Infections of Cardiac Implantable Devices

A Comprehensive Guide

Igor Diemberger
Giuseppe Boriani
Editors

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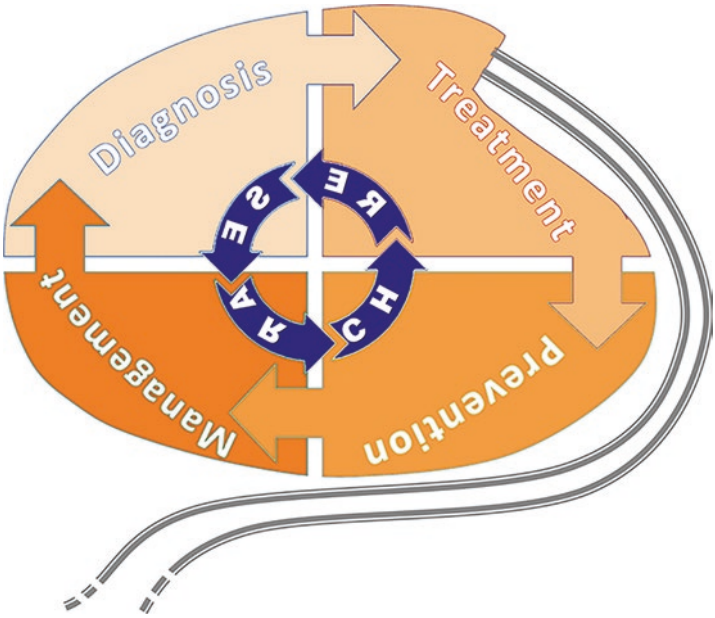

- The battle against CIED infections starts well before extraction of the implanted hardware and antibiotic therapy, and it does not end with them. Teamwork and resilience are the keywords to succeed and each part of the process presents several reflections into the others... -

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Contents

1 Infection of Cardiac Implantable Electrical Devices: An Emerging Epidemiological Issue

Giuseppe Boriani and Marco Vitolo

1.1 Cardiac Implantable Electronic Devices: Trends in Implantation Rates

In the last five decades, the use of cardiac implantable electronic devices (CIEDs), which include permanent pacemakers (PMs), implantable cardioverter-defibrillators (ICDs), and cardiac resynchronization therapy (CRT) devices, has dramatically increased [1]. It is difficult to have a complete assessment of the number of CIEDs currently implanted all over the world, but a worldwide survey undertaken for calendar year 2009 showed in all countries an increase in implant numbers compared to a similar assessment performed 4 years before [2]. In this survey performed among 61 countries (25 from Europe, 20 from the Asia Pacific region, 7 from the Middle East and Africa, and 9 from the Americas), an overall number of 1,002,664 PM implants, (737,840 new implants and 264,824 replacements) and 328,027 ICDs (222,407 new implants and 105,620 replacements) was collected [2]. The USA had the largest number of cardiac pacemaker implants (225,567) and Germany the highest number of new PM implants per million population (927) [2]. Also for ICDs and devices for cardiac resynchronization therapy, the largest amount of implants was reported for the USA (133,262) with 434 new implants per million population. Also for biventricular ICDs, which showed an important increase in implants as compared to the previous survey, the largest number of implants was found in the USA (49,255 devices in 2009). A systematic review that analyzed CIED implant rates in Europe taking into account 58 studies published in the years 2004–2014 found an important rise over time in CIED implants with large geographic differences [3]. The ratio between the regions with the highest and lowest implant rates within the same

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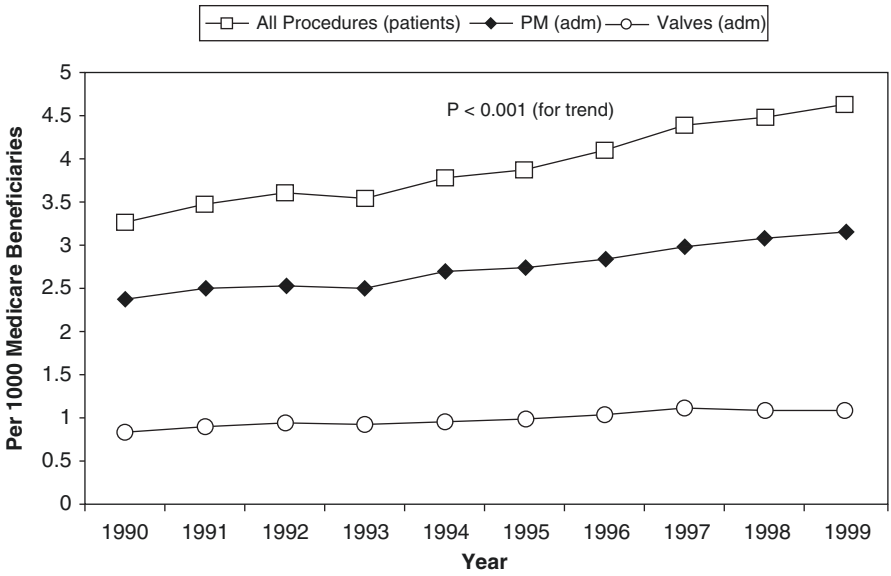

Fig. 1.1 Rates of prosthetic valve/cardiac device implantation and infection: 1990–1999 (Cabell CH et al., Am Heart J 2004;147(4):582–6)

country ranged between 1.3 and 3.4 for pacemakers and between 1.7 and 44.0 for defibrillators. The ratio between the countries with the highest and lowest implant rates ranged between 2.3 and 87.5 for pacemakers, between 3.1 and 1548.0 for defibrillators, and between 4.1 and 221.0 for resynchronization therapy devices. Implant rate variability appeared to be influenced by healthcare, economic, demographic, and cultural factors [3]. Nevertheless, the majority of the data available so far on device implantation rates come from retrospective studies or hospital discharge registries, and for this reason they may have some limitations. In the last 15–20 years, guidelines have expanded the indications for CIED implantation leading to a significant increase in their use [4, 5]. Furthermore, the improvement in survival among patients with heart disease who can develop the indication for an implanted cardiac device contributed to the increase in the number of CIED implants [6, 7]. An analysis of claims files from the Health Care Finance Administration for Medicare beneficiaries between 1990 and 1999 found an increase of cardiac device implantation rate of 42%, from 3.26 procedures per 1000 to 4.64 procedures per 1000 Medicare beneficiaries (Fig. 1.1) [8]. The implantation rate for PPMs and ICDs has increased by 19% and 60%, respectively, in the USA based on recent data report [9]. Additional data that support the increase of CIED implantations come from the National Hospital Discharge Survey (NHDS) that records data on approximately 1% of all discharges from nonfederal hospitals in the USA. Between 1999 and 2003, NHDS reported a 49% increase in the number of new CIED implantations, and, after 2003, a 12% increment of implantation rates (from 199,516 in 2004 to 222,940 in 2006) was also found [10]. An additional analysis based on administrative data at discharge from

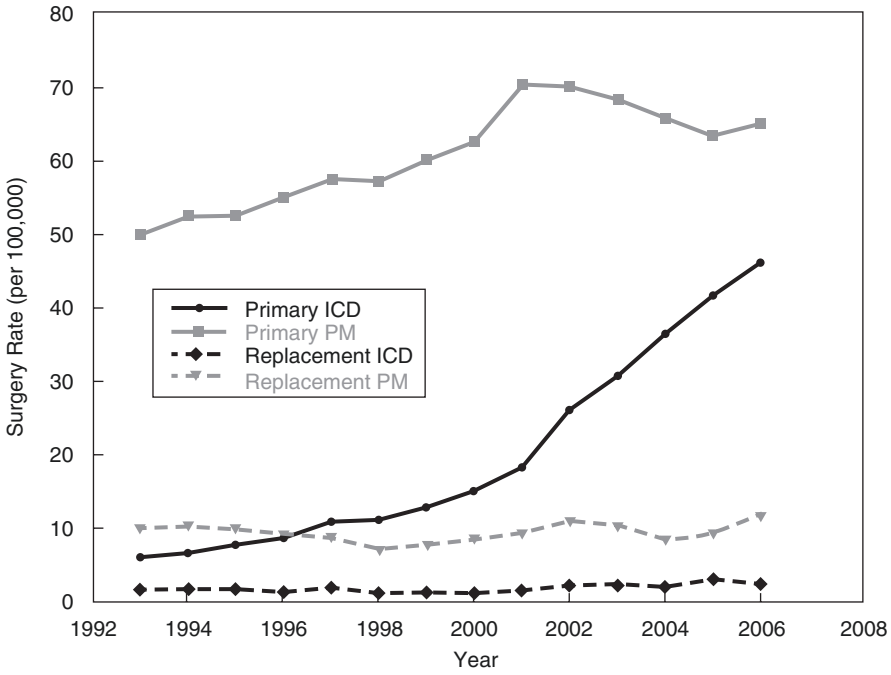

Fig. 1.2 The rate of operations per 100,000 persons of population for pacemakers and implantable cardioverter-defibrillators in primary procedures and replacements (From Kurtz SM et al., Pacing Clin Electrophysiol 2010;33(6):705–11)

1993 to 2006 showed that in the USA 2.4 million patients received a primary PM and 0.8 million received an ICD, while there were 369,000 PM replacements and 74,000 ICD replacements [11]. The rate of operations per 100,000 persons of population for pacemakers and implantable cardioverter-defibrillators in primary procedures and replacements. The marked increase in the rate of implants per 100,000 persons of population for ICDs is shown in Fig. 1.2 [11].

Greenspon et al. reported between 1993 and 2008, in the USA, an overall CIED implantation increase of 96% (average of 4.7% per year), and it was mainly due to ICD implantation resulting in an increase in implantation rates of 504% (Fig. 1.3) [12].

1.2 Epidemiology of CIEDs-Related Infections

Despite of the use of antibiotic prophylaxis at the time of device implantation, rates of device-related infection increased in recent years, and cardiac implantable electronic device infection is a more and more serious problem with high morbidity and mortality. It is important to underline that the rate of CIED infections increased faster and disproportionate as compared to the rate of CIED implantations. Possible

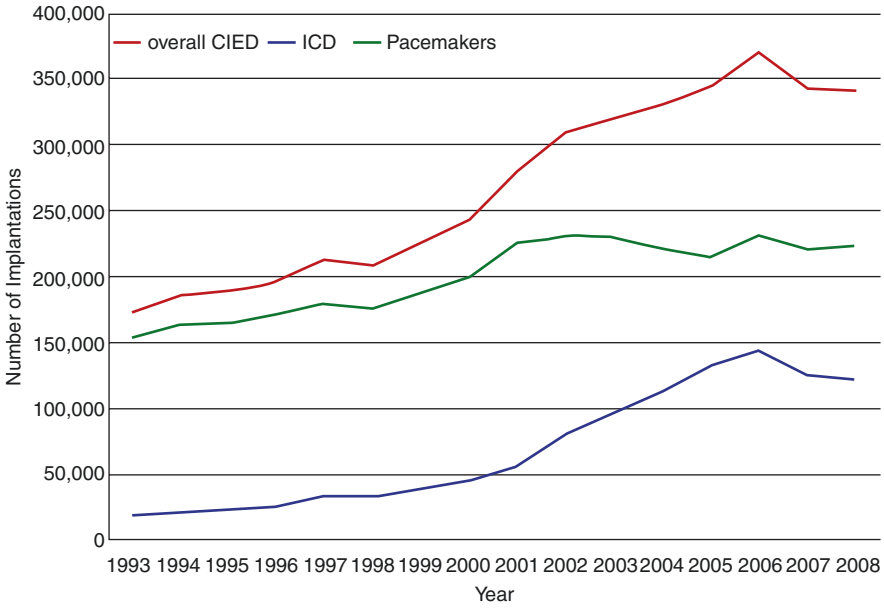

Fig. 1.3 Number of PM and ICD Implantations from 1993 to 2008 (From Greenspon AJ et al., J Am Coll Cardiol 2011;58(10):1001–6)

explanations for such a disproportionate rise in CDI rate are broader indications for CIED implantation, the growth in the number of complex procedures such as ICD and CRT implantations, and the increase in the prevalence of coexistent comorbidities among CIED recipients [13]. The rates of cardiac pacemaker implantations as well as the age distribution of populations have shown a series of changes in the populations. We are experiencing nowadays the so-called demographic transition in which the decline in death rate and birth rate may change the age structure. The imbalance between fertility rates and life expectancy leads to an increase in median age in the population especially in developed countries. Geriatric population, and more generally people aged 65 and over, is rapidly growing counting today 8.5% of people worldwide (617 million). Future predictions estimate that this percentage will rise up to 17% of the world's population in 2050 (1.6 billion) (Table 1.1) [14].

