Chapter

Endocarditis and Cardiac Device Infections

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Abstract

The growing number of electronic intracardiac devices (pacemakers, resynchronizers and defibrillators) and non-electronic devices (percutaneous occluders) implanted, combined with certain common characteristics in the treated population (underlying heart disease, advanced age, kidney disease, multiple associated pathologies), have led to a change in the spectrum of presentation of endocarditis, with an increase in cases related to these devices. These infections pose diagnostic and therapeutic challenges due to the complexity of the patients, the microorganisms involved –who frequently generate the formation of biofilm- and the percutaneous or surgical techniques involved in the removal of material. All these circumstances require a multidisciplinary approach.

Keywords: endocarditis, cardiac implantable electronic device (CIED), infection, biofilm, prophylaxis

1. Introduction

Endocarditis is defined as the inflammation of the endothelium. The first case of endocarditis was described by Lazare Rivière in the seventeenth century. Since then, the clinical, etiological, epidemiological and therapeutic knowledge around it has expanded remarkably. Nevertheless, it is a complex disease in constant evolution that requires a multidisciplinary approach. Most endocarditis has an infectious cause of bacterial origin. Being a disease of the endocardium, it not only affects native structures -more frequently the valves or cardiac structures subjected to special hemodynamic conditions such as in congenital heart disease-, but also other endothelizable surfaces, such as valve prostheses, catheters, electrodes, or percutaneous devices.

In this chapter we will address endocarditis on Cardiac Implantable Electronic Devices (CIED).

2. Endocarditis and cardiac implantable electronic devices (CIED) with leads

2.1 Epidemiology

Infective endocarditis is a serious disease, whose incidence, despite therapeutic advances, remains relatively stable (although data regarding countries with low health resources are scarce). In developed countries, its incidence is estimated

at 1 per 1000 hospital admissions and 1.5–9.6 cases per 100000 inhabitants [1, 2]. While in countries with limited resources it continues to be closely related to rheumatic valve disease, in developed countries it is fundamentally related to degenerative valve disease, valve prostheses and CIED. The use of implantable cardiac electronic devices (pacemakers [PM], implantable cardioverter-defibrillators [ICD], cardiac re-synchronized therapy [CRT]) has increased by 4.7% annually between 1993 and 2009 with a growth of 96% in the entire period. The number of implanted pacemakers increased by 55.6% (especially bicameral), while that of defibrillators did so by 504% [3, 4]. Such increase is due to a number of factors: the aging of the population, the complexity of their pathologies, the new indications and the advance in implantation techniques. However, the growth of infections associated with these devices has raised disproportionately and is estimated at 210% between 1993 and 2008 [4, 5].

2.2 Classification of CIED infections

- **Post-operative wound inflammation:** occurs within 30 days of implantation, with wound inflammation or 'stitch abscess', in the absence of definite evidence of infection and not necessarily requiring antimicrobial therapy (possible skin reaction to dressings, sutures or antiseptics) [6].

- **Uncomplicated generator infection:** cellulitis confined to the generator site, including purulent discharge, abscess, fistula or device erosion in the absence of systemic involvement, and negative blood cultures.

- **Complicated generator infection**: generator infection plus involvement of any part of the lead or development of systemic involvement (signs or symptoms or positive blood cultures).

- Lead infection.

  ○ Definite:

  a. Symptoms/signs of systemic infection, NO signs of generator pocket infection AND echocardiography consistent with vegetation(s) attached to lead(s) AND presence of major Duke microbiological criteria.

  b. Symptoms/signs of systemic infection, NO signs of generator pocket infection AND culture, histology or molecular evidence of infection on explanted lead.

  ○ Possible.

  a. Symptoms/signs of systemic infection AND echocardiography consistent with vegetation(s) attached to lead(s), BUT NO major Duke microbiological criteria present.

  b. Symptoms/signs of systemic infection AND major Duke microbiological criteria present, BUT NO echocardiographic evidence of lead vegetations.

  c. Pulmonary emboli are considered supportive evidence of lead infection in the absence of definite evidence of infection.

- CIED -associated native or prosthetic valve endocarditis.

Duke criteria for definite endocarditis satisfied, with echocardiographic evidence of valve involvement in a patient with an CIED in situ.

The last two forms are considered by the European Society of Cardiology (ESC) as endocarditis related to CIEDs, and we will now focus on them, not forgetting that they coexist with local infection of the generator pocket in up to 10–50% of cases (although in some recent series, the figure is closer to 10%, which suggests that causative microorganism reached PM leads by haematogenic way in a high proportion of case) [7].

Different epidemiological studies, with follow-up ranging from 6 weeks to 11 years, estimate the incidence of CDI-related infection at 2% [6, 8], although the figures are highly variable depending on the criteria used (0–6% and up to 19% if intra-abdominal devices are included) [9]. Between 10 and 23% of these infections meet the criteria for endocarditis [2, 7, 10].

A study in 7424 patients who underwent a pacemaker and/or ICD device implantation demonstrated an increasing incidence of IE in pacemakers [7]. It represented almost 10% with an increment from 1.25 to 9.32% of all IE between the period 1987–1993 compared to the period 2008–2013. Another prospective cohort study, using data from the International Collaboration on Endocarditis–Prospective Cohort Study (ICE-PCS), conducted from June 2000 through August 2006 in 61 centers in 28 countries, found that cardiac device infective endocarditis accounted for 6.4% of all cases of definite infective endocarditis [11].

2.3 Risk factors

Several studies have identified the following risk factors for the development of infection on CIED [2, 7, 8, 11–13]:

Factors associated with the patient: Several of them coexist in up to 50% of patients [7].

- Age, probably a confounding factor due to the higher number of comorbidities.
- Male sex.
- Diabetes Mellitus.
- Renal insufficiency.
- Other comorbidities such as heart failure or (chronic obstructive pulmonary disease (COPD).
- Neoplasia.
- Use of corticosteroids.
- States of immunosuppression.

Factors associated with the procedure

- Non-first implant: Infection is more frequent in replacement or update procedures (1–4%) than in first implantation (0.5–0.8%) The risk of CIED infection is much greater after generator change or device revision. It has been suggested that this is related to bacterial contamination of the avascular pocket that is formed around the generator, which may impede penetration of

systemic antimicrobials and inflammatory cells during generator replacement. For this reason, some operators advocate the removal of the capsule in battery replacement.

