



Microbiological Background: Biofilm, Culturing, and Antibiotics

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2.1 Epidemiology and Clinical Presentation

Cardiovascular implantable electronic device infections (CIEDI) are increasing worldwide. In the United States (USA), according to the Nationwide Inpatient Sample database, the number of hospitalized patients with CIEDI increased from 5308 in the year 2003 to 9948 in 2011 [1]. During the same time period, the incidence of CIED infection increased by 210% [2]. Several factors underlie this increasing trend in CIEDI prevalence. First, with the broadening of indications, the number of cardiovascular implantable electronic device (CIED) implants is growing year by year. Second, the improved life expectancy has led to a dramatic increase of number of fragile patients treated with CIED implant, including elderly, immunocompromised, and comorbid patients [3, 4]. In addition to morbidity for patients, CIED infection has been linked to increase of both short-term and long-term mortality [5, 6] and to a significant increase of healthcare costs [5] (*for a complete perspective on CIEDI epidemiology, costs, and outcomes, see also Chap. 1*).

Commonly, CIEDI should be distinguished as pocket-related infections (Fig. 2.1) or CIED-related endocarditis (Fig. 2.2). In fact, these two groups of infections show complete different clinical presentation, management, and outcome [7, 8]. Another distinctive feature of these two groups of infection is the prevalence. A retrospective review of 189 cases of patients with CIED-infections admitted to Mayo Clinic Rochester from 1991 to 2003 revealed that generator pocket infection constituted the 69% of cases, while device-related endocarditis was diagnosed in 23%. In another study conducted at the Cleveland Clinic, among 412 cases of CIED infections, 59% involved only the device pocket, whereas 41% of cases had an endovascular involvement [3]. The different presentation may be related to the time of onset

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Fig. 2.1 Cardiovascular device pocket infection. (a) Normal CIED pocket. (b) Infection with pocket decubitus and spillage of purulent material. (c) Overt infection with solution of continuity of the skin and generator exposure



Fig. 2.2 Cardiovascular device lead infection. On the left the echocardiography examination shows a big vegetation on CIED lead. On the right the pieces composing the vegetation after lead extraction

after the index procedure. In fact, a study evaluating early- versus late-onset infection found that the former were more likely to be pocket infections as compared with the latter [9].

A different clinical manifestation of CIEDI is the presence of *Staphylococcus aureus* bacteremia (SAB) without evidence of CIED involvement. A prospective study suggested that the overall prevalence of CIEDI in patients presenting with SAB may be as high as 45% and may reach 71% of cases when SAB occur within 1 year after device placement [10]. In 60% of these patients, no local signs or symptoms are commonly identified [10]. Among all cases of SAB occurring in CIED carrier, the risk of underlying a CIED infection is higher in the case of carriers of permanent pacemaker (vs. defibrillator), presenting a more prolonged bacteremia and those with history of repeated CIED procedures [11]. According with this data,

any patients carrying a CIED and developing a SAB should undergo extensive evaluation that includes follow-up blood cultures, echocardiography, and screening for septic embolization with either computed tomography or fluorodesossiglucose-positron emission tomography [12–16]. Similar studies conducted in patients with CIED developing gram-positive bacteremia, other than SAB, found similar results in terms of prevalence of CIEDI [17]. By contrast, an association between gram-negative bacteremia and either endocarditis or pocket infection was not confirmed [18].

2.2 Microbiology: Available Methods and Etiology

A key point for a correct management of CIEDI is the achievement of a microbiological diagnosis. The main component of a successful microbiological diagnosis relies on correct sampling and good microbiological methods (Table 2.1). Sterile technique for sampling, fast submission to the microbiology laboratory, and seeding of the removed hardware are essential to optimize the management of CIEDI. Different studies compared the diagnostic yields of blood cultures, pocket swab, and hardware culturing after removal. In a Japanese study of 208 patients with CIEDI, blood culture, lead culture, and swab culture were positive in 27%, 81%, and 73% of cases, respectively [19]. In an older study conducted in Italy and including 118 lead extractions, 87% of which due to infection, lead cultures were positive in 92% and 100% in patients presenting with decubitus/fistula or local acute infection, respectively. Blood cultures were positive in 58% of patients presenting with sepsis. Despite concordance between blood cultures and lead cultures was high especially in the case of *S. aureus* isolation, concordance between lead or tip and pocket cultures was less satisfactory [20].