In this scenario, noncommunicable diseases, also known as chronic diseases, are becoming the major causes of death and contributors to the burden of disease and disability. The rise in morbidity of device implantations could be related to a higher prevalence of concurrent diseases including CKD and diabetes mellitus in CIED recipients; these comorbidities may facilitate device-related infections because of a weakened immune system as commonly reported in patients with diabetes mellitus and renal insufficiency. It is known that hyperglycemia favors the colonization and growth of a variety of organisms (i.e., *Candida albicans*), and many common infections are more frequent and severe in diabetic patients. Furthermore, some rare infections are observed almost exclusively among the diabetic population. This is

Table 1.1 Population aging: number and distribution of persons aged 60 years or over by region, in 2017 and 2050

	Population age +60 (millions)		Percentage change between 2017 and 2050
	2017	2050	
World	962.3	2080.5	116.2
Africa	68.7	225.8	228.5
Asia	549.2	1273.2	131.8
Europe	183	247.2	35.1
Northern America	78.4	122.8	56.7
Latin America and the Caribbean	76	198.2	160.7
Oceania	6.9	13.3	92.6

Modified from United Nations, Department of Economic and Social Affairs, Population Division (2017). World Population Ageing 2017—Highlights (ST/ESA/SER.A/397)

even more relevant if we consider that worldwide rates of type 2 diabetes are dramatically increasing. The WHO estimated 422 million adults were living with diabetes in 2014, compared to 108 million in 1980, and over 60 million of these are currently living in Europe. Today, the global prevalence (age-standardized) of diabetes is around 8.5% in the adult population [15]. Since the year 2000, the International Diabetes Federation (IDF) has collected data on diabetes prevalence. According to recent data in 2011, about 285 million people worldwide were affected by diabetes, but this number is expected to rise to 439 million by 2030 (Fig. 1.4) [16]. A similar trend was found by the Institute for Alternative Futures that made a prediction for the prevalence of diabetes among Americans forecasting a 54% increase in 2030 (people with type 2 and type 1 diabetes will increase by 19,629,000–54,913,000 between 2015 and 2030). In addition to this, the annual number of people with diabetes with new end-stage renal disease will increase by 27,370 and the annual number of diabetes-related deaths will rise by 106,630 [17]. Similar to diabetes, also chronic kidney disease (CKD) is a common risk factor for infection in patients with a CIED and is an independent predictor of all-cause mortality in different conditions. As shown in Fig. 1.5, heart disease, arrhythmias, and CKD exert a series of negative influences on outcomes with harmful clinical implications [18]. Prevalence of CKD in the USA, recognized as a major noncommunicable disease, has recently been estimated as 11.6% of the adult population (23 million), compared with 10.6% (23.4 million) for diabetes, 33.3% (73.6 million) for hypertension, and 36.3% (80.0 million) for CVD [19]. According to the CKD Health Policy Model, the prevalence of CKD in adults aged 65 years or older in the USA is expected to be 36.4% in 2020 and 37.8% in 2030 (all CKD-stage combined), while stage 3a is expected to remain the most prevalent stage until at least 2030 [20]. The global incidence of CKD was around 11 million in 1990 and increased to more than 21 million people in 2016, thus with a 89% increase in incidence over the last 27 years [20] (Fig. 1.6).

As reported by Greenspon et al., the incidence of four major comorbidities (renal failure, respiratory failure, heart failure, and diabetes) in patients with CIED

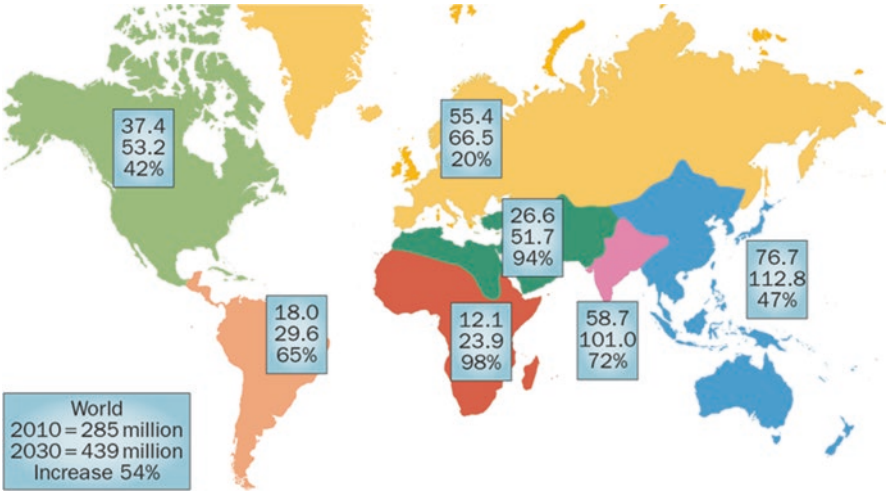

Fig. 1.4 Diabetes worldwide prevalence in 2010 and projections for 2030. The first two values for each box represent the number of people affected by diabetes mellitus (in millions) for each of these seven world regions (identified by colors) for 2010 and the projection for 2030, respectively. The last number shows the relative increase from 2010 to 2030 (From Chen et al. [16], reproduced with permission)

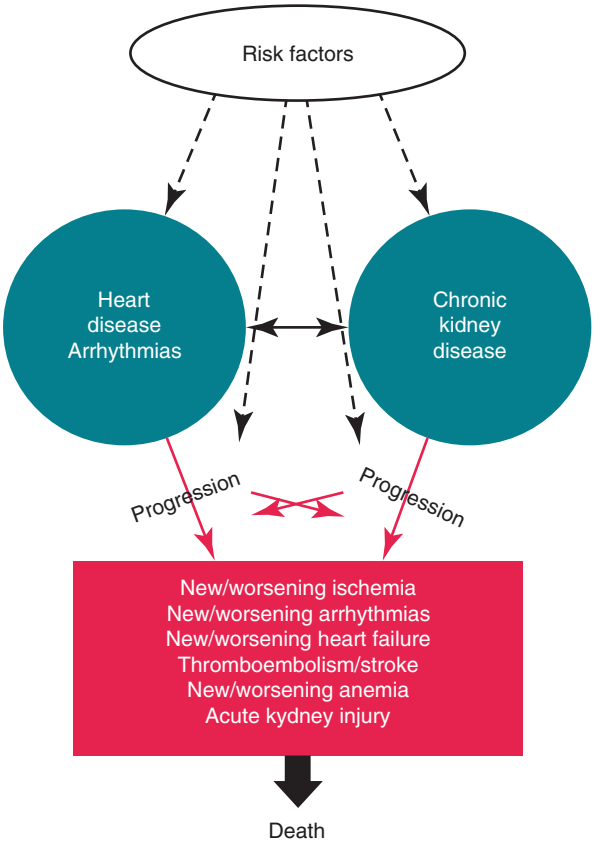

Fig. 1.5 The complex interplays between heart disease, arrhythmias, and chronic kidney disease, in relationship with risk factors, progression of the diseases, complications, and death (From Boriani G et al., Europace 2015;17(8):1169–96)

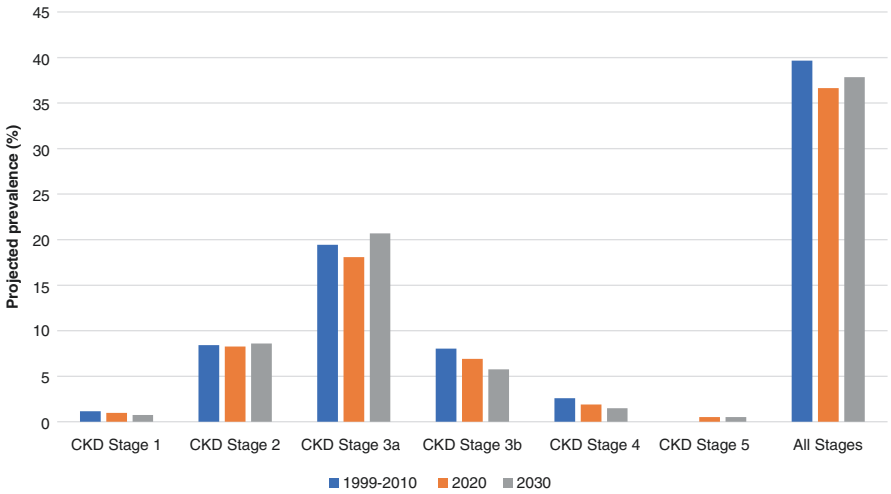

Fig. 1.6 Projected prevalence of chronic kidney disease (CKD) in 2020 and 2030 in individuals with 65 years or more [20]

infection remained relatively constant from 1993 through 2004 when a noticeable increase was seen, and in parallel, the similar trend was observed in the infection rate during the same period [12] (Fig. 1.7).

These observations support the hypothesis that the pacemaker population, suffering from a large variety of chronic diseases, such as diabetes or chronic kidney dysfunction, is more susceptible to infection. In 2015 Polyzos et al. performed a systematic review and meta-analysis founding significant host-, procedure-, and device-related risk factors for infection after CIED implantation: variables associated with a significant increase in the risk of CIED-associated infection at multivariable analysis are summarized in the Table 1.2 [21].

However, the real etiology of the rate increase in CIED infection and particularly the discrepancy between the rise in CIED infections and implantation rates are not completely clear, although the older population and the increasing burden of comorbidities appear to play a major role. Despite of the conduction of many studies so far, the real incidence of CIED's infection is unknown, with a reported prevalence among CIED patients ranging from 0.13 to 19.9% [22]. This reported variety in the occurrence of CIED-related infection is probably due to the poor quality of the data that come from retrospective studies or single-center registries and nonuniform definitions of CIED infections. Indeed, there are no standardized definitions for CIED infections, and in the literature the occurrence was measured in different ways [23]. Moreover, the absence of accurate denominators and different follow-up periods also prevents the exact knowledge of CIED incidence rate [24]. In addition to this, in the majority of the studies, CIED infections are identified using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes for cardiac or vascular device infection, endocarditis, and in general any infection in the setting of CIED implantation regardless if they have been clearly related to the CIED itself or not. For this reason, some authors incorporated multiple distinct

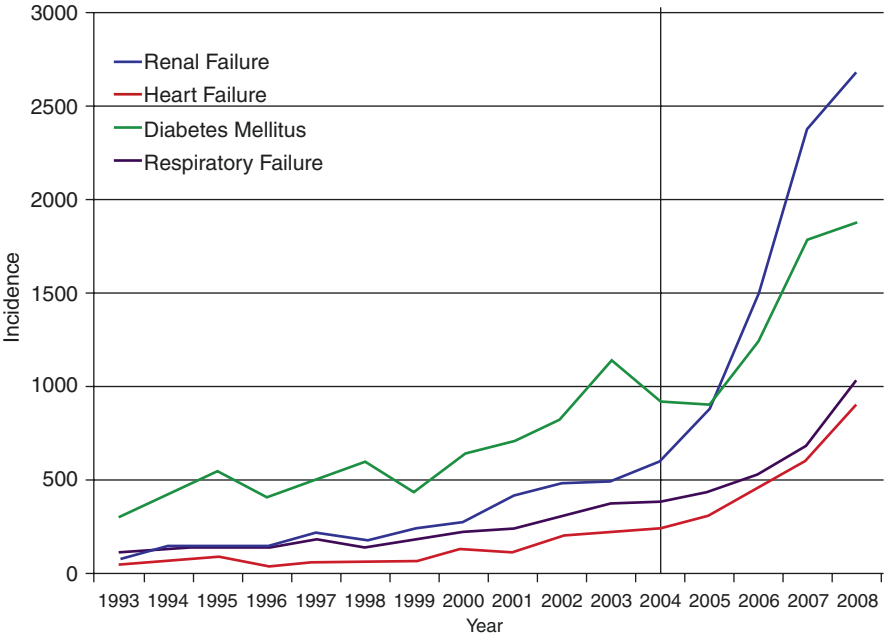

Fig. 1.7 Incidence of comorbidities in patients with CIED infection (From Greenspon AJ et al., J Am Coll Cardiol 2011;58(10):1001–6)

code-based criteria to increase the sensitivity of the search [25]. A wide range of values of CIED infection's incidence has been reported in the literature. In the Danish PM register, more than 460,000 patients who underwent pacemaker implantation between 1982 and 2007 were analyzed, and incidence of infection was 1.8 per 1000 pacemaker-years after the first implantation and 5.3 per 1000 pacemaker-years after pacemaker replacement [26]. The analysis of the Nationwide Inpatient Sample discharge record (NIS) showed that between 1993 and 2008, the overall infection rate was 1.6%, and within the study period, approximately 690,000 patients were treated for CIED infections. More in detail, the incidence of infections increased by 210%, from 2660 cases in 1993 to 8230 cases in 2008, and the rate of infections increased significantly, from 1.53% in 2004 to 2.41% in 2008. Nevertheless, the annual rate of infections did not change until 2004 (Fig. 1.8) [12]. Voigt et al., using the National Hospital Discharge Survey database from 1996 through 2003, reported a 49% rise in the number of new CIED implantations and an increase of 3.1-fold of a total number of hospitalizations with CIED infection (2.8-fold for PMs and six-fold for ICD). As mentioned above, they also found an excessive increase of infection rates compared to the number of implantations according to previous studies [1]. Carrasco F et al. conducted one of the largest series of infective endocarditis diagnosed with vegetation on cardiac devices. More than 7000 patients which undergone a PM or ICD implantation with a follow-up period >25 years (from 1987 to 2013) were evaluated. A significant increase of infective endocarditis incidence

