.br;*

ABBREVIATIONS

ICD: implantable cardioverter defibrillator; CED: cardiac electronic devices.

1. INTRODUCTION

In the 1960s, the first pacemaker with transvenous electrodes was implanted. Over the years, there have been advances in technology in this area, with the use of smaller size devices, and with several functions (multifunctional pacemaker). With the use of long-life lithium battery in the 1970s, the advent of pacemaker dual chamber in mid-1980 and the incorporation of sensors, there was an expansion of the indication and the number of pacemaker implants. Other technological refinements were automatic mode switching, sensors sensitive to temperature, pH, intraventricular pressure, QT interval, and automatic adjustments. These advances reflected in new indications of these devices beyond the treatment of bradyarrhythmias, including the treatment of tachyarrhythmias and cardiac resynchronization therapy [1,2].

The initial experience with the automatic implantable cardioverter defibrillator (ICD) also occurred in the late 1960s, with the first implant in 1980 and approval for its use in 1985 [3,4]. With this expansion of the indications for implantation of these cardiac electronic devices (CED), there was an increase of these procedures and 4.2 million patients underwent implantation of these devices between the years 1993-2008. During this period, there was an increase of 96% of the implantation of CED, especially ICD, whose increase was 504%. And therefore, in the same period, the incidence of infections related to CED increased by 210% [5]. Therefore, this issue is relevant and current, due to its high incidence and its poor prognosis.

2. EPIDEMIOLOGY (MORBIDITY AND MORTALITY)

The first report of infection related to the pacemaker was made in 1971 [6]. With the increasing number of implants of CED and life expectancy, the incidence of infection can reach 20% [7,8]. The risk of infection depends on device type and the number of implantation procedures. This risk is 0.5 to 1% of patients with pacemakers, 1.7% in those with ICD, and 9.5% in patients with cardiac resynchronization therapy in the period 6-24 months after the procedure [9]. After device replacement or upgrade, the risk for CED infection is up 5%, an increase 2 to 4 times compared with the risk of infection of primary implant [9,10]. The incidence rate was 4.82/1000 pacemaker-years after primary implant, and 12,12/1000 pacemaker-years after replacement among patients underwent implantation between 1982 and 2007 [11]. Besides the association between risk of infection and device replacement, other factors such as male gender, young age, number of procedures, lack of prophylactic antibiotics and multiple comorbidities have also been associated with an increased risk of infection CED [5,11].

Apart from significant morbidity, in-hospital mortality ranges from 6% to 14% and total mortality is approximately 20% in one year, reaching 26.9% during follow-up of 5 years [7,12-13]. There are variables associated with unfavorable outcomes and/or mortality predictors such as patient age, use of temporary pacemaker, devices revisions, *Staphylococcus* agent as etiology, presence of heart valve prosthesis, device removal time, kidney failure, need blood transfusion and presence of endocarditis [7,14-18]. Heart failure, cancer, use of corticosteroids and CED-related infective endocarditis were also identified as long-term predictors of mortality [19]. The increased risk of death associated with CED infection depends on of device types. The risk of mortality persists for at least 3 years with single or dual-chamber pacemaker, and for 2 years with ICD [20]. This risk is higher among patients with endovascular infection compared with pocket infection [10].

The economic impact is also important. The financial cost is responsible to 47% increase in hospital charges related to CED infection per decade [5]. The financial burden is due to several factors such as prolonged hospital stay, cost of antibiotic therapy, cost of extraction and implant procedure.

3. MICROBIAL CAUSES

The microorganisms that cause infections can be acquired endogenously from the skin of patients, or exogenously from the hospital environment or the hands of hospital staff. Gram-positive species are the most frequent, and *Staphylococcus* is

responsible for over 80% of these infections and may be methicillin-resistant species. Other micro-organisms involved include *Corynebacterium* species, *Enterococci*, Gram-negative bacilli, anaerobes, and mycobacteria. Rarely fungi other than *Candida*, nontuberculous mycobacteria and polymicrobial species are identified as pathogens in CED infection. The culture is negative in 15% of cases [7,9,10].

4. CLINICAL PRESENTATION

Pocket infection is the most common presentation with local inflammatory changes such as erythema, tenderness, drainage, warmth, and cutaneous erosion with percutaneous exposure of the generator and/or leads (Figs. 1 and 2).