Table 2.1 Pros and cons of different microbiological methods for etiological diagnosis in CIED infection

Method	Pros	Cons
Pocket swab culturing	Easy to perform	Low diagnostic performance Possible misleading results
Intraoperative samples culturing	Most reliable sample for etiological diagnosis	More difficult to perform, require device removal Turnaround time
Blood cultures	May suggest endocarditis May help for establish re-implant timing	Several localized infection may show negative blood cultures
Sonication	Higher sensibility than standard techniques Sampling site is directly the surface of the device	Lack of availability of sonicator in most centers
Broad-range sequencing of bacterial DNA	Higher sensitivity than standard techniques	Risk of false-positive results Lack of studies on CIED infection

A novel microbiological method for device-related infection is the use of sonication. This technique is mainly applied in the management of prosthetic joint infection, but it may be used in any device-related infection [21]. Sonication is the process of converting an electrical signal into a physical vibration that can be directed toward a substance. In microbiology, and more specifically in device-related infections, the use of low-intensity ultrasounds to remove biofilms from hardware and subsequently fluid culture is a novel promising method to improve sensibility of cultural methods. The main advantages of sonication are that the sampling site is directly the surface of the device allowing the detection of larger number of microorganisms. In this case, additional susceptibility test may be performed in different colonies consenting the detection of hetero-resistance, particularly for *S. aureus* strains [22]. In a study enrolling 42 patients undergoing lead extraction for non-infectious cause and 35 patients with CIED infection, use of sonication was compared with conventional cultures. In the group of patients with infection, significant bacterial growth was observed in 54% of sonicate fluids, significantly greater than the sensitivities reported for pocket swab culture (20%), device swab culture (9%), or peri-device tissue culture (9%) [23].

Broad-range sequencing of bacterial 16S ribosomal DNA represents an alternative approach for establishing the underlying organism in device-related infections. Unfortunately, it has been poorly studied in CIEDI. In studies performed in patients with infective endocarditis, the use of broad-range 16S rDNA polymerase chain reaction (PCR)-sequencing for molecular diagnosis shows that heart valve PCR may improve microbiological diagnosis in up to 20% of patients and may be associated to high sensitivity and specificity [24, 25]. Advantages of molecular methods rely on rapid turnaround time and high sensitivity also in patients previously exposed to antimicrobial treatment which, in turn, may be paradoxically a limitation. In fact, PCRs are exposed to contamination and may result in false-positive results. Contamination can occur through environmental DNA or from PCR reagents despite using nucleic acid-free compounds. False-positive PCR findings can be due to circulating cell-free DNA from dead bacteria or fungal DNA in the absence of infection—the so-called DNAemia rather than a true bacteremia or fungemia [26, 27]. In addition, an infection successfully controlled by the immune system or by an efficient anti-infectious therapy will release pathogenic DNA that can persist several days in the blood.

Another limitation of conventional cultures is the poor concordance between different microbiological methods as demonstrated by different studies [20]. More specifically, acceptable concordance was found for isolation of *S. aureus*, gram-negatives, mycobacteria, and fungi. However, unsatisfactory concordance was found especially for other common skin contaminants [19, 20]. Additionally, colonization of device may occur without clinical relevant infection. In a study including 115 lead extractions for non-infectious cause, devices were analyzed with standard swab cultures and device sonication. Of the 115 devices analyzed, 44 (38%) resulted positive in sonication fluid cultures and 30 (27%) in swab cultures. Most of the pathogen found were CoNS and *Propionibacterium acnes* [28].