Table 1.2 Variables associated with a significant increase in the risk of CIED-associated infection at multivariable analysis

Number and type of studies	
Host-related factors	
Age	3 retrospective studies
Male sex	1 case-control study, 1 retrospective study
Diabetes mellitus	1 case-control study, 1 retrospective study
Chronic kidney disease/dialysis	1 prospective study, 2 case-control studies
COPD	1 prospective study, 1 case-control study
Anticoagulants	2 case-control studies
Corticosteroids	1 case-control study
CVC	1 retrospective study
History of device infection	Opinion of experts
Implant site trauma	Opinion of experts
Procedures-related factors	
Lack of antibiotic prophylaxis	2 prospective studies, 1 case-control study, 2 retrospective studies
Device replacement/revision	2 prospective studies, 3 case-control studies, 2 retrospective studies
Reintervention	2 prospective studies
No. of prior device-related procedures	1 retrospective study
Temporary pacing	1 prospective study
Procedure duration	1 prospective study
Operator experience	1 retrospective study
Lead dislodgement	Opinion of experts
Post-operative hematoma	1 prospective study
Device-related factors	
ICD device	1 prospective study
CRT	2 retrospective studies
Dual-chamber system	1 case-control study
Number of leads	1 case-control study
Abdominal pocket	Opinion of experts
Epicardial leads	1 case-control study

Based on Polyzos KA et al., Europace 2015;17(5):767–77
COPD chronic obstructive pulmonary disease, *CVC* central venous catheter, *ICD* implantable cardioverter-defibrillator, *CRT* cardiac resynchronization therapy

was found during the follow-up, and more interesting they observed an increasing trend in incidence: from 1.4/1000 of all implanted pacemaker in the period of 1987–1993 to 2.5/1000 in 1994–2000, 3.3/1000 in 2001–2007, and 4.5/1000 in the period of 2008–2013 [27]. Similar results were found in a retrospective cohort study of residents of Olmsted County in Minnesota, between 1975 and 2004; the incidence of definite device infections was 1.9 per 1000 device-years over a total person-time of follow-up of 7578 years [28]. In a multicenter and prospective survey of the incidence and risk factors of CIED infections after PPM or ICD implantations (The PEOPLE study), a total of 6319 patients were enrolled and followed for

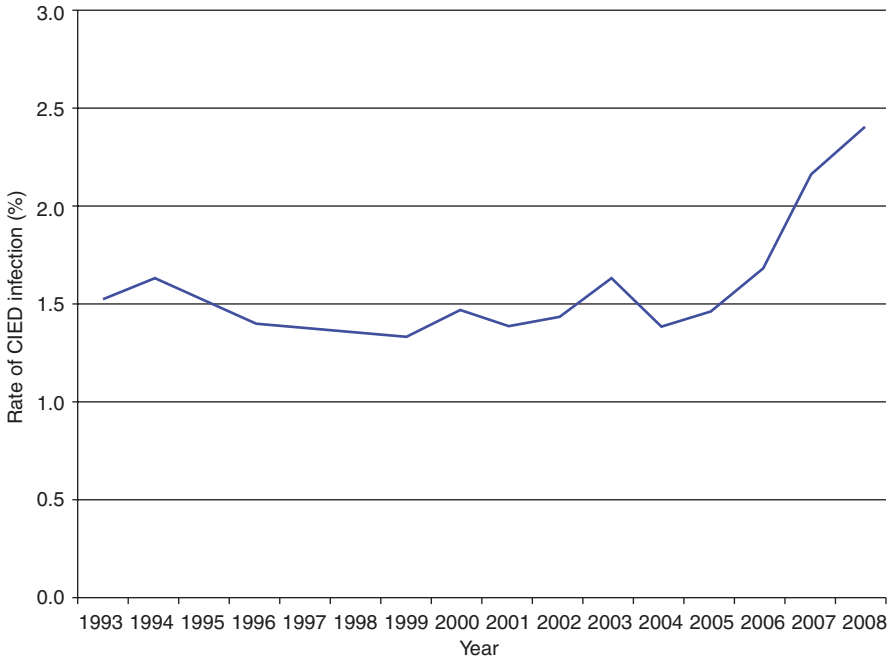

Fig. 1.8 Rate of CIED infection (From Greenspon AJ et al., J Am Coll Cardiol 2011;58(10):1001–6)

12 months in 44 centers in France. Among this cohort, the incidence of CIED infections was 0.56% after de novo implantation and 0.99% for non-de novo procedures [29]. Although previous studies, according to several national databases, reported a rate of CIED infections between 2 and 4% with a 124% and 57% rise in infection rate from 1990 to 1999 and from 2004 to 2006, respectively, most recent data shows that the mean incidence of CIED is 0.1–0.7% for PPM infection and 0.7–1.2% for ICD [30]. Furthermore, a recent European survey has described a great variation in CIED infection rates across different centers reporting an infection incidence <0.5% in 27% of centers, while 22% of them presented an incidence of >2% [31]. In addition, recent data report that the risk of infection may increase up to tenfold if the patient is undergoing a lead replacement or a device upgrade [32]. In a cohort of more than 200,000 patients reported from the National Cardiovascular Data Registry in the USA, a higher infection rate in patients who underwent a generator replacement compared to those who underwent initial implantation (1.9% versus 1.6%) was shown [33]. Moreover, some studies suggest that infection rates vary across different types of CIEDs reporting a greater risk of infection in implantable cardioverter-defibrillators rather than in permanent pacemakers [34]. The more complex CIED system is implanted, the higher is the infection risk, so the infection risk is higher in patients that receive ICDs and even more relevant in CRT [35]. The longer implantation time that requires ICD or CRT-D/P devices may lead to a higher risk of infection due to longer exposure times and prolonged manipulation during

the procedure [36]. Mortality associated with CIED infections is significant and it is device-dependent. As reported by Sohail et al., the standardized adjusted total long-term mortality was 26.5–35.1%, and mortality continues to be high for many years even after successful treatment of the acute CIED infection [25]. Analysis of more than 200,000 admissions with a CIED procedure in 2007 showed that the mortality of the patients with CIED infection at the end of the first year was approximately twice compared to those without device infection. This mortality persisted for at least 3 years after the resolution of CIED infection, but the real cause of this persistent increased risk of death remains uncertain [37].

1.3 The Financial Burden of CIED-Related Infections

In view of the increased awareness of the clinical importance of CIED-related infections, in recent years an increasing interest emerged on their financial burden. CIED infections result in prolonged hospitalizations, prolonged antimicrobial therapy, need for device extraction, and frequently need for device reimplantation. In 2011 Sohail et al. reported on the risk-adjusted total and incremental admission mortality, long-term mortality, admission length of stay, and admission cost associated with infection in a retrospective cohort of more than 200,000 Medicare patients admitted for CIED generator implantation, replacement, or revision during year 2007. A total of 5817 admissions with infection were recorded, and in these cases, significant increases in length of hospital stay and in adjusted in-hospital and long-term mortality were found. Approximately half of the incremental long-term mortality occurred after discharge. The standardized adjusted incremental and total admission costs with infection were $14,360–16,498 and $28,676–53,349, according to device type, respectively. The largest incremental cost with infection was intensive care, which accounted for more than 40% of the difference. Adjusted long-term mortality rate and cost ratios with infection were significantly greater for pacemakers than for implantable cardioverter-defibrillators or cardiac resynchronization therapy/defibrillator devices [25]. More recently, Greenspon et al. conducted a retrospective cohort analysis of 5401 Medicare patients who developed a device-related infection in the year following implantation/upgraded CIED [38]. In the year following infection, 64% of patients underwent device extraction, of whom 39% had their device replaced and 25% had their device extracted without replacement, with around 62% of patients hospitalized and around 25% of patients who died. The cost for Medicare was on average $62,638 for patients who required device extraction and replacement and $22,856 for patients who required device system extraction, with no need for device reimplantation. These data clearly outline that management of CIED infection is associated with high healthcare expenditures in the year following infection as well as with very severe outcomes in a substantial proportion of patients. Hospitalizations were the largest cost driver among patients with infection in this current investigation and infection-related costs, including cost of extraction and replacement, which accounted for more than half of total costs [38]. Also some European analyses confirm that CIED infections are expensive and associated with

significant health-economic burden. Data from the UK collected between 2013 and 2015 for 84 patients showed that the cost of infection ranged from £5139 (PPM) to £24,318 (CRT-D). Different treatment strategies were adopted, and 49% of the patients underwent CIED extraction and reimplantation during the same admission, while 51% underwent extraction but were then discharged home to be readmitted for day-case reimplantation [39]. Data on the costs associated with CIED infections were also collected in Germany for ICDs implanted over 2010–2013 through analysis of German health insurance claims data. The risk of CIED-associated infection was 3.4% overall, either 2.9% for de novo procedures or 4.4% for replacement procedures. Mean 3-year incremental expenditure per patient for patients with CDI compared with controls was €31,493 for de novo implant patients and €33,777 for replacement patients. Mean incremental expenditure was €59,419 per patient with a major infection. All these data highlight that CIED-associated infections are highly expensive for healthcare providers, thus stressing the need for strategies to minimize their occurrence [40]. A strategy for reducing the risk of CIED infection is the use of the TYRX antibacterial envelope and in a modelling study from the UK; the TYRX envelope was found less costly and more effective over a 12-month time horizon than conventional care when utilized in patients with an ICD or CRT-D [41].

Average costs of infection per patient and data from some European countries are reported in Fig. 1.9 [42–45].

Given the epidemiological burden of arrhythmic conditions requiring CIEDs, the importance and clinical implications of CIED infections, the complexity of managing CIED infections, as well as the important financial implications of infections, the ideal approach to this complex topic should be that of health technology assessment (HTA), in order to provide a multidimensional and multidisciplinary approach,

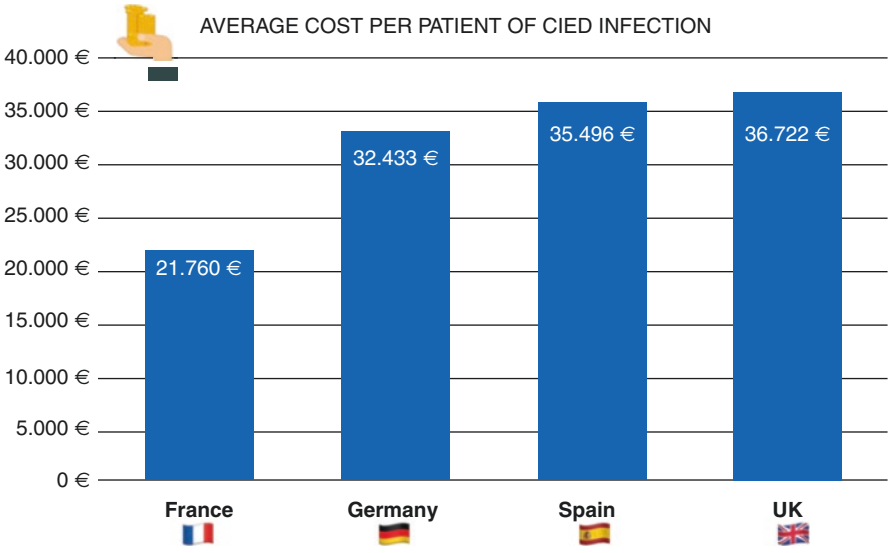

Fig. 1.9 Average costs of infection per patient from some European countries [42–45]

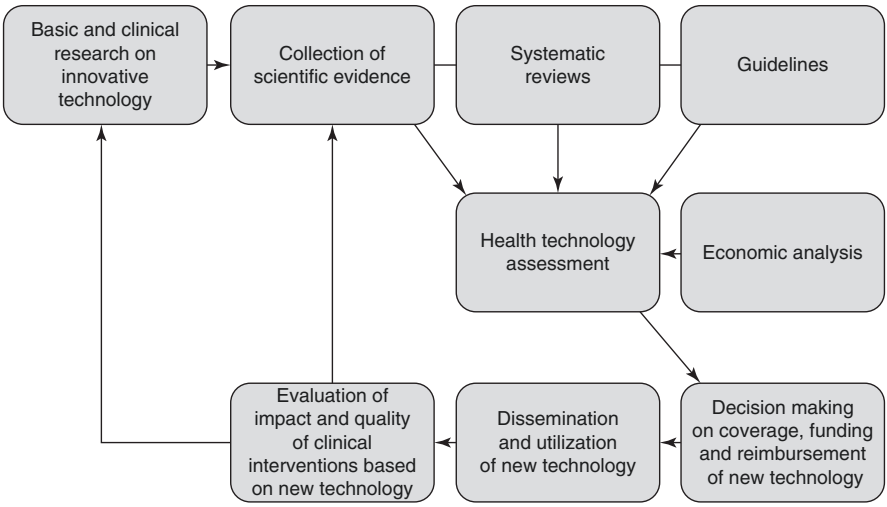

Fig. 1.10 The virtuous circle of health technology assessment (From Boriani G. et al., Eur Heart J 2013;34(25):1869–74)

putting together inputs from clinicians, clinical guideline groups, epidemiologists, biostatisticians, economists, commissioners, and health policy-makers (Fig. 1.10) [46].