- Shaving the skin with a blade (risk of disruption of the skin barrier).
- Poor preparation of the skin.
- Not using antibiotic prophylaxis.
- Fever in the previous 48 hours.
- Hematoma.
- Number of electrodes and complexity of the procedure.
- Duration of the procedure.
- Operator experience.

Factors related to other procedures and health care

- Previously carrying a transvenous transitory pacemaker.
- Invasive procedures related to health care (nosocomial and non-nosocomial) and or hospitalization, which may produce bacteremia leading to CIED infection, were identified in the previous 6 months in about 45–50% of the IE-ICED [7–11].

2.4 Physiopathology and etiology

According to estimates from the U.S Food and Drug Administration (FDA) and the European trade association representing the medical technology industries, (MedTech Europe), more than 500000 types of medical devices have currently entered the global market. Invasive medical devices, including indwelling and implantable devices, represent just a fraction of these [14, 15]. More than a million cardiovascular electronic devices are implanted worldwide each year [16]. Devices used in cardiovascular surgery and interventionism are inserted into the body tissues by breaching the skin or mucous membranes. No matter where the surgically invasive device is placed, it is a foreign body. Even a mild tissue response alters the local immune defenses, creating a "locus minoris resistentiae", which is vulnerable to bacterial attack. Especially the devices in contact with the bloodstream, can potentially cause sepsis.

CIED infection, can have a local or a distant origin.

2.4.1 Local origin

Human skin is very resistant to infection. This resistance is due to physical (thickness, exfoliation), chemical (pH, secretions) and immunological (cellular and humoral) factors.

The resident flora is also an important factor. This flora is made up of bacteria that live attached to the skin and under normal circumstances, they do not cause infection and prevent the proliferation of other strains as well. When the skin barrier is broken, the entry of microorganisms from the adjacent skin is facilitated. Most infections from these devices are caused by coagulase negative staphylococci

(CoNS), which are the most common microorganisms in the normal flora of the upper part of the skin of the thorax (especially *Staphylococcus epidermidis*). *Staphylococcus aureus* is not part of this resident flora, but it can become a persistent colonizer of the nasal mucosa, pharynx, and skin, especially in kidney patients, diabetics, some skin diseases, and hospital workers.

Phases of infection

- **Colonization** of the CIED pocket by microorganisms from the surgical equipment (air or personnel) or more frequently from the patient's own skin. Disinfection reduces the number of bacterial colonies, but in the presence of a foreign body, the inoculum to produce an infection is lower. The susceptibility of surgically invasive devices to bacterial colonization is due to reduced effectiveness of human immune defenses at the implant–tissue interface [12]. The longer the procedure, the higher the rate of colonization of the surgical sites.

However, colonization is not synonymous with infection, since it must occur: Adhesion and BIOFILM formation (**Figure 1**) [13, 14].
Biofilm formation occurs in five steps:

- *Initial reversible anchoring* of bacteria in "planktonic" or "free" form to surfaces by unspecific forces.

- *Irreversible anchorage*: Once anchored, a bacterial monolayer will begin to form and an extracellular protective matrix composed of extracellular polysaccharides, extracellular proteins, cellular debris and nucleic acids will begin to be produced. Both, along with the collagen and fibrinogen deposited in damaged tissues and on biomaterials, favors the anchorage of bacteria with specific receptors. The formation of hematomas facilitates this process.

- *Maturation:* the development of a biofilm favors the growth of the colonies, with a complex three-dimensional framework and a great resistance to antibiotics. Sometimes different bacterial species can coexist in the same biofilm. There are complex genetic interactions between the bacteria in these biolayers known as "quorum sensing".

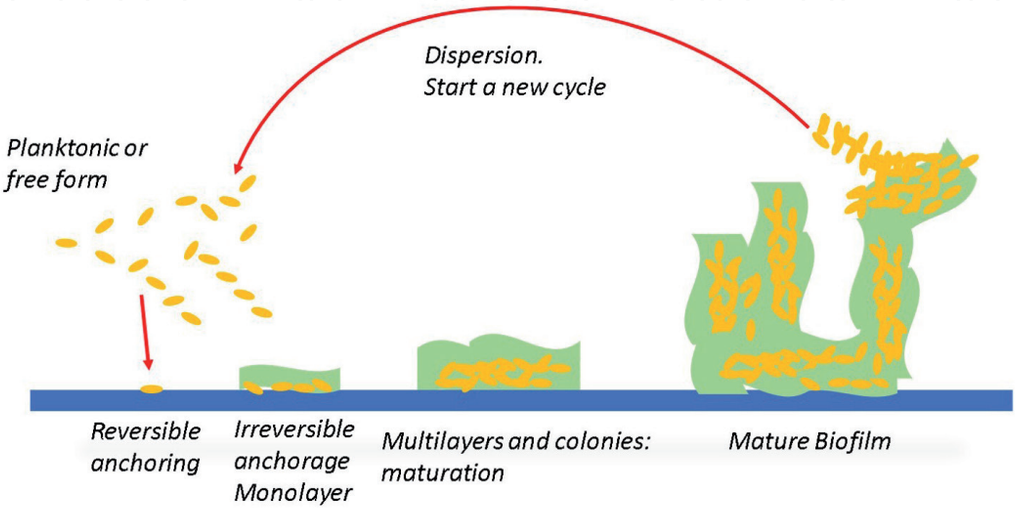

Figure 1.
BIOFILM formation.

- *Dispersion.* In the last step, some cells of the mature biofilm begin to dissociate and disperse again through the environment as planktonic cells to start a new cycle and thus the infection is dispersed.

2.4.2 Remote origin

During the early post-implant period, damage to the vascular wall and the formation of hematomas can favor the settlement of germs from the bloodstream in the implant area; thus, it is very important to avoid the development of bacteremia by removing unnecessary intravascular and urinary catheters.

The infection can spread to the endovascular structures, during the healing and resorption phases of hematomas, from the pacemaker pocket.

Conversely, and generally later, endovascular elements (electrodes) can present fibrin and platelet deposits on erosions produced by friction, deterioration or turbulent flows, on which bacterial colonies can settle and proliferate in a process similar to that of endocarditis, which can also spread to the adjacent endocardium.

Concomitant valve involvement is estimated in about 37.2% of cases, most frequently tricuspid valve [11], aortic or mitral valve vegetations are present in 10–15% of patients with CIED endocarditis and valve involvement in CIED infection is associated with higher in-hospital mortality.