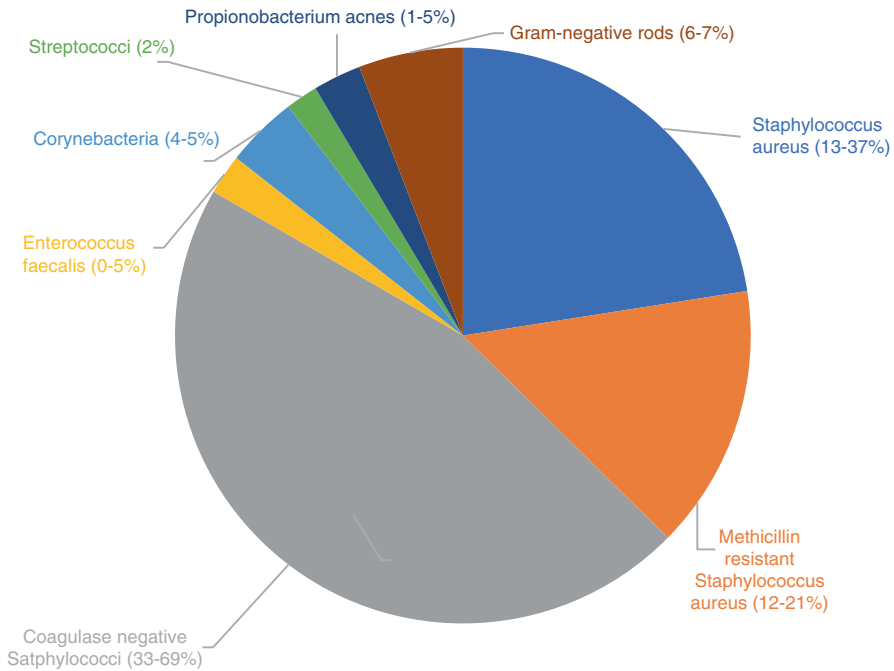


Fig. 2.3 Etiology of cardiovascular implantable electronic device infection. Graphic shows the most common etiology of cardiovascular device infections and their relative prevalence. The risk of biofilm for each pathogen is reported in the graph

Detailed bacterial etiology of CIEDI is summarized in Fig. 2.3. Commonly gram-positive bacteria are responsible for more than 90% of infections. Coagulase-negative staphylococci (CoNS) are cultured in 33–69%. Among CoNS, *Staphylococcus epidermidis* is found in 70–81% of cases. *S. aureus* is the second most important pathogen, being found in 13–27% of cases. Lastly, negative cultures may occur in about 9–13% of cases [4, 19, 29–31]. Few studies compared microbiology of early- versus late-onset infection defined as infection diagnosed 1 year after last CIED-related procedure (for non-infectious cause). In the study of Welch et al., *S. aureus* was found more frequently in early infection, and by comparison CoNS were more frequent in late infection [32]. Similarly, in the study of Jan et al., *S. aureus* was isolated in 11.5% of early infection and in 6.9% of late infections [33]. This finding is not surprising as early device-related infections are commonly caused by more virulent strains. In fact, early infections are more likely to present with pocket erythema, swelling, and pain, whereas late infections were more likely have pocket erosion and valvular vegetations [32]. Late infections are also more likely to be caused by methicillin-susceptible strains [33]. Studies comparing etiology of pocket infection with CIED-associated endocarditis did not report significant differences [33].

Other emerging pathogens should be always kept in mind when dealing with CIED infection. Even if very rare, rapidly growing mycobacteria are increasingly reported and may be associated to outbreaks in the setting of major heart surgery or electrophysiology. In a recent review of 32 cases reported in the literature, the most common mycobacteria associated to CIED infection belong to the *Mycobacterium fortuitum* group followed by *Mycobacterium abscessus*, *Mycobacterium smegmatis*, and *Mycobacterium chelonae* [34–36]. All these pathogens are characterized by challenging diagnosis and treatment as may not be detected by standard cultures or require prolonged incubation. Correct identification of these agents is relevant for effective treatment since it entails long-term antibiotic treatment in addition to device removal [34].