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Microbiological Background: Biofilm, Culturing, and Antibiotics

2

Michele Bartoletti and Pierluigi Viale

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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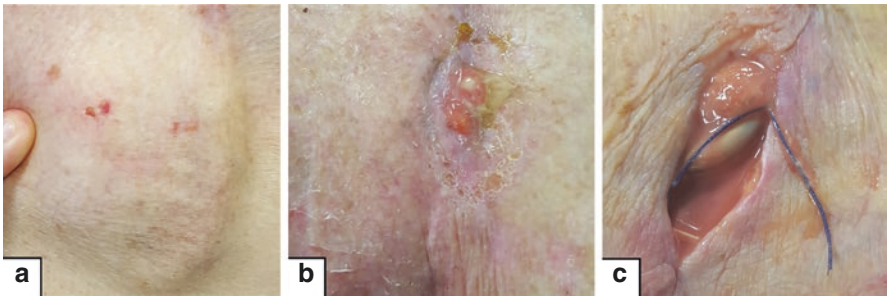

Fig. 2.1 Cardiovascular device pocket infection. (**a**) Normal CIED pocket. (**b**) Infection with pocket decubitus and spillage of purulent material. (**c**) Overt infection with solution of continuity of the skin and generator exposure

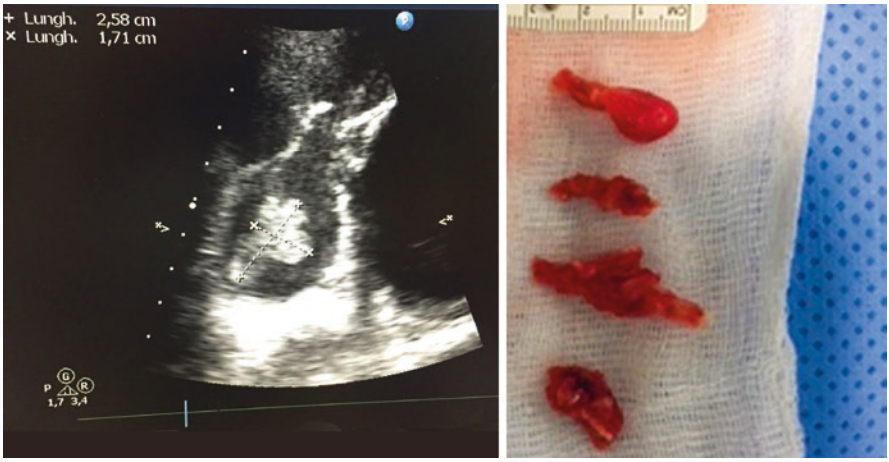

Fig. 2.2 Cardiovascular device lead infection. On the left the echocardiography examination shows a big vegetation on CIED lead. On the right the pieces composing the vegetation after lead extraction

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].

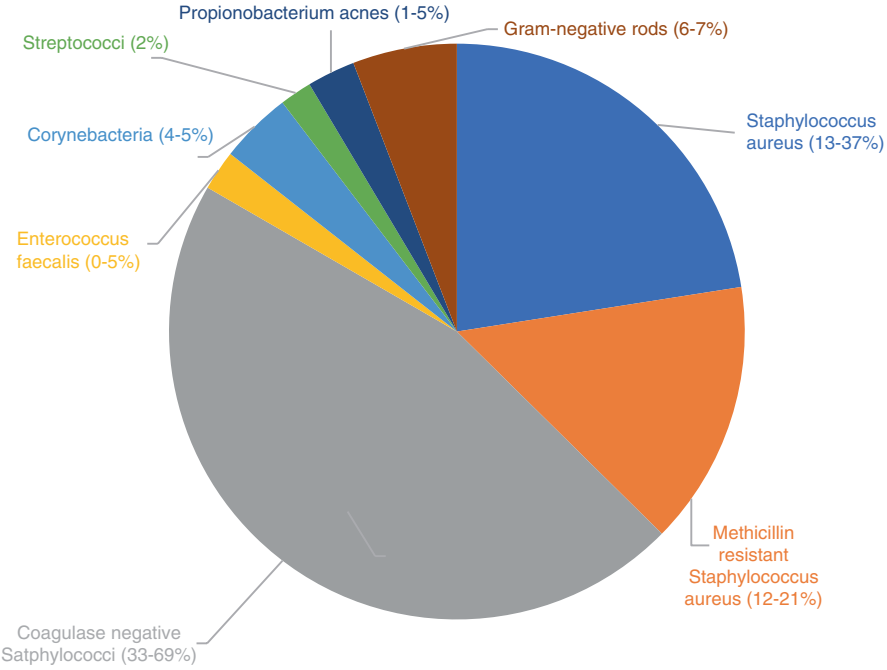

Fig. 2.3 Etiology of cardiovascular implantable electronic device infection. Graphic shows the most common etiology of cardiovascular device infections and their relative prevalence. The risk of biofilm for each pathogen is reported in the graph

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 more 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

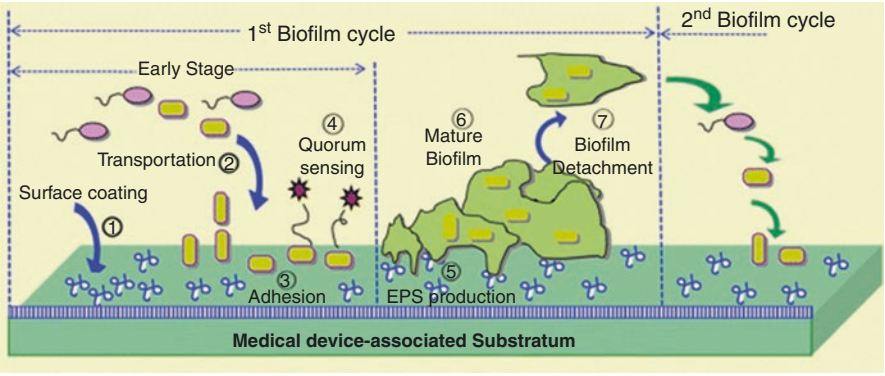

Fig. 2.4 Biofilm formation on medical devices. At first, the surface of medical devices is coated with a layer of proteins and glycoproteins (1), and then cellular colonization takes place (2) with adhesion to the surface of the coated medical device (3) and subsequent release of signaling molecules 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 us 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 heterogenous, 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.

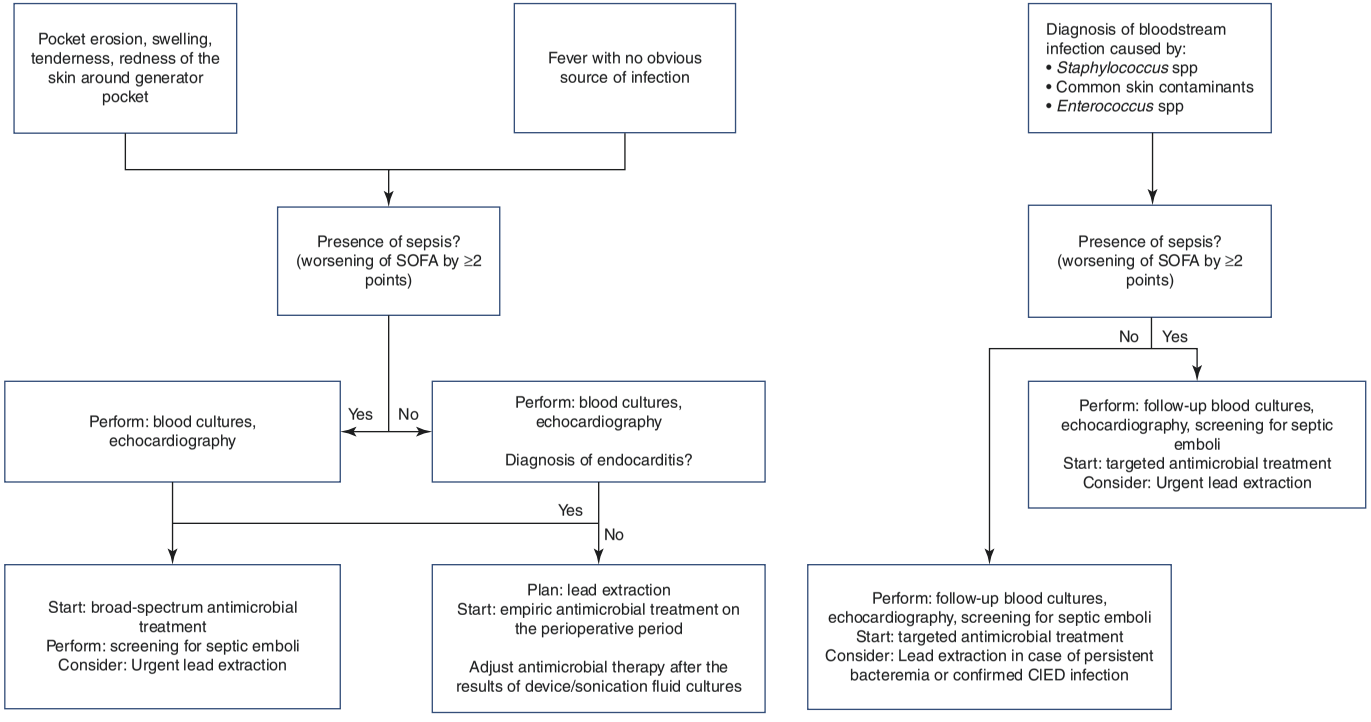

Fig. 2.5 Common clinical presentation of cardiovascular implantable electronic device infection and its medical management. CIED infection management algorithm. Suspect of CIED infection may be posed for the evidence of local signs of pocket infection/fever of unknown origin (left side of the diagram) 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
Staphylococcus aureus carriage status	Screen all candidates to CIED implant with nasal swab. *S. aureus* 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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3 The Risk Factors for Cardiac Device Infections: Patient, Physician, Device, and Procedure

Carina Blomstrom-Lundqvist

3.1 Introduction

The incidence of infections related to cardiac implantable electrical devices (CIEDI) is increasing over time [1–3], partly related to an increasing numbers of cardiac implantable electronic device (CIED) implants due to widening indications and increasing numbers of generator replacements. While the proportion of more complex CIED systems implanted, such as implantable cardioverter defibrillator (ICD) and cardiac resynchronization therapy (CRT) devices [1, 4–6], is increasing, infections are increasing for all device types, particularly for CRT devices [2]. From 2000 to 2012, device-related infections increased from 1.45% to 3.41% ($p < .001$) [2]. The risk of infection for CRT devices was the highest, peaking in 2012 (adjusted odds ratio [OR] 2.43, $p < .001$) [2]. Although the exact reasons for increasing device-related infections remain unclear, it seems to be coupled to implantations in 'higher-risk' patients with comorbidities or conditions leading to immune compromise [1, 2].

Infection is a serious complication of CIED implantations leading to substantial morbidity and mortality with reported in-hospital mortality rates of 3.7–11.3% [1, 7–10].