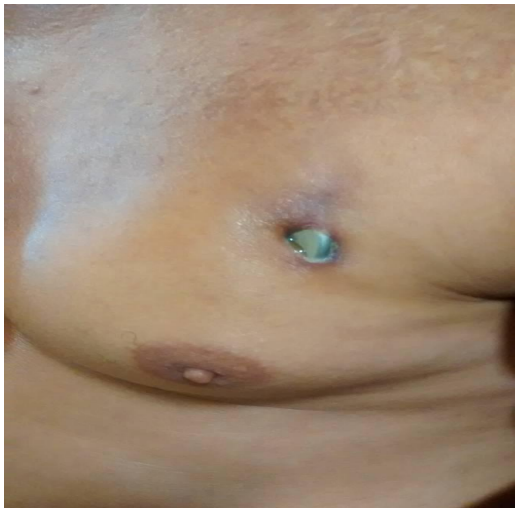

Fig. 1. Pocket infection with erythema, purulent discharge and extrusion of the generator

Systemic symptoms and signs, including fever, chills, and malaise, can be present [7,10]. Pulmonary embolism occurs between 10% and 27% of patients with right cardiac involvement. Systemic embolism occurs in up to 14% of cases. A serious complication is infectious endocarditis, which can occur between 10% and 20% of infections related to CED [21]. It results in a mortality rate of 17.4% to 36% [17,18]. This endocarditis represents 6.4% of all cases of infective endocarditis [8]. Patients with early endocarditis, less than 6 months of device implantation, present most of the times signs of local infection pocket. Patients with late endocarditis usually show signs of systemic infection, including sepsis signals. Thus, lead-associated endocarditis can develop months or years after the procedure [12]. There is an association between presence of prosthetic heart valve and occurrence of CED-related infective endocarditis [14].

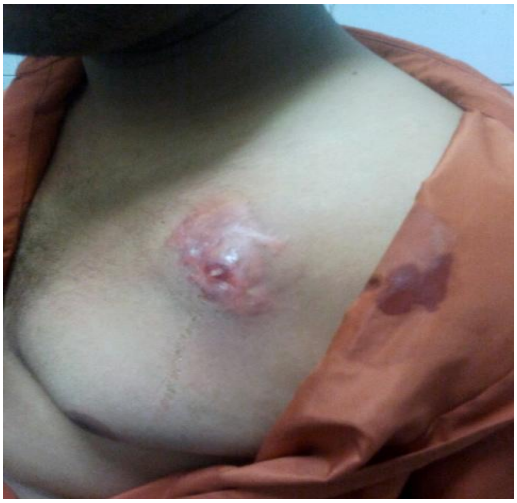

Fig. 2 Pocket infection with erythema and pus

5. DIAGNOSIS

The diagnosis is clinical, associated with laboratory tests, but it is necessary a high index of suspicion. In the clinical condition previously described, at least two blood cultures should be obtained before the use of empiric antibiotics. Blood cultures should be taken from peripheral sites within an interval of at least 6 hours between collections. However, this interval should be up to an hour in patients with severe sepsis or septic shock [7,9,22]. It should not be made percutaneous aspiration of the generator pocket. At the time of removal of the generator and electrode, tissue cultures and lead-tip culture must also be taken, since they have greater sensitivity for the diagnosis than the swab culture [7]. Blood cultures should be repeated 48 to 72 h after explant the device [22].

Transesophageal echocardiography (TEE) should be done as soon as possible, within 24 hours of the diagnosis of infection. TEE can show vegetation, thrombus, pericardial effusion, ventricular dysfunction. The absence of mass adherent to a lead does not exclude infection. TEE cannot differentiate non-infected thrombus or fibrous masses and vegetation. And there is a limitation due to the distance between the transesophageal probe and the right ventricle. Thus, the diagnosis of infectious endocarditis is

established using the modified Duke criteria [7,9,22]. Another useful but invasive technique is the intracardiac echocardiography. It showed a higher diagnostic power for vegetations, with high sensitivity (100%) but a lower specificity (82.8%) compared with TEE [23]. The fluorine-18 marked fluorodeoxyglucose (18F-FDG) positron emission tomography and computed tomography were not recommended routine, but may be useful in patients selected [22].

6. MANAGEMENT

6.1 Antibiotic Therapy

After the diagnosis of infection, should be initiated empirical antibiotic therapy. Then, this therapy will be modified according to the results of blood cultures. The initial empiric antibiotic should be vancomycin. If the culture result demonstrates oxacillin-susceptible staphylococcus, the exchange of antibiotic should be made by cefazolin or nafcillin [7]. Antibiotic therapy time depends on the clinical condition and the presence of endocarditis. Conservative treatment with antibiotics alone can be done for patients with small abscesses in suture site few days after implantation without compromising the pocket [9]. When the infection is limited to the site pocket, the antibiotic therapy time is 7 to 10 days of treatment, after removal of the device. However, if there are inflammatory changes, the antimicrobial therapy recommended time is 10 to 14 days. When the blood culture is positive, the antimicrobial therapy time should be at least two weeks after device removal. If the blood cultures remain positive after 24 h of device removal, the time of treatment with antibiotics should be 4 weeks, with or without endocarditis documented. If there is endocarditis, osteomyelitis or septic thrombophlebitis, duration of antimicrobial therapy should be at least 4 to 6 weeks (Table 1) [7].