As previously mentioned, between 40 and 50% of patients with CIED have a history of admission, manipulation or invasive procedure in the previous 6 months, potentially responsible for bacteremia. The risk is especially high when the bacteremia is due to *Staphylococcus aureus* (35–45%) [6].

In any case, given that many "presumed local" infections can progress to the intravascular components of the device and vice versa, the barrier between local and endovascular infection can be difficult to establish. Once the generator or proximal leads have eroded through the skin, a device should be considered infected, whatever the mechanism that caused the erosion.

2.5 Microbiology

Gram-positive bacteria are responsible for the vast majority of CIED infections (68–93%). Staphylococci, account for 60–80% of cases. Depending on the series, there is a predominance of infections caused by S Aureus or coagulase-negative staphylococcus (CoNS), although with few differences in their prevalence. Among the CoNS, *Staphylococcus epidermidis* and Staphylococcus Saprophyticus stand out. Methicillin resistance (MR) among Staphylococci varies among studies A high rate of MR in CoNS is associated with a healthcare environment source, reaching 50% in some series. For S aureus the rates of MR range between 2.6% (Germany) and 55% (USA). Gram-negative bacteria (GNB) are also identified in a percentage close to 15%. The higher proportion of GNB may be due to the large rate of different comorbidities, which is associated to more frequent invasive diagnosis or treatment measures. Polymicrobial infection sometimes involves more than one species of CoNS, (2–24% according to series). In a percentage between 8 and 15%, it was not possible to cultivate the responsible germ. Cases related to fungi are anecdotal [5, 6, 17–19].

2.6 Diagnosis

The diagnosis of IE-CEID, as in valve prostheses, is inconclusive in up to 30% of cases, according to the Duke criteria [20]. For this reason, in the guidelines published by the European Society of Cardiology in 2015, three additional criteria were proposed to increase sensitivity in diagnosis [19].

In any case, the IE-CEID diagnosis is based on three points [19, 21].

2.6.1 Clinical presentation

The clinical manifestations of IE-CIED can be variable, since it can combine signs and symptoms of local infection, with symptoms and signs of systemic infection.

When there is involvement of the pacemaker pocket, diagnosis can be easier since there will be typical signs of inflammation, such as pain, redness and increased temperature in the implantation area. In addition, there may be an increase in size, either due to the presence of hematoma related to the implant (which should alert to an increased risk of infection) or fluctuation due to the formation of pus, adhesion of the skin as well as spontaneous and sometimes intermittent pus drainage due to dehiscence of the suture or fistulization of the skin (**Figure 2**).

Any exteriorized device should be considered infected (although initial exteriorization was related to aseptic necrosis of the skin due to tension of the device in a small pocket).

Once the pocket is infected, the electrodes are frequently affected in its subcutaneous and extravascular portion, and affect the intravascular portion as well. When there is involvement of the intravascular components, that is, endocarditis of the leads and vascular part of the system, signs and symptoms of systemic infection will appear, with fever, chills, asthenia and anorexia. These data can appear larvae and in the absence of associated involvement of the pacemaker pocket, they can be more difficult to interpret. In a low percentage of patients, signs and symptom of frank sepsis will appear. In case of associated valvular involvement, data of valvular dysfunction and heart failure may also appear.

Clinical manifestations related to septic lung embolism may also appear from vegetations of the PM leads or tricuspid valve.

Among laboratory results data, the acute phase reactants (C-reactive protein, increased sedimentation rate, leukocytosis and procalcitonin) increase. Although these alterations point us towards a systemic infection, acute phase reactants can also appear in local infections.

Regarding the chronology of infections, several aspects must be taken into account:

- In the first 30 days, skin or exudate or superficial erythema may appear in relation to infection of the suture or allergic reaction,
- Depending on the responsible germ, the temporary clinical course may vary. In the case of S Aureus infections, parturition is usually earlier and

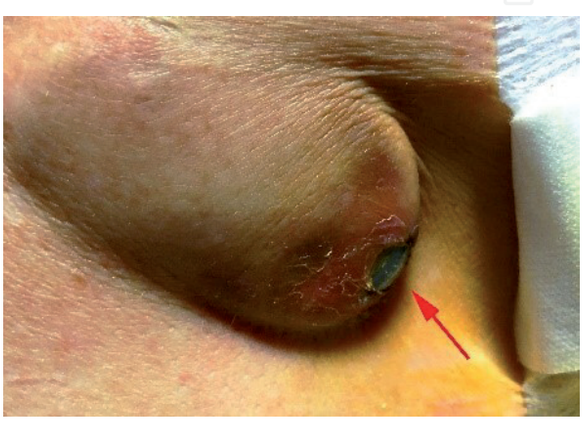

Figure 2.
Exteriorized device.

the progression to systemic disease faster than in the case of germs such as S Epidermidis or *Propionibacterium acnes*, in which it can be latent and even reactivate late with delayed handling.

2.6.2 Microbiological evidence

We have already discussed the main agents involved, now we will address how and when microbiological samples should be collected and processed. Appropriate microbiological samples include: culture of blood, lead fragments (ideally distal and proximal), lead vegetation (proximal and distal tips), generator pocket tissue and pus from a generator pocket wound.

Blood sample extraction [6, 21].

- Should be collected as soon as possible, and whenever possible before starting antibiotic treatment.

- Collection of multiple samples increases diagnostic sensitivity: three sets of aseptically collected, optimally filled blood cultures should be taken from peripheral sites with ≥6 h between them, especially in patients with non-acute presentation.

- To avoid an undesirable delay in patients with suspected IE-CIED and severe sepsis or septic shock at the time of presentation, two sets of optimally filled blood cultures should ideally be taken at different times within 1 h and prior to the start of empirical antimicrobial therapy.

- Follow -up blood cultures should be obtained 48 to 72 h after antimicrobial therapy is begun, and every 48–72 hours until clearance of bacteremia is documented.

- Blood cultures should be taken 48–72 h after removal of an infected CIED.

Regarding blood culture, the following considerations must be taken into account:

- In a variable percentage, around 10%, it will not be possible to grow any microorganism.

- The interpretation of a single positive culture for an organism, common contaminant of the skin flora, should not be interpreted systematically as bacteremia and should be evaluated within the overall clinical context.

- In case of bacteremia originated at a clear distant infectious focus (abdominal, urinary, respiratory) and due to germs that do not frequently cause endocarditis on devices (enterobacteria, pneumococci), affectation of the device should not be assumed unless proven otherwise.

- All cultured samples must be processed in different culture media and in specific media for slow-growing organisms.