Comorbidities associated with higher mortality during admissions for procedures related to device infection were stroke (OR, 3.19; $p < .001$), end-stage renal disease (OR, 2.91; $p < .001$), malnutrition (OR, 2.67; $p < .001$), cirrhosis (OR, 2.05; $p = .001$), organ transplantation (OR, 2.16; $p < .001$), congestive heart failure (OR, 2.00; $p < .001$), venous thromboembolism (OR, 1.68; $P < .001$), and chronic lung disease (OR, 1.43; $P < .001$) [2].

Device removal and systemic antibiotic therapy is the standard of care [11], which is based on randomized controlled trials including meta-analysis showing

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that antibiotic prophylaxis reduces the risk for CIED infectious complications [12, 13].

Given this background, it is highly warranted to identify valid risk factors for device infection as it may allow for preventive measures that may result in better infection control strategies for high-risk patients and which also can improve risk assessment in the management of device revisions.

3.2 Pathogenesis

Device infections occur most commonly when leads and pulse generator are contaminated during implantation or later manipulation when crossing skin barrier. Contamination and subsequent bacterial colonization result in pocket infection which is the most common presentation of CIEDI [9, 14]. It commonly tracks along leads and can cause secondary bloodstream infection with progress to systemic infection and endocarditis. A less common mechanism is spread of bacteria from a distant infectious focus with secondary involvement of the CIED system by a bloodstream infection (Fig. 3.1).

The pathogenesis of CIEDI consists of multiple factors, of which device-related factors are those associated with bacterial adherence to the generator or lead surfaces. Adherence is better on irregular and/or hydrophobic device surfaces. The propensity for bacterial adherence is higher for polyvinylchloride and silicone among the commonly used polymers than it is for polytetrafluoroethylene, while it is higher for polyethylene than polyurethane. Further bacterial adherence is higher for stainless steel than it is for titanium (Fig. 3.2).

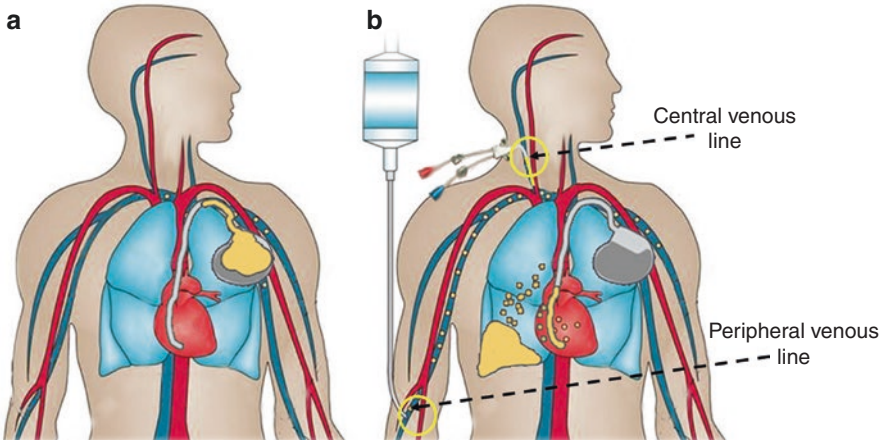

Fig. 3.1 Different pathogenetic mechanisms of CIED infection. (**a**) The infective process (in yellow) usually starts from the device pocket due to contamination, usually occurred during an intervention on the pocket (first implant, revision, generator replacement). Infection then spreads along the leads, reaching bloodstream. (**b**) An infection started elsewhere (from peripheral or central venous access in this example) and spreads through bloodstream; subsequently bacteria colonize the device leads (and lungs) as a metastatic infection

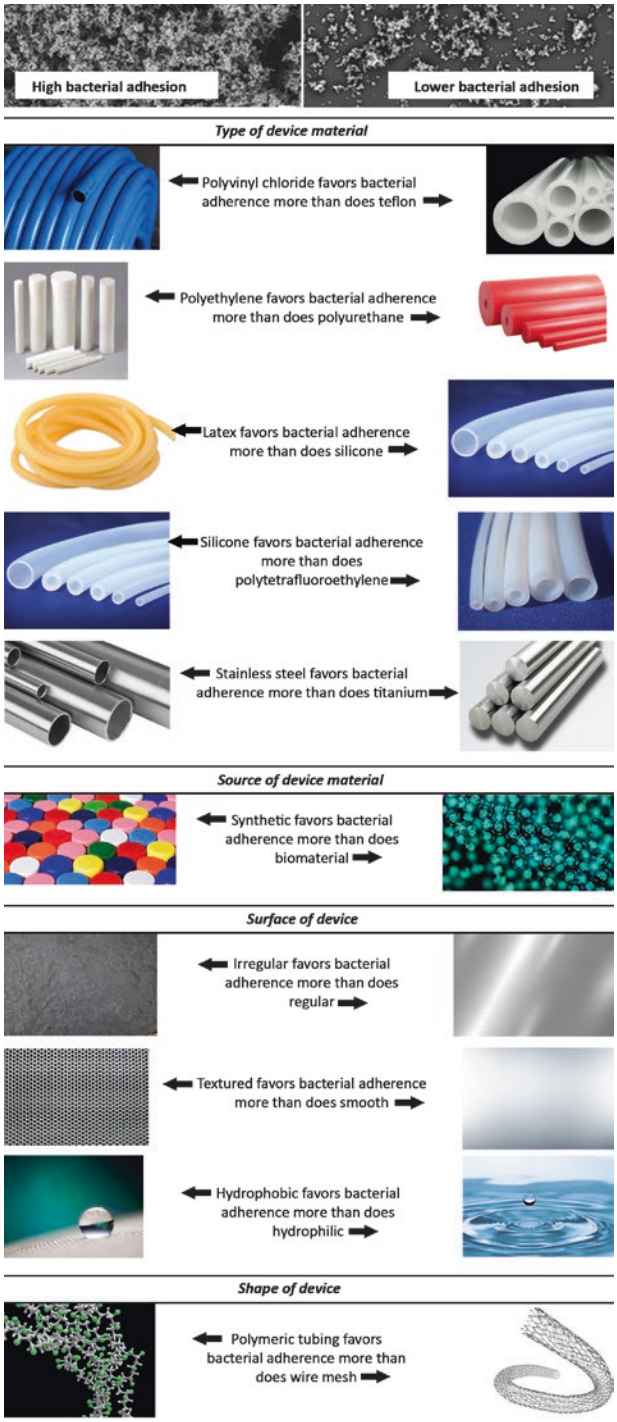

Fig. 3.2 Different characteristics of materials used for implantable devices in relation to their influence on bacteria adherence

While the normal endothelial lining of the heart is resistant to bacterial adhesion, bacteria (especially gram-positive species) are able to adhere to abnormal or damaged endothelium using surface adhesins, which are specialized proteins that mediate attachment to extracellular host matrix proteins. Bacterial adhesion gives rise to colonization eventually leading to formation of a mature vegetation [15]. Many of the microorganisms associated with CIEDI produce biofilms allowing bacterial populations to be encased within an extracellular polysaccharide slime-like matrix, which once established protects bacteria from host immune defences and inhibits antimicrobial efficacy [16]. Biofilm-forming capacity is an important determinant of virulence in the development of staphylococcal device-related infections [17].

Most infections are caused by bacteria from the normal skin flora of the patient. Gram-positive species are most frequent and *Staphylococcus* species remain the most common pathogens causing nearly 70% of CIEDI. Coagulase-negative species (37.6%) were more common than *Staphylococcus aureus* (30.8%) of these, while, altogether, methicillin-resistant staphylococci were isolated in 33.8% of CIEDI (49.4% of all staphylococcal infections) according to a large study of over 800 consecutive patients with confirmed CIEDI [18]. Gram-negative pathogens were identified in 8.9% of cases and 13.2% were with negative cultures. Other microbes including streptococci, enterococci, anaerobes, fungi, and mycobacteria species are rare [9, 19].

Of pocket infections, 40% of early and over 50% of late infections were related to coagulase-negative staphylococci while most endovascular infections were related to *Staphylococcus aureus*. The distribution of pathogens as reported from this series is shown in Table 3.1 [18]. (For additional readings on microbiology and culturing please see Chap. 2.)

Table 3.1 Pathogens in device-related infections

Pathogens	%
Sum of Staphylococcus species:	68.4
Methicillin-resistant *Staphylococcus aureus*	15.0
Methicillin-sensitive *Staphylococcus aureus*	15.8
Methicillin-resistant coagulase-negative staphylococcus	18.8
Methicillin-sensitive coagulase-negative staphylococcus	18.8
Negative culture	13.2
Gram negative	8.9
Sum of Enterococcus species:	4.2
Vancomycin-sensitive enterococci	2.8
Vancomycin-resistant enterococci	1.4
Streptococci	2.5
Anaerobes	1.6
Fungal	0.9
Mycobacteria	0.2

The table is adapted from Hussein, AA et al., including 816 consecutive patients who underwent lead extraction or removal for device infection between 2000 and 2011 [18]

3.3 Risk Factors for CIEDI

Risk stratification for device infection is important as it increases awareness and may allow for preventive measures. While some risk factors are modifiable, such as avoiding temporary pacing and delaying implantation in case of fever, some are not, such as the presence of diabetes. Although many risk factors cannot be modified, most of them can be specifically targeted for optimized therapy.

Risk factors are by tradition classified as patient-related, procedure-related, device-related factors and as environmental and organizational. Risk factors reported to contribute to the development of CIEDI include patient factors (comorbidities, medications, self-care, microbiome), procedural and device factors (pre-procedural preparations, type of device—surgery, contamination, complications, operator, and antimicrobial use), environmental and organizational factors (patient safety culture, facility barriers, quality of environmental cleaning), and microbial factors.

Most studies that have attempted to identify risk factors for CIEDI are retrospective or based on small cohort investigations and many are limited by including only few variables. There are, however, few systematic analyses of large databases and meta-analysis of available evidence on risk factors for CIEDI listed in Table 3.2**.**

Table 3.2 Systematic reviews and meta-analysis of available evidence on potential patient-, physician-, device-, and procedure-related risk factors for CIED infections

	Number of studies/patients included			
Study and reference	Retrospective	Case control	Prospective cohorts or RCT	Sum
[a]Meta-analysis, Polyzos, KA, Europace 2015 [20].	30/180,004	9/352	21/26,172	60/206,528
[b]Database study, Koneru, JN, J Am Heart Assoc 2018 [21].	40,837			40,837
[c] Database study, Joy PS, Heart Rhythm 2017 [2].	4,144,683			4,144,683
[d]Database study, Prutkin JM, Circulation 2014 [22].	200,000			200,000
[e]Database study, Lin YS, Medicine 2015 [23].	40,608			40,608

[a]Electronic searches (up to January 2014) in PubMed, Scopus, and Web of Science databases

[b]Administrative claims database for privately insured and Medicare Advantage enrollees; patients with de novo ICD or cardiac resynchronization therapy defibrillator (CRT-D) device implanted from January, 2003, to June, 2015

[c]National Inpatient Sample database in the United States from 2000 to 2012 with device-related procedures providing data on 85,203 (2.06%) device-related infections

[d]ICD Registry from 2006 to 2009 matched to Medicare fee-for-service claims data including 200,000 ICD recipients; ICD infections identified by ICD-9 codes estimated to 1.7% within 6 months of hospital discharge after implantation

[e]National population-based cohort study from Taiwan National Health Insurance Research Database; enrolling all healthcare data between January 1997 and December 2010 including 40,608 patients with infection incidence rate of 2.45 per 1000 CIED years

In a large meta-analysis with data from 60 studies and over 200,000 patients, pooled to identify risk factors for CIEDI, the average device infection rate was 1–1.3% [20]. The risk factors identified in this meta-analysis are summarized in Table 3.3. Another study used an administrative claims database for privately insured and Medicare Advantage enrollees and collected data from 40,837 patients with de novo ICD or cardiac resynchronization therapy defibrillators (CRT-D) implanted from January 1, 2003, to June 30, 2015 [21]. Patients were followed for a mean 2.3 ± 2.1 years until they had the procedure or their last active date in the database. Of 20,580 device procedures, 771 (1.9%) had device-related complications [21]. The 5-year rate of freedom from an infectious complication requiring an intervention was 97.1% and 96.1% for patients with an ICD and a CRT-D, respectively. Acute infections (defined as occurring in the first 90 days after implantation) were recorded in 0.9% of patients. Another recent large study used data from 4,144,683 device-related procedures in the National Inpatient Sample database in the United States and reported 85,203 (2.06%) device-related infections (Table 3.2) [2]. The risk factors identified in these database studies are also summarized in Table 3.3. One study including patients from the Taiwan National Health Insurance Database reported that old age and high-volume centres (>200 per year) were protectors against CIEDI. The study included 40,608 patients and the risk factors identified are listed in Table 3.3**.**