2.3 Role of Biofilm

Biofilm development is an ancient prokaryotic adaptation [37] and represents a mode of growth that allows bacteria to survive in hostile environments and to colonize new niches by various dispersal mechanisms [37]. Biofilm is a multicellular community held together and embedded in a hydrated matrix of extracellular polymeric substances [38]. The formation of biofilm occurs when prokaryotic cells encounter a surface such as a foreign body or a medical device [39]. Classically the formation of biofilm can be divided into different stages that include adhesion to the surface, growth of a heterogenous multilayer slime, and detachment [Fig. 2.4]. Both

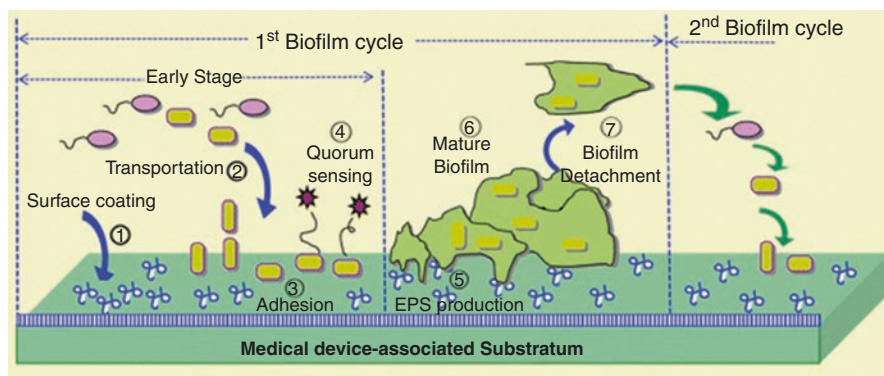


Fig. 2.4 Biofilm formation on medical devices. At first, the surface of medical devices is coated with a layer of proteins and glycoproteins (1), and then cellular colonization takes place (2) with adhesion to the surface of the coated medical device (3) and subsequent release of signaling molecules with increased up-regulation of transcription due to the high concentration of (“quorum sensing”) (4). This results in an increased production of extracellular polymeric substance (5) and progressive maturation of biofilm (6). After its formation, biofilm parts may detach and be carried by bloodstream, possibly leading to secundarism of infection (7) (Reproduced from Zhang, Z, Wagner, V, *Antimicrobial Coatings and Modifications on Medical Devices*, Edited by Springer, 2017, page100 with permission)

and non-mutually exclusive genetic predisposition and environmental adaptation are involved in this process.

There are several hypotheses to explain the benefit of biofilm formation and its association with surfaces, such as devices. Surfaces offer a stable environment to grow, and biofilm formation offers the opportunity to defend from environmental challenges such as UV exposure [40], acid exposure [41], and phagocytosis [42]. In addition, biofilm growth is associated to antimicrobial tolerance for several reasons. First, cells included in the biofilm are metabolically heterogeneous, comprise nutritionally variant colonies, and therefore can be hardly detected through conventional cultures [43]. Second, metabolically variant colonies and more specifically cells that result in a stationary-phase dormancy may be unaffected to antibiotic therapy [44]. Third, the diffusion of antimicrobial agents in the matrix is impaired, and therefore the proportion of drug that may reach the cell is reduced. Similarly, biofilm cells may produce efflux pump or other antibiotic-degrading enzymes. Factors that may influence the antibiotic activity are cell density and biofilm age which are strongly correlated [45]. Studies on *Pseudomonas aeruginosa* showed that the activity of antimicrobials is greater in younger cells than older cells, especially for beta-lactams [46, 47]. Similarly, a meta-analysis of different studies showed that the efficacy of antimicrobials in biofilm-related infection is reduced for large or dense biofilm [45]. All of these factors link the production of biofilm with clinical failure or relapse when attempts of conservative treatment with antimicrobial therapy alone were tested.

2.4 Antibiotic Treatment of CIEDI

As stated in the previous paragraph, the formation of biofilm, which is common in device-related infection, hampers any conservative approach consisting in antibiotic treatment alone. Whenever feasible, device removal should be primarily considered for CIEDI. Attempts of conservative treatment can be considered only when there are strong contraindications to device removal. Choice of antibiotic treatment should be based on clinical presentation and diagnosis of CIEDI. As previously mentioned, CIEDI should be divided into pocket-related CIEDI and CIED-related endocarditis. Beyond, these two classical presentations, several patients may exhibit bacteremia without underlying clinically significant signs of device involvement. In observational studies of patients having a CIED and presenting SAB without clinical signs of device pocket infection, an actual CIED involvement was found in 34–40% of cases [10, 11]. A higher proportion of CIEDI are reported in the case of CoNS bacteremia [17]. In accordance, a different therapeutic management for each of these three situations should be considered. Clinical severity should also be considered in order to select the correct timing of antibiotic administration. Lastly, duration of antimicrobial treatment is strongly correlated by therapeutic approach, being different in conservative treatment or when device removal is carried out. Figure 2.5 represents a possible diagnostic and therapeutic algorithm for pocket-related infection, CIED endocarditis, and patients with SAB.