- When interpreting the results of the cultured electrodes, it should be considered their potential contamination when extracted through the explant area.

- To the contrary, in the presence of remote bacteremia by S Aureus, the risk of device infection is very high (35–45%).

2.6.3 Imaging

Different imaging techniques are used for the diagnosis of IE – CIED and, therefore, we will speak of Multimodal imaging when referring to them [21, 22].

First line technique, due to its availability and safety, is echocardiography. Initially, an echocardiogram should be performed in all patients with CIED infection, either local or systemic. Transthoracic echocardiogram (TTE) will allow us to globally assess all the structures of the heart as well as their function (**Figure 3**). Despite the advantage of the proximity of the right cavities to the thoracic wall, the presence of metallic electrodes generates artifacts that make it difficult to assess associated vegetations. Occasionally, images compatible with vegetations can be identified, associated with the electrodes, the valves or the endocardium; although their absence does not exclude the diagnosis, since sensitivity is low.

Regardless of the result of the TTE, a Transesophageal echocardiography (TOE) should be performed in all patients with CIED infection suspected of systemic involvement, and probably in carriers of intracardiac devices in the presence of S Aureus bacteremia (**Figure 4**). Even though the sensitivity is higher than in ETT, it is still less than 100% in the case of devices. The reasons for the low sensitivity include: the small part visualized of the cava, the difficulty to assess electrodes in the coronary sinus, or the lesser proximity to the transducer. Three-dimensional (3D) echo, if available, can provide information about vegetation's morphology and size (**Figure 5**). On the other hand, there are images that are difficult to interpret as they may correspond to fibrin strands or small thrombi adhering to the surface of the leads, more frequent in the right cavities due to a slower flow.

In some centers, intracardiac echo (ICE) is also used for the diagnosis of vegetations based on electrodes, with greater sensitivity for the detection of vegetations in the case of high suspicion without diagnostic images. As drawbacks, it is an invasive and expensive technique [23].

In the case of uncertain diagnosis and high suspicion of endocarditis in the absence of diagnostic criteria or doubts about the extent of a local infection,

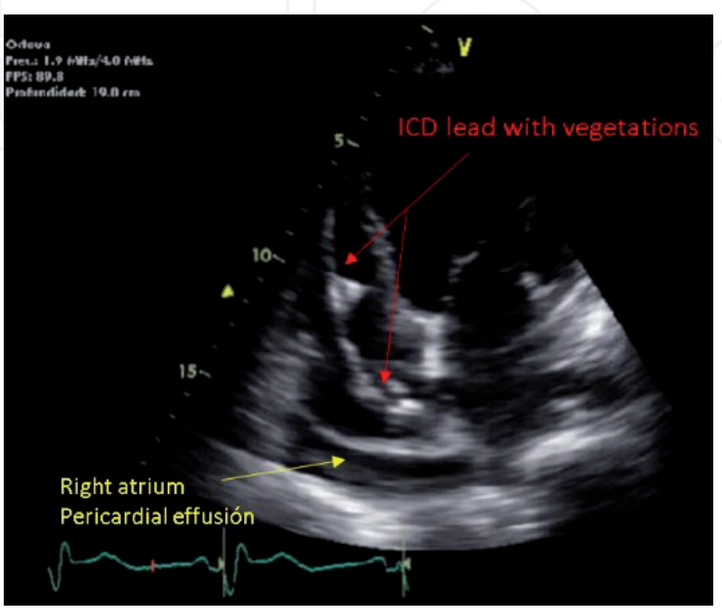

Figure 3.
Lead vegetation TTE.

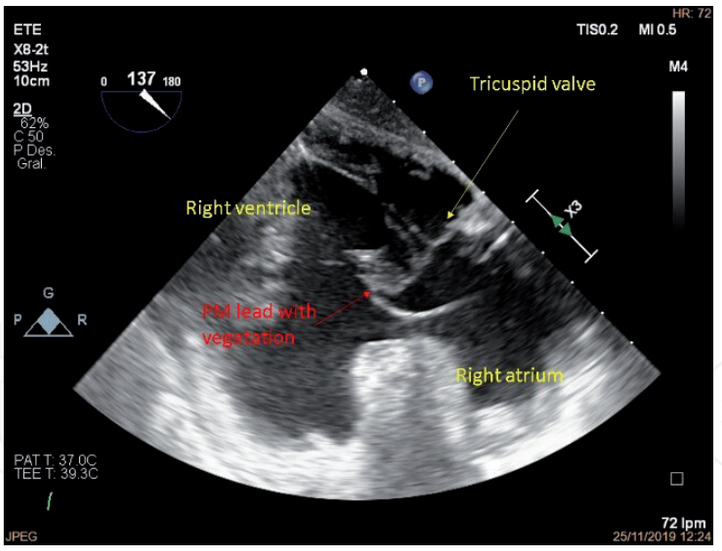

Figure 4.
Lead vegetation TOE.

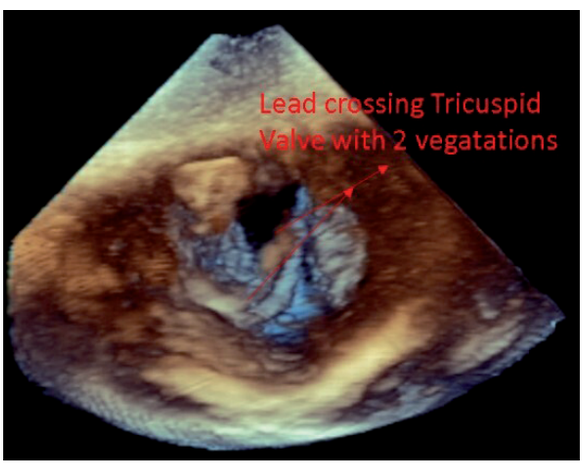

Figure 5.
Lead vegetation 3D echo.

Nuclear Medicine or hybrid technique can be used, based on the detection of metabolic or inflammatory activity.

Positron Emission Tomography-CT (PET-CT) is generally performed using a single acquisition (generally at 1 h) after administration of 18F-FDG, which is actively incorporated in vivo by activated leucocytes, monocytes, macrophages and CD4+ T-lymphocytes accumulating at the sites of infection. Its limitations are the low resolution for foci smaller than 5 mm, its price, the high radiation and the early post-implant or post-surgery period, since the isotope uptake can occur in any inflamed tissue or with metabolic activity, including thrombi and tumors. Sensibility of this test it is estimated around 87% and its specificity around 94% (**Figures 6** and 7).