3.3.1 Patient-Related Risk Factors

Of the *patient-related risk factors* for infection, end-stage renal disease and history of a previous device infection (Table 3.3) was associated with the highest risk emphasizing the importance of carefully evaluating whether CIED therapy is really indicated in these patients (Table 3.3). Even though only few studies were available to be pooled for host-related factors in a meta-analyses after exclusion of retrospective studies, diabetes mellitus, NYHA class ≥2, and pre-procedural fever remained significant predictors of infection [20]. Other strong patient-related risk factors as reported from a large database of procedures for device-related infections were haematoma (OR, 2.44; $p < .001$), malnutrition (OR, 2.66; $p < .001$), venous thromboembolism (OR, 2.37; $p < .001$), and organ transplantation (OR, 2.37; $P < .001$) as listed in Table 3.3 [2]. Even though most of the comorbidities are not modifiable per se, many of them can be subject to optimized treatment interventions, such as optimizing heart failure and diabetes, which in itself may lower the risk for device-related infections. Peri-implantation device infections were reported to be more likely in patients with atrial fibrillation, diabetes mellitus, renal disease, and CRT-D device, while those appearing as chronic infections were more likely in patients aged <65 years at implantation, male sex, diabetes mellitus, renal disease, and heart failure [21]. The strongest risk factors for CIEDI in the more recent years are conditions that compromise the patient's immune status, including diabetes, end-stage renal disease, rheumatologic diseases (which often necessitate steroid use), and malnutrition [2]. Long-term steroid therapy suppressing immunity and delaying

Table 3.3 Risk factors predisposing to CIED infection with pooled effect estimates

Risk factor	Prospective/ total no. of studies[d]	Patients (n)	Pooled estimate OR [CI]	P value	Other trials[d]
Patient-related factors					
Diabetes mellitus	7/18	11,839	2.08 [1.62, 2.67]	<0.000001	[2, 21]
Renal insufficiency [a]	0/5	2033	3.02 [1.38, 6.64]	0.006	[2, 21]
End-stage renal disease[b]	0/8	3045	8.73 [3.42, 22.31]	0.00001	[2, 22]
Congestive heart failure	0/6	1277	1.65 [1.14, 2.39]	0.008	[21]
NYHA class ≥2	2/3	2447	2.47 [1.24, 4.91]	0.01	
COPD	2/6	2810	2.95 [1.78, 4.90]	0.00003 (NS P)	[22, 23]
Malignancy	0/6	1555	2.23 [1.26, 3.95]	0.006	
Skin disorders	2/4	6810	2.46 [1.04, 5.80]	0.04 (NS P)	
Pre-procedural fever	2/3	6652	4.27 [1.13, 16.12]	0.03	
Oral anticoagulants	3/9	8527	1.59 [1.01, 2.48]	0.04 (NS P)	[22]
Heparin bridging	0/2	6373	1.87 [1.03, 3.41]	0.04	
Corticosteroid use	3/10	3432	3.44 [1.62, 7.32]	0.001 (NS P)	
History of device infection	0/4	463	7.84 [1.94, 31.60]	0.004	[23]
Malnutrition	[2]		2.66	0.001	
Venous thromboembolism	[2]		2.37	<0.001	
Organ transplantation	[2]		2.37	<0.001	
Peripheral vascular disease	[21]		1.32 [1.02, 1.71]	0.034	
History of atrial fibrillation	[21]		1.56 (1.26, 1.93)	<0.001	
Age ≥ 65 years	[21]		0.82 [0.67, 1.00]	0.052	[23]
Male sex	[21]		1.39 [1.10, 1.76]	0.005	[23]
Cerebrovascular disease	[22]		1.17 (1.076, 1.276)	0.0003	
Previous valvular surgery	[22]		1.53 (1.375, 1.692)	<0.0001	
Procedure-related factors					
Antibiotic prophylaxis	11/16	14,166	0.32 [0.18, 0.55]	0.00005	
Device replacement/ revision	8/26	21,214	1.98 [1.46, 2.70]	0.00001 (NS P)	[22, 23]
Generator change	6/20	12,134	1.74 [1.22, 2.49]	0.002 (NS P)	[22]
Reintervention for lead dislodgement	4/5	1755	6.37 [2.93, 13.82]	0.000003	[22]
Post-operative haematoma	6/12	14,228	8.46 [4.01, 17.86]	<0.000001	[2]

(continued)

Table 3.3 (continued)

Risk factor	Prospective/ total no. of studies[d]	Patients (n)	Pooled estimate OR [CI]	P value	Other trials[d]
Temporary pacing	4/10	10,683	2.31 [1.36, 3.92]	0.002	
Procedure duration	6/9	4850	9.89 [0.52, 19.25]	0.04	
Inexperienced operator[c]	2/2	1715	2.85 [1.23, 6.58]	0.01	
Device-related factors					
Dual-chamber systems	7/14	45,224	1.45 [1.02, 2.05]	0.04 (NS P)	
Positioning of ≥2 leads	0/6	1146	2.02 [1.11, 3.69]	0.02	
Abdominal pocket	2/7	4017	4.01 [2.48, 6.49]	<0.000001	
Epicardial leads	0/3	623	8.09 [3.46, 18.92]	0.000001	[2, 21, 22]
Environmental/organizational					
Centre volume > 200	[23]		0.54 [0.36, 0.80]	0.002	

Risk parameters statistically significant for retrospective and prospective data are shown. Adapted from Polyzos et al. [20] with additional risk factors added from other large databases or meta-analyses as indicated [2, 21, 22]

COPD, chronic obstructive pulmonary disease; *NA*, not available; *NS P*, not statistically significant in prospective studies; *NYHA*, New York Heart Association; *OR*, odds ratio; *CI*, confidence interval

[a]Glomerular filtration rate (GFR) <60 mL/min or creatinine clearance (CrCL) <60 mL/min

[b]GFR ≤ 15 mL/min or haemodialysis or peritoneal dialysis

[c]<100 previous procedures

[d]Other trials supporting the same OR

wound healing has been associated with device-related infections and is likely the reason why patients with chronic obstructive pulmonary disease and rheumatologic diseases, who are often on steroid therapy, have higher risk of infection, as also seen in our analysis [2, 20, 24]. Age and gender were not associated with increased risk in the meta-analysis [20] (Fig. 3.3).

3.3.2 Procedure-Related Factors

Procedure-related factors with the highest predictors of CIED infection included lack of antibiotic prophylaxis with a 70% relative risk reduction in infection [20].

The use of routine antibiotic prophylaxis at CIED implantations is largely based on a meta-analysis of randomized trials showing significantly reduced risk for pacemaker (PM)-related infections by antibiotics on short term after implant [12], later confirmed on long term by a large prospective study [5]. Other strong predictors for device infections were post-operative haematoma associated with an eightfold increased risk [20] with similar risk for all types of devices [2]. This observation was further confirmed by the randomized BRUISE-CONTROL INFECTION study, which demonstrated a strong association between clinically significant haematoma and subsequent device infection (hazard ratio for infection 7.7; 95% CI, 2.9–20.5; $p < 0.0001$) with as many as 11% risk of developing infection over 1-year follow-up

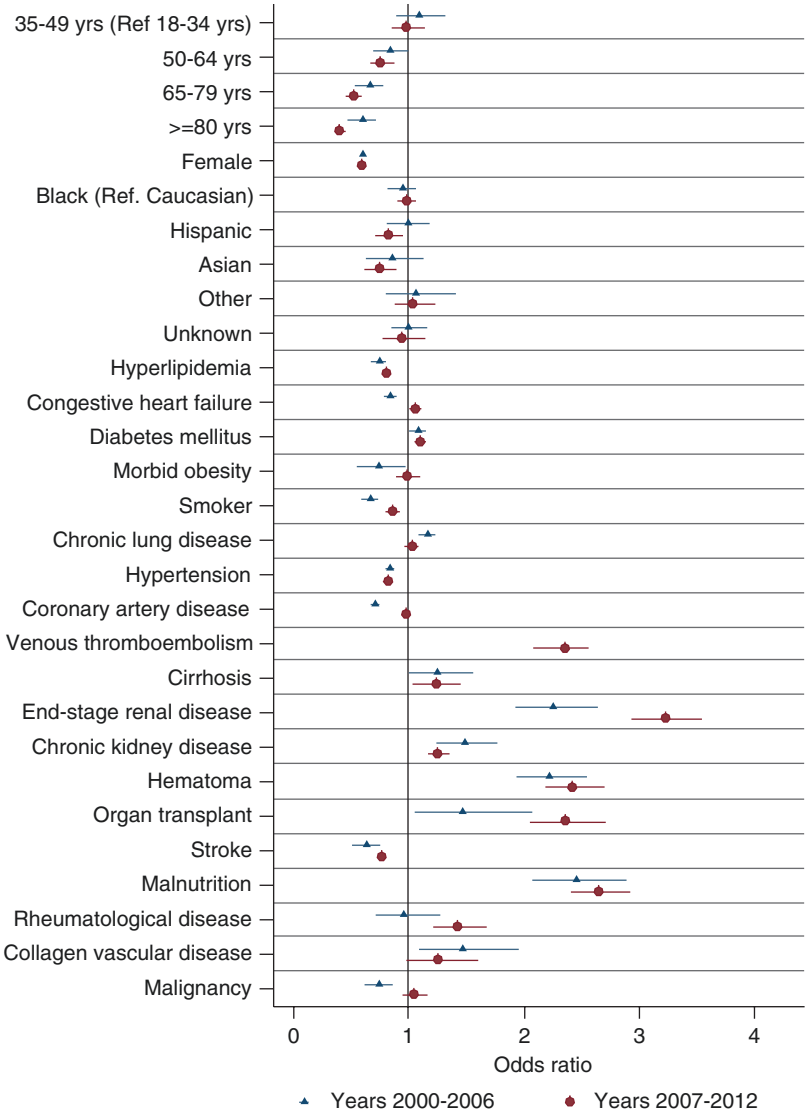

Fig. 3.3 Conditions with high risk of CIEDI. Results of the multivariable analysis with procedures for device-related infections from 2000 to 2006 vs. 2007 to 2012 recorded in the National Inpatient Sample (NIS) US database (Reproduced from Joy et al. [2] with permission)

[25]. Given this knowledge, special attention should be given on adequate haemostasis, particularly in patients with increased risk for perioperative bleeding.

Another clinically significant predictor for infection was reintervention for lead dislodgement with a sixfold and generator change with roughly a twofold risk for infection, which may be related to activation of pre-existing bacterial colonization

or reduced penetration of antibiotics into the encapsulated generator pocket [20], also confirmed by others [6, 22]. This knowledge is of particular importance in the present era of frequent generator or lead recommendations and recalls and a decision to replace a device should therefore be made on a risk versus benefit ratio weighting the risk for death due to device failure, the rate of device failure, and the risk for procedure-related death.

In a recent prospective registry study CIEDI occurring after initial implantation (178 patients) had a higher Charlson comorbidity score, were more likely to have had a solid organ transplant (2.8% vs. 0%, $p = 0.011$), and be on immunosuppressive medications (10.1% vs. 4.3%, $p = 0.03$) than those occurring after reoperation (254 patients) [24]. They were also more likely to present with metastatic foci of infection (16.9% vs. 8.7%, $p = 0.016$) and sepsis (30.9% vs. 19.3%, $p = 0.006$). Pocket infections occurred more likely after a reoperation (70.1% vs. 48.9%, $p < 0.001$) and with coagulase-negative staphylococci as the most frequently isolated organism ($p = 0.029$). No differences were seen in age, sex, or device type. There were no differences in in-hospital (7.9% vs. 5.2%, $p = 0.31$) or 6-month mortality (21.9% vs. 14.0%, $p = 0.056$). Device-related infections after initial implant thus occur earlier, more aggressively, and are often due to *Staphylococcus aureus*, while those after reoperation have more indolent manifestations and are due to coagulase-negative staphylococci [24].

Procedure duration was also associated with multifold risk (Table 3.3), but when only studies with adequate definition were pooled, all listed procedure factors except for procedure duration were still associated with higher infection rates [20].