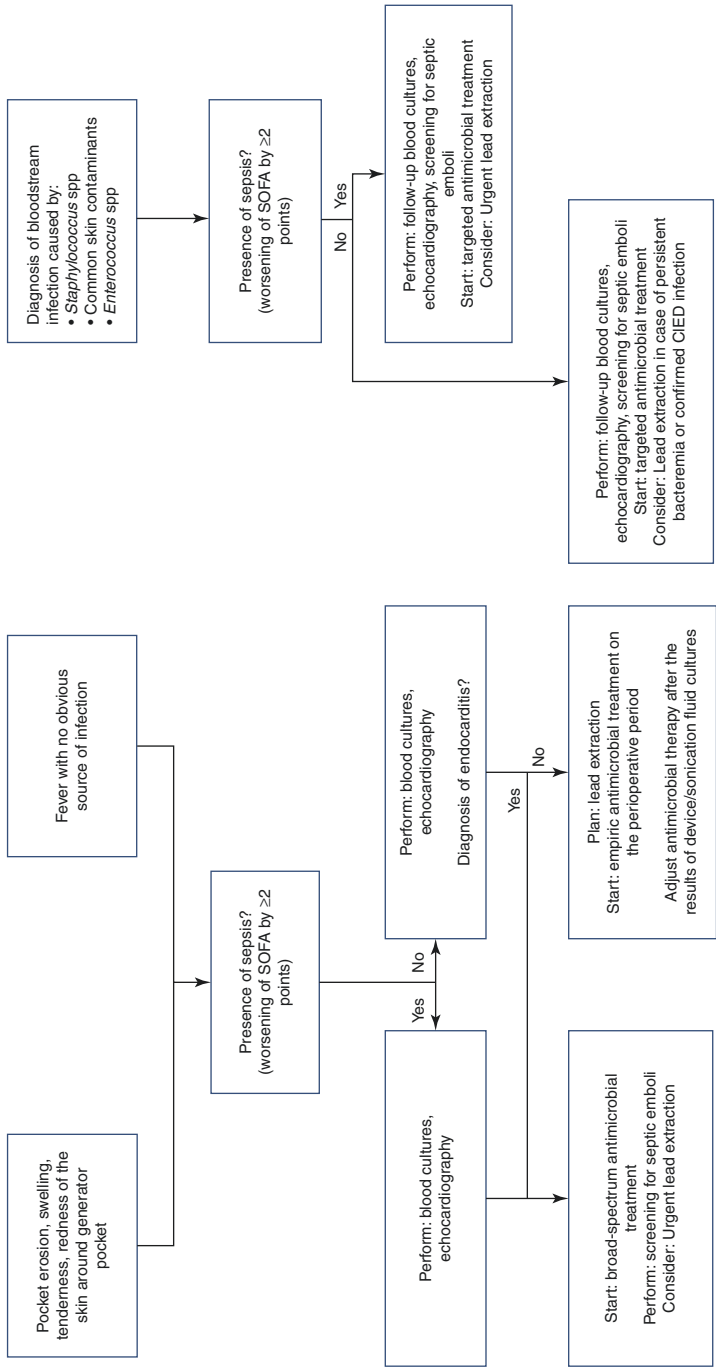


Fig. 2.5 Common clinical presentation of cardiovascular implantable electronic device infection and its medical management. CIED infection management algorithm. Suspect of CIED infection may be posed for the evidence of local signs of pocket infection/fever of unknown origin (left side of the diagram) or by the evidence of positive blood cultures. An assessment of the risk of sepsis, or sepsis severity score worsening, should be performed. The presence of endocarditis should be also investigated (echocardiogram, blood cultures), and the need of screening for septic emboli must be decided accordingly. Lastly, the need of lead extraction should be assessed. *CIED* cardiac electronic implantable device, *SOFA* Sequential Organ Failure Assessment (*SOFA*) Score