Scintigraphy (SPECT) with labeled leukocytes can be combined with CT. Compared to PET-CT, it has the disadvantages of a lower availability, a longer duration -since it requires 2 separate acquisitions (2 and 24 hours)- and the use of blood products. On the other hand, it is cheaper, has greater utility in the post-implantation/postoperative period, exposes less radiation and a greater specificity is reported, close to 100% (except for non-pyogenic agents such as Candida or Coxiella, rarely implicated in CIED infection) [24, 25].

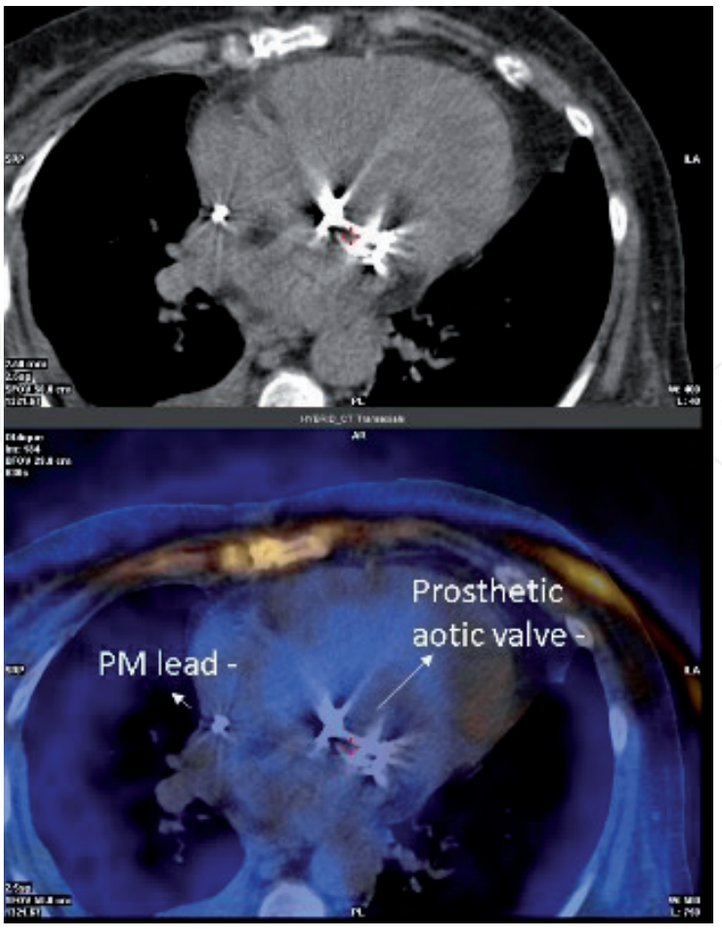

Figure 6.
PET-TAC-.

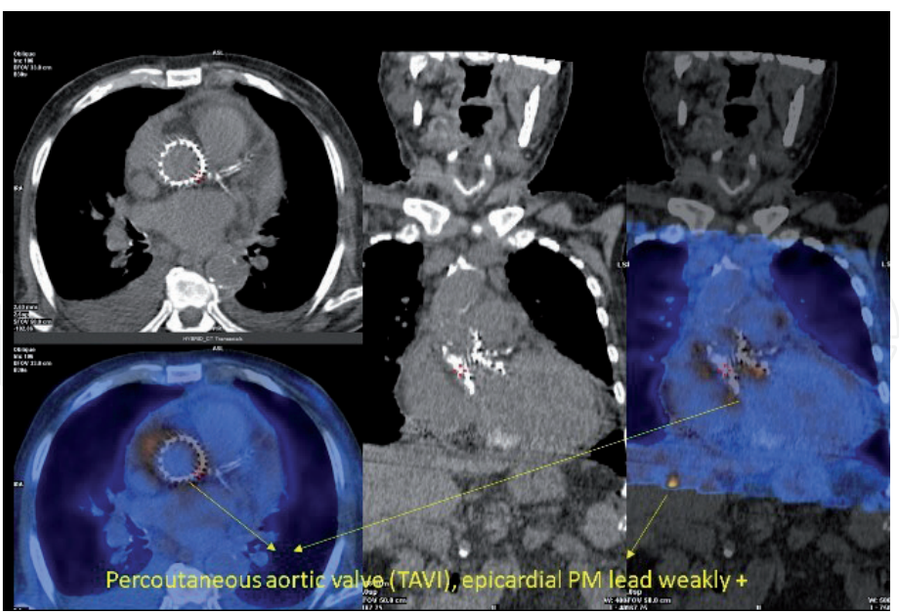

Figure 7.
PET-TAC+.

Beyond imaging techniques focused on evaluating of vegetations and inflammatory activity, a chest radiograph in 2 projections or even a CT should be performed to assess the type of device (sometimes unknown), the presence of breakage, torsion or dislocation of the electrodes or the generator displacement, and to assess

the pulmonary parenchyma as there may be images suggestive of septic embolism or infectious pulmonary involvement (**Figure 8**).

2.7 Prevention and prophylaxis

Before addressing the treatment of IE-CIED we will discuss how to prevent infectious complications.

2.7.1 General measures

Any implant procedure must be performed following the usual aseptic surgical standards. Additionally, it is recommended to adhere to the following guidelines:

- Carry out the procedure in an appropriate place, with adequate ventilation. The air requirements specified for cardiac catheterization laboratories (15 air changes/hour) are less than the 25 air changes/hour recommended for the operating room [6].

- Do not shave the skin with blades. When trimming hair, shave with a single-use electric head or with depilatory cream, before the procedure and outside the implant room [6, 30].

- Prepare the skin with an alcoholic solution of chlorhexidine (minimum 2%) or as an alternative for allergic individuals, use povidone iodine in alcohol [6, 18, 27–29].

- Avoid unnecessarily long procedures, best if performed by a first operator or an experienced supervisor [6, 11, 26, 30].

- Carry out a correct hemostasis to avoid the formation of hematoma. In the case of anticoagulated patients in whom anticoagulation should not be interrupted, do not use bridging therapy with heparin and look for an INR close to 2. Individualize treatment in the rest of antiplatelet or anticoagulated patients. Local thrombin solutions can be considered to facilitate hemostasis [18, 26].

- Do not perform procedures in patients with suspected active infection or fever in the past 48 hours [6, 11, 18].