Temporary pacing is associated with a twofold increased risk for device infections, which may be related to deviations in managing sterility in urgent situations. Indication for temporary transvenous pacing should therefore be carefully considering alternatives such as backup transthoracic pacing or infusion of rate-accelerating drugs (Table 3.3). Inexperienced operator, in particular thoracic surgeon, is associated with an almost threefold risk for CIEDI (Table 3.3) [26].

3.3.3 Device-Related Risk Factors

Device-related factors with the highest risk for infection were abdominal pocket with a fourfold risk and CRT device with an eightfold risk (Table 3.3). Although abdominal pocket was the only remaining significant risk factor after pooling only prospective studies (Table 3.3) [20], several other studies have confirmed that CRT is a major risk factor for device-related infections [2, 21, 27–29].

The infection risk after pacemaker implant, 0.5–1% within the first 6–12 months [4–6], is reported to be higher, 1.7%, with ICDs [19, 22]; even higher in CRT recipients, 9.5% over 2 years [14]; and highest with CRT-D [29]. In a recent analysis of ICD Registry data from 2006 to 2009 matched to Medicare claims data; however,

the infection rate was 1.4%, 1.5%, and 2.0% for single, dual, and biventricular ICDs, respectively ($P < 0.001$) [22]. A greater risk of infection with increasing number of device lead implants has also been reported by others [27, 28]. Other factors that may explain the increased risk of infection for CRT devices are more advanced procedures, reoperation for upgrade to biventricular device, and higher comorbidity burden of CRT patients. Chronic kidney disease and rheumatologic diseases were more common in CRT recipients with device infections than among other device types [2]. In a multivariable regression analysis for independent risk factors for CIEDI, CRT devices and single-chamber pacemakers had higher risk than ICDs [2]. Infections in CRT devices and single-chamber pacemakers carried a higher mortality rate, which may be related to greater severity of cardiovascular disease in CRT recipients.

3.3.4 Environmental/Organizational Risk Factors

High-volume centre was shown to decrease the infection rate if more than 200 procedures were performed annually (Table 3.3) [23].

Nasal carriers of *Staphylococcus aureus* are at increased risk for healthcare-associated infections with this organism [30]. Rapid identification of *S. aureus* nasal carriers by means of a real-time polymerase-chain-reaction (PCR) assay, followed by treatment with nasal ointment and chlorhexidine soap, reduced the risk of hospital-associated *S. aureus* infection to 3.4% in the mupirocin-chlorhexidine group, as compared with 7.7% in the placebo group (relative risk of infection, 0.42; 95% CI, 0.23 to 0.75) [31]. There are no reports on risk factors for device-related infections depending on minimum standards for the environment for CIED procedures such as operating room standards for sterile procedures.

3.4 Conclusions

Comparison of the comorbidities associated with greater risk for device-related infections suggests that currently the strongest risk factors are disease states that compromise the patient's immune status including diabetes, end-stage renal disease, rheumatologic diseases, and malnutrition [2]. The greater rise in device-related infections for CRT recipients may reflect a combination of more complex procedures performed in patients with higher comorbidity burden, which is unmodifiable in the short term. Efforts should therefore be made to target risk factors that are modifiable in order to modify and reduce the risk for device-related infections and further to optimize treatment of any comorbidity that imposes increased risk for infection. Examples of risk stratification and modification are delineated in Table 3.4**.**

Table 3.4 Modifiable risk factors for device-related infection to be considered prior to implant or reoperation

Modifiable risk factor	Modifying action
CIED replacement	Is it medically indicated? Consider alternative approach to a transvenous system
Upgrade to a more complex CIED	Is an upgrade medically indicated?
Early CIED re-intervention	Can it be postponed? Consider alternative approach to a transvenous system
Fever/systemic infection	Delay procedure
Indwelling lines	Remove indwelling lines
Temporary pacing	Avoid and replace by drugs or transthoracic pacing?
Corticosteroid treatment	Is dose reduction or withdrawal possible?
Anticoagulation/ antithrombotic drug	Consider withdrawal if not clearly indicated
Pocket haematoma	Can anticoagulation temporarily be interrupted? Avoid heparin bridging Can antiplatelets be discontinued for a week?
Long procedure time	Shorten procedure time—experienced operator and planned technique
Low operator experience	Refer to experienced operator
Low-volume centre with limited facilities	Refer patient to high-volume centre with appropriate environment, adequate surgical technique
Topical *S. aureus*	Screen and decolonize nasal carriers of *S. aureus* on admission
Comorbidities Renal insufficiency Chronic skin disease COPD Diabetes Heart failure	Optimize medical treatment, for example, better glycaemic control

COPD, chronic obstructive pulmonary disease

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Cardiac Device Infections: A Lesson from the Registries

4

Valentina Barletta, Davide Morolla, Veronica Della Tommasina, Luca Segreti, Andrea Di Cori, Giulio Zucchelli, and Maria Grazia Bongiorni

4.1 Registry Reports on CIED Infections

The number of CIEDs has enormously increased in the past decades, with estimates of approximately 3.5 million pacemakers/defibrillator leads currently implanted in patients all around the world and approximately 500.000 to 1.000.000 new leads implanted worldwide every year [1].

CIED infections have an incidence of 1.9 per 1000 device-years although these data vary among studies [2]. Several registries showed that CIEDI rate is rising faster than the implantation one. Although it is not entirely clear why this acceleration in the infection rate has occurred, it has been suggested that this may reflect the growth in CIED use boosted by an increased sensitivity to this complication based on the growing understanding of different CIEDI presentations and patient management. However, other possible explanations encompass an evolution in patient's clinical profile. In particular this can be related to a significant increase in the proportion of CIED candidates older than 70–80 years [3].

The principal estimate of the incidence of CIED infections in unselected populations comes from data collected by Medicare in the USA for 12 months in 2007 on more than 200,000 patients. In this report the authors showed a 1-year incidence of 5817 cases of CIEDI, equal to 2.9% of the entire population, with a mortality of 11.3% in the analyzed period and of 35.1% at 15 months from infection [2]. An analysis of the 2006 National Hospital Discharge Survey (NHDS), based on ICD-9 CM discharge codes analysis, counted for 12979 diagnosis of CIEDI. This incidence is equal to 5.8% of the 222940 CIED implants carried out in the same year (but not necessarily connected to them) [4]. In 2013, Medicare noted the high mortality and costs associated with treating CIED infections and suspended

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reimbursements for CIEDI. From these observations, the need arises to perform national data analysis to verify the infectious risk factors proposed in recent international literature and to define their prevalence in clinical practice.

Risk factors for CIED infection development include first of all the patient profile, intended as the presence of comorbidities (i.e., heart failure, diabetes mellitus, renal failure, pocket hematoma) and the use of specific drugs like corticosteroids or antithrombotic agents. Other risk factors are strictly connected with the implantation procedure: adequate preoperative antimicrobial prophylaxis, fever, signs and symptoms of infection within the 24–48 h before implantation, type and site of intervention (first implantation or device revision), use of pre-procedural temporary pacing, operator experience, and center procedure volume [2]. In particular, several multicenter studies showed a high incidence of CIED complications, including CIEDI, after CIED replacement/upgrade procedures (Table 4.1) [5–17]. Notably, diagnosis of CIEDI is not always straightforward since presentation can vary, especially after recent procedures. Clinical features of pocket infection include: pain at the pocket site, edema, erythema, frank incision dehiscence, and erosion with or without purulent discharge. On the opposite systemic involvement of CIEDI can appear as sudden/recurrent fever, malaise, pneumonia and all the other manifestations of endocarditis [1].

It has to be considered that occurrence of CIEDI is not a static phenomenon. During the last decades we have seen several changes in patient demographic, device characteristics, CIEDI preventive measures, and large use of broad-spectrum antibiotics. It is not known the effect of all these changes on the epidemiology of the agents involved in CIEDI over time. Similarly, although many infections are thought to be related to the index implant procedures or system revisions, a significant number of pocket or endovascular infections occur more than 1 year after device-related interventions, and it is difficult to know whether there are microbiological differences in early versus late CIEDI. Very recently, a large prospective observational study of 816 consecutive patients with confirmed CIEDI who underwent transvenous lead extraction has been conducted [18]. The registry reported the evolution of the microbiology of CIEDI during 12 years at a high-volume tertiary care center. Temporal trends of pathogens and microbiological profiles of late versus early infections have been assessed. Staphylococcal species remained the most common pathogens involved (68.4%), especially coagulase-negative species (37.6%) and *Staphylococcus aureus* species (30.8%). Methicillin-resistant staphylococci were the pathogens in 33.8% of all CIEDI and accounted for 49.4% of all staphylococcal infections. Gram-negative pathogens were identified in 8.9% of cases, whereas 13.2% were with negative cultures. CIEDI related to streptococci (2.5%), enterococci (4.2%), anaerobes (1.6%), fungi (0.9%), and mycobacteria species (0.2%) were less common. Of pocket infections, 49.5% occurred more than 1 year after pocket manipulation, and 53.6% of these were related to coagulase-negative staphylococci. In contrast, most endovascular infections were related to *Staphylococcus aureus*, which was more likely to cause early than late CIED pocket infections, for the higher aggressive nature of this pathogen. Most of the endovascular infections occurred after 1 year from CIED implantation or pocket

Table 4.1 Main multicentric studies assessing long-term complications after cardiac electronic devices upgrade/replacement

Author	Year	Design	No. of patients	Type of procedure	ICD patients (%)	CRT-D (%)	Follow-up (mo)	Death (%)	Major complications (%)	Minor complications (%)
Gould	2006	R	533	ERI[a]	100.0	<5.0	2.7	0.3[b]	5.8	2.3
Costea	2008	P	222	ERI[a]	92.3	18.5	3.0	NA	4.1	4.1
Gould	2008	R	451	ERI[a]	100.0	30.0	11.8	0.4[b]	5.9	3.1
Poole	2010	P	1031	ERI	48.7	34.9	6.0	0.0[b]	4.2	7.4
			713	UP	51.8	13.3	6.0	1.1[b]	16.4	7.7
Bogale	2011	P	2367	N + UP	71.3	100.0	12.0	7.9	5.0	4.1
			692	UP	69.9	100.0	12.0	8.6	6.8	4.2
Krahn	2011	P	1081	ERI + UP	100.0	32.2	1.5	NA	5.1	1.9
Erkapic	2013	P	510	ERI	100.0	<1.0	22.0	9.8	2.0	NA
Kramer	2013	R	463,978	ERI + N	100.0	37.4	29.1	9.5	1.8	1.0
			103,985	ERI	100.0	43.1	24.5	9.9	0.5[c]	0.4
Kirkfeldt	2013	R	66	UP	0.0	0.0	44.4	0.0	16.7	4.6
Palmisano	2013	R	2671	ALL	37.8	46.1	27.0	NA	4.2	0.4
			1160	N + ERI + UP	39.9	49.9	27.0	NA	2.8	0.9
Botto	2014	P	605	ERI	8.0	0.0	24.0	8.7	3.8	NA
Kirkfeldt	2014	R	5918	N + ERI + UP	25.7	29.3	6.0	5.5	5.6	4.2
			1136	ERI	23.5	23.2	6.0	NA	3.5	2.6
			427	UP	48.2	58.3	6.0	NA	8.4	7.2
Biffi	2017	P	784	ERI + UP	100.0	46.3	6.0	NA	2.4	0.9

CRT-D, cardiac resynchronization therapy defibrillator; *ERI*, elective replacement procedures; *ICD*, implantable cardioverter-defibrillator; *N*, new implant procedures; *NA*, not available; *P*, prospective study; *R*, retrospective study; *UP*, upgrade procedures

When provided by the original paper, the results of the subgroup of elective replacements or upgrade procedures are reported after the entire population