Based on microbiological data, empirical treatment should include coverage for methicillin-resistant *S. aureus* (MRSA), especially in area with high prevalence of MRSA. Vancomycin is considered the treatment of choice for MRSA infection in most cases. Although superiority of other drugs versus vancomycin was poorly demonstrated in clinical trials, observational studies suggest that alternative regimens could be associated with improved outcome in specific situations [48, 49]. More specifically, with the spread of strains with reduced susceptibility to vancomycin, treatment failure with this drug was reported [50]. In a meta-analysis including 22 studies, higher mortality was reported in infections caused by MRSA strains with vancomycin MIC ≥ 2 mg/mL, especially in the case of BSI [51].

Daptomycin is a lipopeptide characterized by high bactericidal activity and good biofilm penetration. In one case-control study of patients with *S. aureus* bacteremia, use of daptomycin was associated to improved outcome compared to vancomycin [48]. Daptomycin activity seems to be enhanced by combination with beta-lactams, fosfomycin, or rifampin and using higher dosage, especially in device-related infection. Dosages of daptomycin have been recently debated. Daptomycin exhibits a concentration-dependent bacterial killing. That means that higher dosage is associated to higher antimicrobial activity and daptomycin resistance [52, 53]. In a study of patients enrolled in the CORE database (a multicenter retrospective register of patients treated with daptomycin), the efficacy of high-dose daptomycin (≥ 8 mg/kg/day) was evaluated. The clinical success rate for MRSA infection was 83% among patients receiving high-dose daptomycin [54]. Similarly, in a large multicenter retrospective study including patients treated with high-dose daptomycin as salvage treatment after failing vancomycin therapy, clinical and microbiological success was assessed in 84% and 80% of cases, respectively [55]. In a single-center study focused on 25 cases of CIED infection, daptomycin was administered with a median dose of 8.3 mg/kg. Clinical cure was observed in 80% of cases and microbiological success in 92% of cases [56].

Combination treatment of vancomycin and daptomycin with beta-lactams or other drugs is a matter of debate as well. Some authors suggest that activity of both vancomycin and daptomycin may be enhanced by use of a companion drug. In a pilot randomized trial of 60 patients, vancomycin plus flucloxacillin was associated to a shorter duration of MRSA bacteremia compared with vancomycin alone [57]. In addition, a synergy of daptomycin with beta-lactams, rifampin, and other drugs were observed in both in vitro studies or limited clinical experiences [58–62].

Enterococcus spp. may be also an important pathogen related to CIED infection or CIED-related endocarditis. The majority of enterococcal infection are caused by *Enterococcus faecalis* which is commonly susceptible to ampicillin. Ampicillin alone however may be associated to clinical failure, and therefore the combination treatment with gentamycin or ceftriaxone should be considered as first-line treatment for patients with CIED endocarditis caused by *E. faecalis*. In the case of *Enterococcus faecium*, vancomycin or teicoplanin should be administered. Recently, vancomycin-resistant enterococci (VRE) have emerged as an important threat. The options for treating vancomycin-resistant enterococcus infections are linezolid, daptomycin, or tigecycline. Well-designed comparative studies are not available to

assess the best treatment for VRE. However a meta-analysis of 10 retrospective studies comparing outcome of patients treated with linezolid or daptomycin for VRE bacteremia found an increased risk of mortality in patients receiving daptomycin [63]. More recently a US nationwide retrospective cohort study comparing daptomycin and linezolid for the treatment of VRE bacteremia found a significant higher rate of treatment failure among patients receiving linezolid [64]. This controversy in results of observational studies may be related to the dose of daptomycin used. In fact, a study comparing different dosages of daptomycin demonstrated a clinical benefit of higher dose of daptomycin (≥ 9 mg/kg) compared with low-dose daptomycin for the treatment of bacteremia caused by VRE [65].