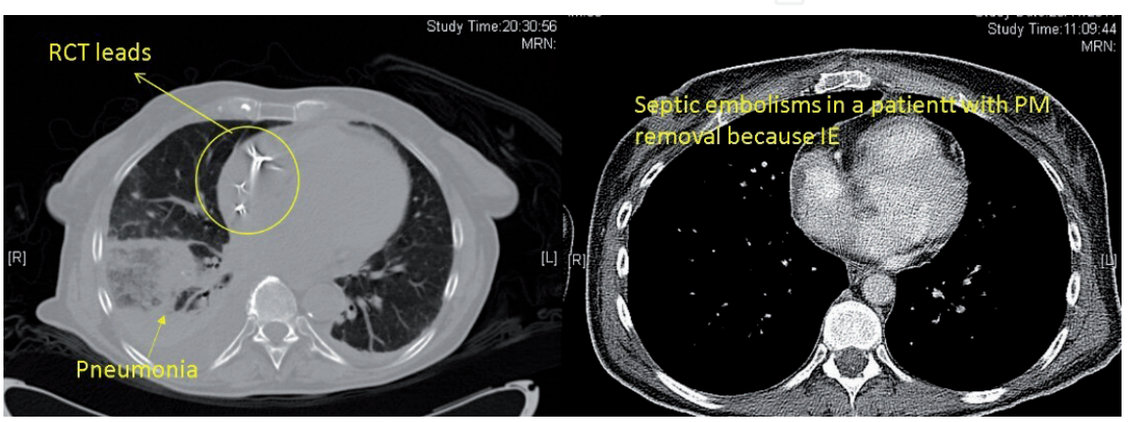

Figure 8.
Pulmonary infectious involvement in IE-CIED. TC.

- Consider the subpectoral implantation in malnourished or very thin patients [18, 26, 30].

2.7.2 Antibiotic prophylaxis

Antimicrobial prophylaxis should be administered on time to ensure, at the time of incision and throughout the procedure, that the tissue and plasma concentrations exceed the MIC for the microorganisms commonly associated with infection. This would normally be within 1 h for intravenous drugs given as a bolus or short infusion, but for some longer infusions that are given over 30 minutes or more, they may need to be started earlier to ensure that the infusion is completed at least 20 minutes before incision (e.g. vancomycin and fluoroquinolones) [6, 18, 19, 26–30].

Currently, the use of a dose of cefazolin (2 gr) or another first-generation cephalosporin or flucloxacillin (1–2 g) is recommended, one hour prior to the procedure. In patients allergic to Beta lactams or when the local incidence of MR Staphylococci is very high, vancomycin is recommended (vancomycin requires a mg/kg iv slower rate of infusion to prevent systemic vasodilatation and erythema within 2 hours before incision) or teicoplanin as an alternative regimen. If a glycopeptide is to be used, teicoplanin has some practical advantages over vancomycin in terms of administration as it can be given as a bolus (400 mg iv 5 minutes) rather than a long infusion. Teicoplanin resistance is more frequent than vancomycin resistance among Staphylococci (including CoNS), but both are uncommon. In case of allergy to both, assess linezolid/daptomycin.

In very prolonged procedures or in case of heavy bleeding, a second dose of intraprocedural antibiotic can be considered [12].

For elective procedures, *S. aureus* colonization can be detected by nasal swabs. Nasal treatment with mupirocin and chlorhexidine skin washing can reduce colonization and has been shown in some surgical studies to reduce the risk of infection, but there are no studies relating specifically to CIED interventions [6, 18, 30].

Antibiotic doses after wound closure are not recommended [6, 30]. The use of local antibiotic delivery is not recommended [6, 21, 30] as well.

Antimicrobial 'envelopes' have been developed to deliver antimicrobial agents locally into the generator pocket at the time of implantation or generator replacement. A product that delivers rifampicin and minocycline locally was tested in a randomized, controlled clinical trial WRAP-IT to assess its safety and efficacy in a population of patients who were at increased risk for CIED pocket infection. The envelope was significantly more effective at preventing infection than standard protocols. There is no formal recommendation for the use of these covers but it could be considered in high-risk patients [29, 30].

Antimicrobial prophylaxis is not recommended for dental or other invasive procedures not directly related to device manipulation to prevent CIED infection, except in case of infected tissue manipulation [26].

2.8 IE-CIED treatment

Treatment is based on two pillars: the removal of the device and antimicrobial therapy.

2.8.1 The removal of the device

Complete removal of the device, electrodes, or abandoned remains, is indicated in patients with any CIED infection, with the exception of superficial infections

related to the incision and provided that they do not occur with exteriorization of the device or erosion of the skin [24, 30–32].

Explantation is indicated in case of:

- local pocket infections without data of systemic involvement (negative blood cultures).
- infections of the pocket with systemic involvement, without vegetations on the electrodes or valves.
- infections of the pocket with systemic involvement, with evidence of vegetations in electrodes and/or valves and/or embolisms.

The device should also be removed in CIED carriers in case of [21, 30]:

- bacteremia or fungaemia caused by S Aureus, CoNS, Cutibacterium spp. and Candida spp.
- bacteremia with Alpha- or Beta-Hemolytic Streptococcus spp. and Enterococcus spp. as first-line treatment or as a second step in case of recurrent/continued bacteremia despite appropriate antibiotic therapy.
- bacteremia with non-Pseudomonal/Serratia Gram-negative bacteria or Pneumococci in case of recurrent/continued bacteremia, in spite of appropriate antibiotic therapy when no other identifiable source for recurrence or continued infection is found.
- patients with infective valve endocarditis without definite involvement of the CIED system.

The device must be completely removed as early as possible. Percutaneous removal is indicated as first choice when possible. Surgical approach is indicated when there is an indication for surgery associated with endocarditis in another location or after incomplete percutaneous removal. For large vegetations, greater than 20 mm, surgery may be considered the first option from the outset, due to a hypothetical higher risk of pulmonary embolism, although this cut-off point is arbitrary. The aspiration of large vegetations is reported before the percutaneous extraction of the electrodes. Removal of the system percutaneously is usually relatively simple when it is performed early after implantation, since there is less fibrosis around the device elements and implies more difficulty and risk of complications the longer the period after implantation and the complexity of the device.