6.2 Device Removal

Conservative treatment with antibiotics alone or partial removal of the device (only the generator) has been associated with recurrent infection. Complete device removal (generator and leads) has been associated with higher survival. The immediate complete device removal was associated with a decrease in the mortality rate of 3 times in 1 year [8,9,24,25]. Therefore, complete removal of the device has been recommended for eradication of infection and has low complication rate (1.2%). After debridement necrotic-infected tissue, drainage of purulent abscesses and infection control, implantation of epicardial device should be done, if necessary, for patients at high risk of re-infection or with limited vascular access. The new device re-implantation should be contralateral to the extraction site. When there is valve endocarditis, a time of at least 14 days should be expected after device removal for transvenous lead implantation of a new lead device [7,9,24]. Removal is not indicated if the infection is superficial and incisional and without the involvement of the device and/or leads [7].

6.3 Prophylaxis

Prevention of CED infection should also be taken before device implantation. This should include the use of prophylactic antibiotics, skin preparation, appropriate surgical techniques and the adequate clinical condition of the patient for the procedure. The antibiotic should be administered intravenously 1 hour prior to the procedure, in the case of cefazolin, and 2 hours before the procedure, in the case of vancomycin [7]. A crossover study randomized cluster with 10,800 patients is ongoing to compare the single-dose use of preoperative antibiotics (cefazolin or vancomycin) intravenously, followed by cephalexin/cephadroxil/clindamicyn for two days after surgery, as well use of bacitracin to wash the wound pocket [26]. There are other antibiotic use schemes, as the use of flucloxacillin and gentamicin intravenously 30 minutes before the skin incision. Clarithromycin and gentamicin can be used for patients allergic to penicillin (Table 1). And for high risk patients, gentamicin and teicoplanin can be administered half an hour before the incision, avoiding the use of gentamicin for patients with failure renal [27].

For skin preparation, it is recommended to use antiseptic agents appropriate to minimize the load of microorganisms in skin normal flora. The used antiseptic agents are chlorhexidine-alcohol and povidone-iodine. Studies have shown better results with the first agent [9].

The surgical technique is also important to prevent infection. Some authors recommend the use of double glove and removing one before the skin incision. Furthermore, they recommend the removal of hair at the incision site with electrical clippers [27]. Homeostasis must be done carefully. It was not proven benefit with the use of transparent films or diathermia or substances that prevent bleeding. Haematoma increases the risk of infection.

Table 1. Antibiotics for prophylaxis and treatment of infection related to CED

Approach	Antibiotics
Prophylaxis	Cefazolin (1 h before the procedure) or vancomycin (2 h before); clarithromycin and gentamicin (for patients allergic to penicillin)
Empiric antibiotic	Vancomycin
Oxacillin-susceptible *staphylococcus*	Cefazolin or nafcillin: 7-14 days (for pocket infection); 2-4 weeks (if positive blood culture); 4-6 weeks (if endocarditis, osteomyelitis or septic thrombophlebitis)

Therefore, anticoagulation should be interrupted in patients with low risk of systemic embolism. The intervention for drainage must be avoided unless haematoma tense or painful. Generally, large haematomas without tension are reabsorbed in a few weeks [9].

There are envelopes with antibacterial action made mesh polypropylene that release minocycline and rifampin in the generator pocket after device implantation. The antibiotics are eluted out of the mesh within 7-10 days [9,28]. World-wide Randomized Antibiotic Envelope Infection Prevention Trial (WRAP-IT) is a randomized, prospective, multi-center, single blinded, that will evaluate the ability of a bio-absorbable envelope to reduce major CED infections through 12-months after implantation device. This envelope (TYRXTM Envelope, Medtronic, Monmouth Junction, NJ, USA), that disappearing within 9 weeks, will be used in 7,764 patients scheduled for CED replacement or upgrade process, primary implantation or pocket revision [9,29].

Others aspects are related to the volume of the CED implant procedures and its reuse. This annual volume was directly related the implantation of more complex devices and inversely associated with early surgical complication rates, including infection [30]. Despite the HRS survey respondents support the concept of CED reuse for patients in countries of low and middle income, 64% of them are concerned with infection related to this reuse [31]. Thus, the futures directions are randomized trials with the aim of reduce the rate of infection focusing on prevention.

7. CONCLUSIONS

CED infection is an important health issue. The main microbial agent is *Staphylococcus*. Pocket infection is the most common presentation, but endocarditis may occur in up 20% of patients. A high index of suspicion is necessary for diagnosis. Treatment includes antimicrobial therapy and device removal. Prevention and strategies to minimize the risk factors are the key to reducing the rates and severity of infection.

CONSENT

All the authors declare that informed consent was obtained from patients for the publication of the images that accompany the manuscript.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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