Duration of treatment may depend on the baseline clinical picture. Patients with local infection with negative blood cultures and negative echocardiography may be treated with a 7- to 10-day antibiotic treatment after device removal. In the case of *S. aureus* bloodstream infection, a course of 2–4 weeks of antibiotic treatment should be ensured. Lastly, patients with endocarditis should receive at least 4–6 weeks of treatment [8, 66, 67]. Timing of new device implantation may depend on urgency of pacing and underlying patient condition. The commonest and most safe procedure is to perform a 2-stage procedure consisting in device and lead removal, temporal pacing, and new definitive device insertion. In this case, blood cultures should be negative for at least 72 h before reimplantation [7, 8]. Notably, in a study evaluating 68 patients treated with 1-stage removal and contralateral implant, no relapse of infection involving the new device was detected after a long-term follow-up [68]. However, larger studies should be performed to confirm the safety of a similar approach.

When patients present major contraindication to device removal, usually very old and fragile patients, infection management is more challenging, and the outcomes are poor. In most of the cases, chronic suppression therapy is necessary [7, 8]. In a retrospective study, among 660 cases of CIED infection, 48 patients were treated with chronic suppression antibiotic therapy. The median age was 78 years, and the most preferred drugs were trimethoprim-sulfamethoxazole, penicillin, and amoxicillin. The estimated median overall survival was 1.43 years, and 18% of survivors developed relapse within 1 year [69].

2.5 Prevention

Prevention of CIEDI is extremely important since it is associated with high mortality and increased healthcare costs [5]. Risk factors for CIEDI have been described in the literature. Older and comorbid patients, such as those with congestive heart failure, malignancies, or renal failure, and those receiving corticosteroids are at risk to develop CIEDI. Prevention should include, whenever possible, the reduction of patients' modifiable risk factors including control of blood sugar levels, reduction of international normalized ratio (INR), and discontinuation of steroids [70–73].

One key factor of CIED infection is microbial contamination during device placement. This can occur (a) during manufacture or packaging, (b) before CIED implantation, (c) during CIED implantation, (d) secondary to surgical site infection, (e) via hematogenous seeding from a distant site (especially as a consequence of a SAB) [66, 70], or (f) via contamination after erosion through the skin [70]. Microbial contamination during manufacture is rare but should be considered when there is an outbreak of infection caused by the same organism especially when an environmental, uncommon organism is involved. Even if contamination of CIED during manufacture or packaging is poorly reported in literature, a recent outbreak of *Mycobacterium chimaera* infection was reported in several healthcare facilities performing major heart surgery. In this case, contamination during manufacture of a heater-cooler device used for cardiac surgery was found after extensive investigation [74]. A second important pathophysiological pathway to CIED infection is contamination during implantation or as a consequence of skin erosion or surgical site infection. According to this pathway, inpatients receiving emergent procedure with longer time of implant can be considered at higher risk for infection when compared with outpatients undergoing shorter elective procedures. In this scenario common skin contaminants such as CoNS, *P. acnes*, and diphtheroids are involved [75, 76]. In addition, subsequent device revisions have been linked to augmented probability of infection confirming that multiple manipulation confers higher opportunity for contamination [73, 77, 78]. Strategies to prevent CIED infection according with this mechanism are listed in Table 2.2 (for a complete review of available strategies for CIEDI prevention, see also Chap. 11).

Table 2.2 Main strategies to prevent cardiovascular electronic device infections

Risk factor	Prevention strategies
<i>Staphylococcus aureus</i> carriage status	Screen all candidates to CIED implant with nasal swab. <i>S. aureus</i> carriers should receive preoperative nasal mupirocin ointment and be washed with chlorhexidine
Pocket hematoma	Reduce/stop anticoagulants or use compression device to prevent post-procedural pocket hematoma [79]
Skin preparation	Use of chlorhexidine should be preferred to povidone-iodine preparation despite data on CIED implantation is lacking [80]
Antimicrobial prophylaxis	Antimicrobial prophylaxis with anti-staphylococcal drug should be administered during the procedure. Prolonged duration of antimicrobial is not associated to a lower incidence of CIED infection [81, 82]
Use of antimicrobial envelope	Comparative studies suggest that antimicrobial envelope such as TYRX-A bio-absorbable envelope may reduce the rate of CIED infection; however none of these studies are randomized controlled trials. Considering the high costs of the envelope, further studies are needed to suggest its use [83]

Table reports the main precautions to be observed in order to minimize the risk of future cardiovascular electronic implantable device (CIED) infections before CIED first implantation (preparation of the patient) and at the moment of the procedure

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