The extraction should be done in expert centers by interventional cardiologists, electrophysiologists or cardiac surgeons. The percentage of complete removal of the device is high>90% with the techniques and materials currently available (specific stylets, mechanical dissection sheaths, with radiofrequency or laser, ties, etc.) (**Figure 9**). Implant removal requires centers with availability of urgent cardiac surgery, given that, although the percentage of complications is low, they can be serious and lead to vital compromise. The risk of serious complications is 2–4%, the most severe being cardiac avulsion or tear (CA / T) with tamponade and vascular avulsion or tear (VA/T). In the case of surgical extraction, (**Figure 10**) the percentage of complications observed is higher and it seems related to a greater severity of the patients [30–32].

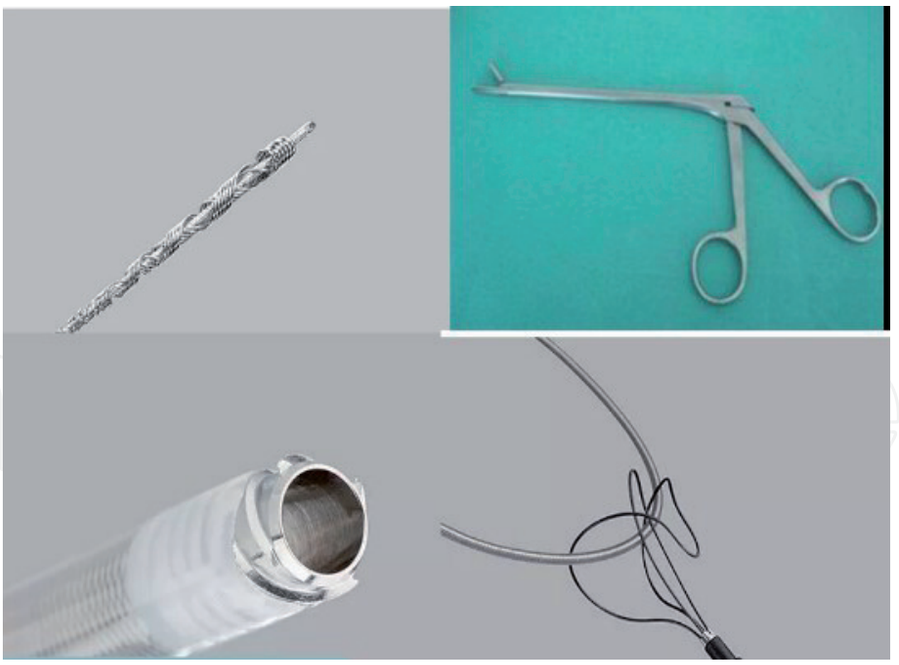

Figure 9.
Materials for percutaneous.

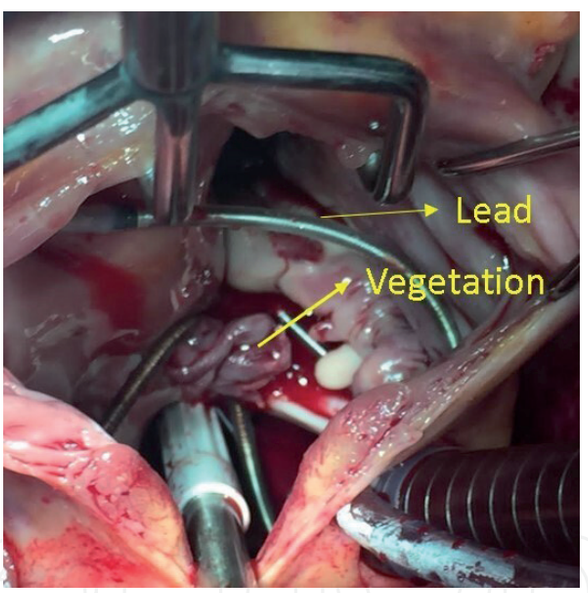

Figure 10.
Lead with big vegetation, surgical removal.

In 3–15% of patients with an indication of removal of the device, this will not be carried out for various reasons, especially a very high surgical risk or the patient's own refusal [6, 10].

2.8.2 The antimicrobial therapy

Intravenous (iv) antimicrobial therapy should be guided whenever possible by microbiological documentation and antibiogram; this is the reason why the correct collection and sample processing is so important.

The empirical antibiotic regimens recommended by a consensus of various scientific societies, European Heart Rhythm Association (EHRA), Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), Latin American Heart Rhythm Society (LAHRS), International Society for Cardiovascular Infectious

Diseases (ISCVID), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), European Association for Cardio-Thoracic Surgery (EACTS)] [30] are listed in **Table 1**. The duration of the treatment will continue once the device is removed as follows:

- Isolated pocket infection (negative blood culture): 10–14 days.
- Systemic infection without vegetation on leads or valves +/− pocket infection:
  4 weeks (2 weeks if negative blood culture after extraction with total treatment duration not shorter than 4 weeks).
- Systemic infection: IE-CIED with vegetation on leads and/or valves + embolism: 4–6 weeks + oral antibiotic therapy follow-up if indicated by secondary infectious focus.

Long-term suppressive therapy with iv antibiotic, according to the recommendations in prosthetic valve endocarditis for 4–6 weeks, is reasonable for patients in whom the device cannot be totally or partially removed, due to the high rates of failure, relapse or reinfection [33].

2.9 New device implant

After the removal of a CIED, the indication for a new implant must be reconsidered. This must be done critically and individually [19, 26, 30].

It is estimated that, in about 30% of patients, implantation of a new device is not indicated. The reason may be that there is no longer any indication, that the explanted device was not correctly indicated, or that the patient himself rejects a new implant. In the case of a new reimplantation, it will be necessary to assess whether a similar device is indicated, or whether it should be different, generally of less complexity or "downgrade" [31, 34].

If the indication for a new implant is confirmed, it should be deferred until the infection is controlled, if possible after obtaining negative blood cultures for at least 72 hours after the explant. In patients dependent on cardiac stimulation, who require temporary stimulation, an electrode ipsilateral to the explant will be used, through a venous access different from that used by the previous one. To prevent manipulations due to instability of the electrode, with a greater risk of contamination, the use of an active fixation electrode connected to an external battery and fixed to the skin is recommended, until it is safe to implant the definitive device [6, 34].

If a device with electrodes (RTC, bicameral pacing) is indicated, it should be implanted initially on the contralateral side. If not, implantation of an epicardial pacemaker or a MicraTM Transcatheter Pacing System (TPS; Medtronic, Minneapolis, MN, USA) femoral leadless pacemaker may be considered. The lead-free pacemaker avoids the possibility of a primary infection of the generator pocket and thanks to its smaller overall surface area and the progressive encapsulation once implanted (**Figure 11**), it would theoretically present less risk of secondary infection in the presence of systemic infection [35].

In the case of patients with an indication for defibrillator reimplantation, without the need for permanent pacing, resynchronization or anti-tachycardia therapy, the implantation of a subcutaneous defibrillator should be considered (the infection rate requiring removal of the device is 2.4% after 3 years of follow up) (**Figure 12**) [36].

Isolated pocket infection	10–14 days post-extraction
-Systemic symptoms	
Empirical treatment/ - blood cultures	-Vancomycin: 30–60 mg/kg/d iv in 2–3 doses
Directed at MR * CoNS and S Aureus	-Alternative: Daptomycin 8–10 mg/kg iv od
+ Systemic symptoms	+/−
(Empirical treatment/ - blood cultures)	-Cephalosporin: standard dose
For additional Gram- coverage	-Alternative: Gentamicin** 5–7 mg/kg iv od
After culture result	Flucloxacillin: 8 g/d iv in 4 doses
If sensitive Staphylococcus	Alternative: 1st generation cephalosporin standard dose
	Partial oral treatment often used
Systemic infections without vegetation on leads or valves +/-pocket infection	
	4 weeks post-extraction_(consider 2w if -blood_cultures)
Empirical treatment/ - blood cultures	Vancomycin: 30–60 mg/kg/d iv in 2–3 doses
Directed at MR Staphylococci and Gram- bacteria	Alternative: Daptomycin 8–10 mg/kg od
	+
	Cephalosporin: standard dose iv
	Alternative: Gentamicin 5–7 mg/kg iv o d
After culture result	Flucloxacillin: 8 g/d iv in 4 doses
If sensitive Staphylococcus	Alternative: 1st generation cephalosporin standard dose
Systemic infections with vegetation on leads or valves +/-pocket infection	
	Lead vegetation: 2 weeks post-extraction (total 4w except S Aureus)
	Native valve vegetation: 4 weeks post-extraction
	Prosthetic valve vegetation: (4-) 6 weeks post-extraction
Empirical treatment/ - blood cultures	Vancomycin:30–60 mg/kg/d iv in 2–3 doses
	Alternative: Daptomycin 8–10 mg/kg od
	+
	Cephalosporin: standard dose
	Alternative: Gentamicin 5–7 mg/kg iv od
Adjust to culture result according to ESC endocarditis guidelines 2015	
If prosthetic valve and staphylococcal infection:	Add Rifampicin after 5–7 days: 900–1200 mg/day orally (or iv) in 2 doses
*adapt to local resistance	
**adjust according to kidney function	od: once day

Table 1.
IE-CIED Empirical antibiotic regimens recommended.

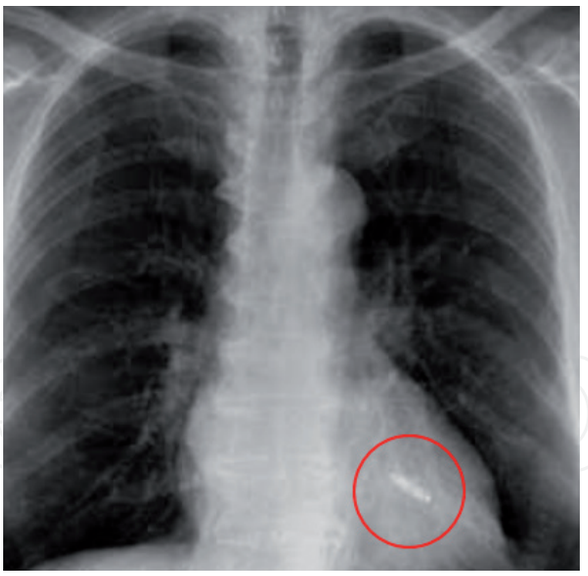

Figure 11.
MICRA.

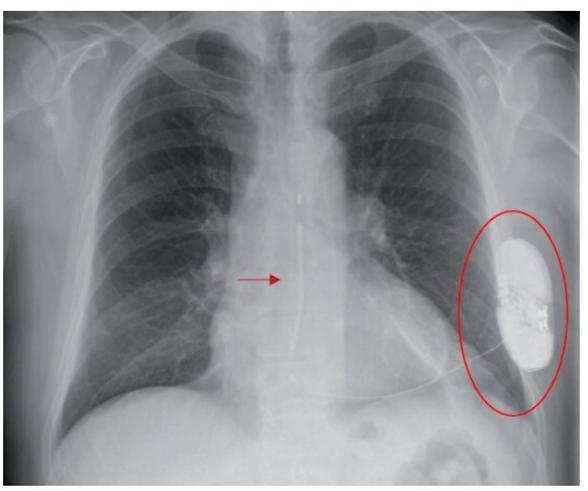

Figure 12.
Subcutaneous defibrillator.

2.10 Prognosis

CIED infection is a serious pathology with a 30-day hospital mortality estimated between 4.6–11% (despite the heterogeneity of the studies) [37]. Studies that included only patients with CIED -IE reported high mortality: 24.5–29% with follow-up periods of up to a year and explant rates of 80–100% [6]. It is associated with systemic infection and sepsis, complications derived from extraction and reimplantation and the own comorbidities of the patients. Long-term mortality is between 1.5 and 2.4 times higher than in CIED carriers without infectious complications. Mortality is high during the first year following CIED infection, but many deaths are not infection related. Abnormal renal function is the most consistently identified risk factor for mortality. Failure to remove an infected device is associated with relapse and mortality. CIED-IE has a higher mortality than localized generator pocket infection.

For all these reasons, infections in patients with CIED and especially those with suspected or confirmed systemic involvement should be considered a medical emergency, that must receive a multidisciplinary approach by a team

made up of specialists in infectious diseases and microbiology, interventional cardiologists, electrophysiologists, clinicians and experts in multimodal imaging, surgeons and experts in other imaging techniques such as radiologists and nuclear medicine [38].

3. Conclusions

Infective endocarditis is a prevalent pathology in developed countries. Its spectrum is changing and its association with intracardiac devices has increased disproportionately in recent decades. Affected patients are especially vulnerable to complications due to both their cardiac and extra-cardiac pathologies and their frequent contact with health-related procedures. Most of these infections are caused by S Aureus and CoNS, many times carriers of antibiotic resistance and must be treated early and aggressively by multidisciplinary teams. We must be careful in the indication and choice of devices and exquisite in the prevention of infections since once established, therapeutic failure entails high morbidity and mortality.

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Conflict of interest

The author declares no conflict of interest.

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