[a]ERI per advisory

[b]Related to complication

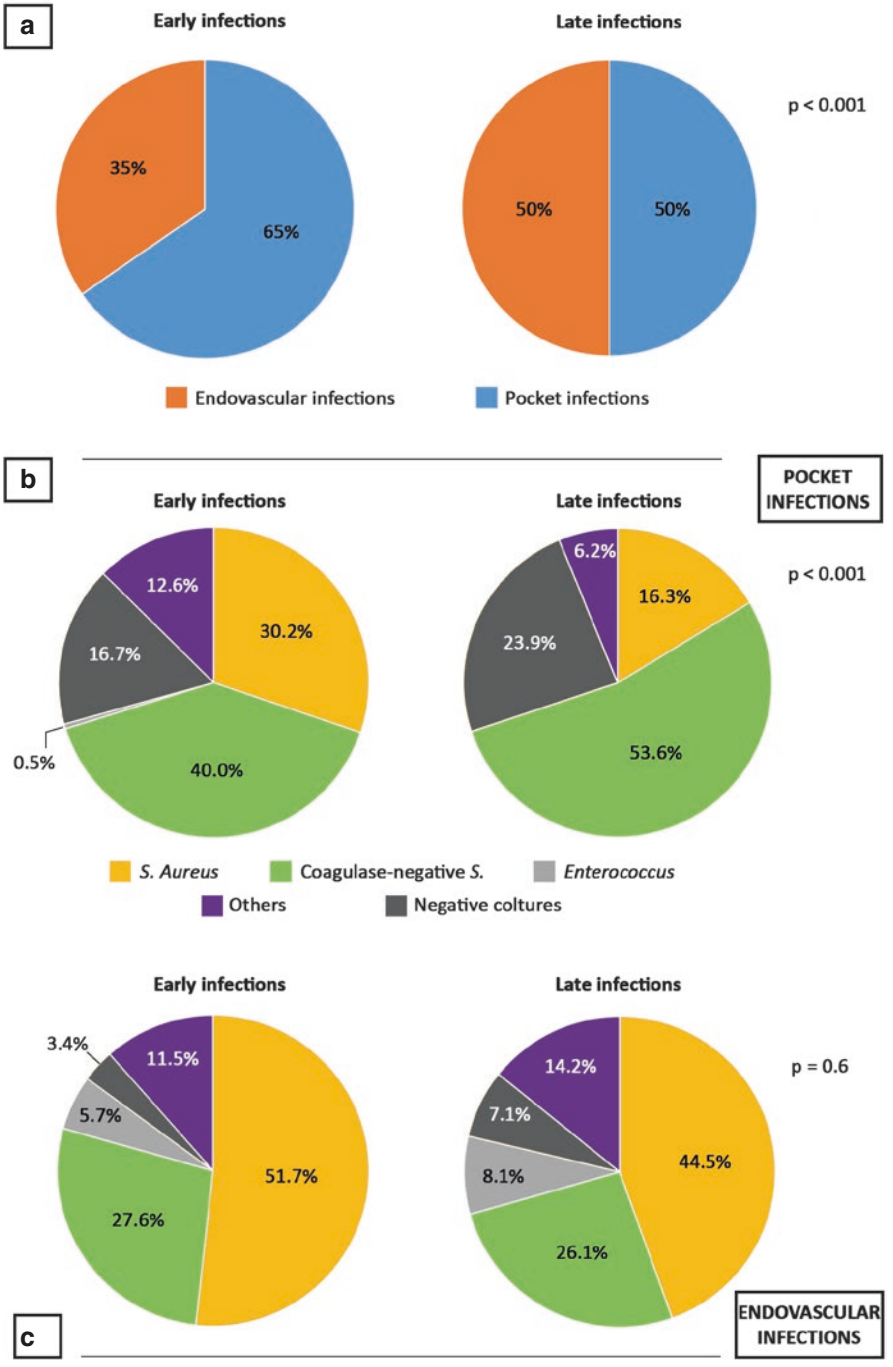
[c]Index admission complication

manipulation (Fig. 4.1). Moreover, the authors showed that over the course of 12 years there did not seem to be a temporal trend in the epidemiology of culprit organisms, suggesting a weak effect of the changes in host factors on the distribution of involved pathogens. However, the rates of methicillin resistance seemed to be higher than those reported in the preceding decade, rising concerns regarding the wide use of broad-spectrum antibiotics and suggesting a high likelihood of acquisition of CIEDI in healthcare environments. There was a trend for higher prevalence of methicillin resistance in systemic/late CIEDI falling just below significance (Fig. 4.2). [Additional data on CIEDI epidemiology and associated costs can be found in Chap. 1.]

4.2 Antibiotic Prophylaxis

Preoperative antibiotic prophylaxis has been consistently associated with a reduced rate of infection and is largely recommended before any cardiac device implantation [19]. Since the late 1990s a meta-analysis of seven studies of 2023 patients undergoing permanent pacemaker implantation concluded that preoperative administration of anti-staphylococcal antibiotics may reduce infection by almost fourfold [20] (Fig. 4.3). A recent randomized, double-blind, placebo-controlled trial confirmed the efficacy of a single dose of cefazolin (1 g) prior to the procedure in preventing CIED infection, with an infection incidence of 0.63% in the cefazolin group and 3.28% in the control group [21]. In a large prospective multicenter observational study (REPLACE Registry) a total of 1744 patients undergoing CIED replacement was evaluated in order to assess procedural complications out to 6 months [22]. Two patient cohorts were predefined: in cohort 1 a generator replacement only was planned, while in cohort 2 generator replacement with a new transvenous lead addition or revision was scheduled. This registry was the first to report details of infection prevention techniques used in current practice: all patients in the study received preoperative systemic antibiotic prophylaxis and 68% of subject received some form of postoperative systemic antibiotics. CIED infection developed in 22 patients (1.3%) among both study cohorts with no difference in rate of infection between the two. Although the majority of patients in this study had post-procedural systemic

Fig. 4.1 Temporal distribution and etiology of CIED infections. (**a**) Distribution of cardiac electronic device (CIED) infections according to the time of occurrence. Pocket infections have a major role among early infections (occurred before 1 year from the last procedure on CIED), while for later ones local and systemic infections account in the same way. (**b**) Etiology of CIED pocket infection. Coagulase-negative staphylococci represent the most common organism for both early and late infections. (**c**) Etiology of endovascular CIED infections. The overall distribution of microbial agents is not significantly different between early and late diseases. As opposite of pocket infection, *Staphylococcus aureus* is the main etiological agent for systemic infection and Gram-negative bacteria have a more prominent role than for local infections. Data from Hussein et al. [18]. S. *Staphylococcus*


a
Early infections
Late infections
p < 0.001
35%
65%
50%
50%
Endovascular infections
Pocket infections
b
POCKET INFECTIONS
Early infections
Late infections
p < 0.001
12.6%
30.2%
16.7%
0.5%
40.0%
6.2%
16.3%
23.9%
53.6%
S. Aureus
Coagulase-negative S.
Enterococcus
Others
Negative coltures
Early infections
Late infections
p = 0.6
3.4%
11.5%
5.7%
51.7%
27.6%
14.2%
7.1%
8.1%
44.5%
26.1%
c
ENDOVASCULAR INFECTIONS

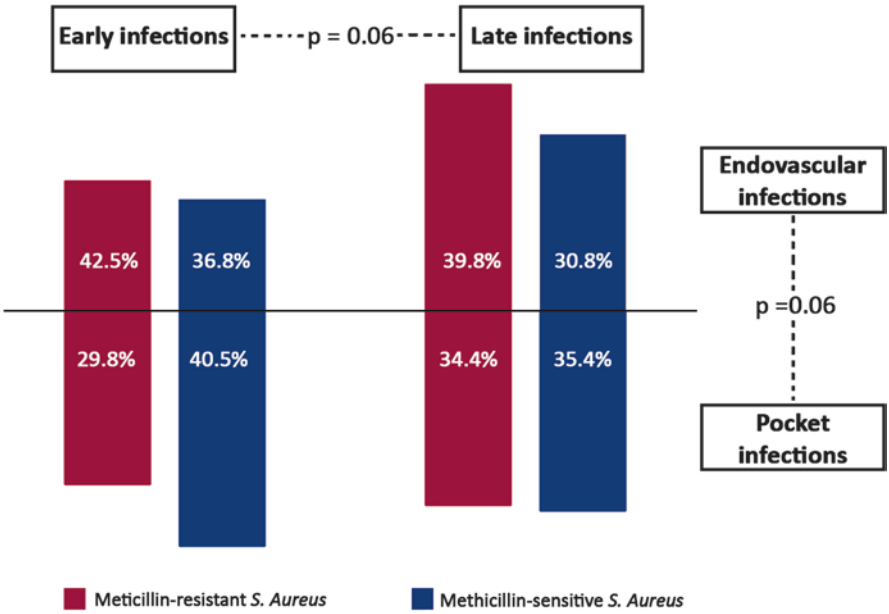


Fig. 4.2 Methicillin resistance in CIED infections. Rate and distribution of methicillin resistance of *Staphylococcus* among patients with cardiac electronic device infection (data from Hussein et al. [18]). There is a trend for higher prevalence of resistance in endovascular/late infections, however not reaching significance

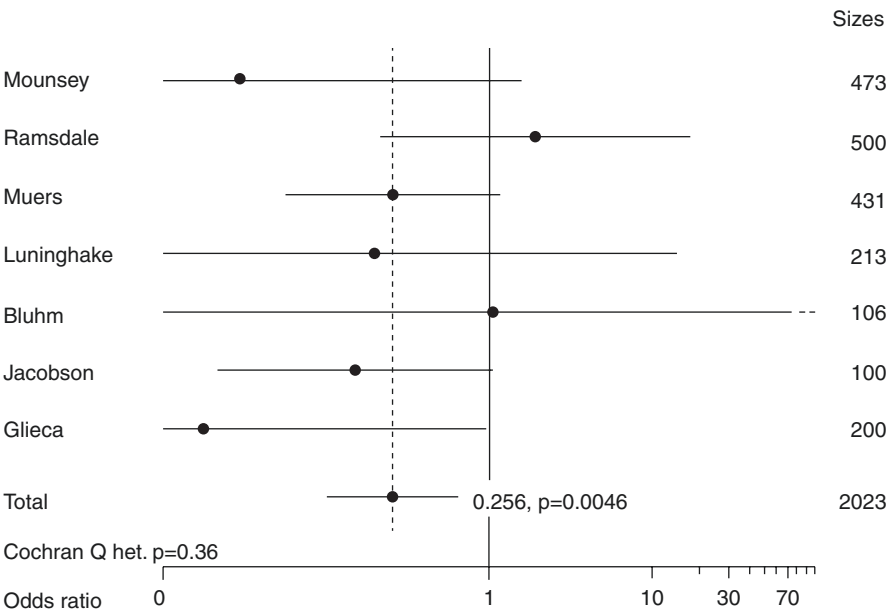


Fig. 4.3 Efficacy of antibiotic prophylaxis for pacemaker implantation. Odds ratio and 95% confidence interval (represented by lines) for the reduction of pacemaker infection with prophylactic antibiotic administration, meta-analysis published by Da Costa et al. [20]

antibiotics, the efficacy of this strategy has not been established. The infection rate among patients receiving additional post-procedural antibiotics was not statistically different than in those receiving no post-procedural antibiotics. For this reason the need for large randomized controlled trials examining the potential benefit and risk with these practices has been highlighted. [Additional data on current pharmacological prevention/management of CIEDI can be found in Chap. 2.]

4.3 Management of CIED Infections: General Recommendations

CIEDI is a disease that requires a collaborative approach for several reasons:

- CIEDI can present with very different characteristics depending on the involved site, the underlying cardiac disease, the microorganism involved, the presence or absence of complications, and the patient's characteristics.
- A very high level of expertise is needed from several specialties: cardiologists, cardiac surgeons, infection disease specialists, microbiologists, neurologists, neurosurgeons, experts in congenital heart disease, anesthetists, and many others.
- Several imaging techniques can be involved: standard echocardiography and intracardiac echocardiography, magnetic resonance imaging, computed tomography, and nuclear imaging. All these approaches have also been shown to be useful for diagnosis, follow-up, and decision-making.
- Treatment of CIEDI requires, but is not limited to, removal of all hardware needing coordination between expert in lead extraction and surgical team for planning the main approach and possible backup strategies.
- Post-extraction management is as important phase as CIED extraction, including: eradication of the infection, prevention of post-extraction complications and CIEDI recurrence, patient monitoring, and reimplantation strategy.

For all the previous considerations the presence of an endocarditis team is crucial as it has been suggested by the ESC 2015 guidelines [19]. Figure 4.4 present a hypothetical CIEDI-team which however has to be adapted to specific organizational settings and patient characteristics. This multidisciplinary approach has already been shown to be useful in other settings [19, 23, 24].

Several guidelines and consensus documents from the principal cardiovascular societies provided in the last years recommendations on treatment of CIEDI and in particular removal of all the hardware (Fig. 4.5). In general transvenous lead extraction (TLE) is the preferred approach for a lower incidence of procedure-related complications of the percutaneous approach in comparison with open-chest treatment. Surgical extraction should be considered when TLE is incomplete or impossible or when is associated with destructive tricuspid infective endocarditis. In patients with large lead vegetations (> 20 mm) treatment strategy (transvenous vs. surgical) should be carefully tailored according to patient profile risk [28]. CIEDI presenting both as local pocket infections and with associated to bacteremia, vegetations, or endocarditis comprise a class I indication for TLE [1, 19, 25–27, 29–32]. However, not all

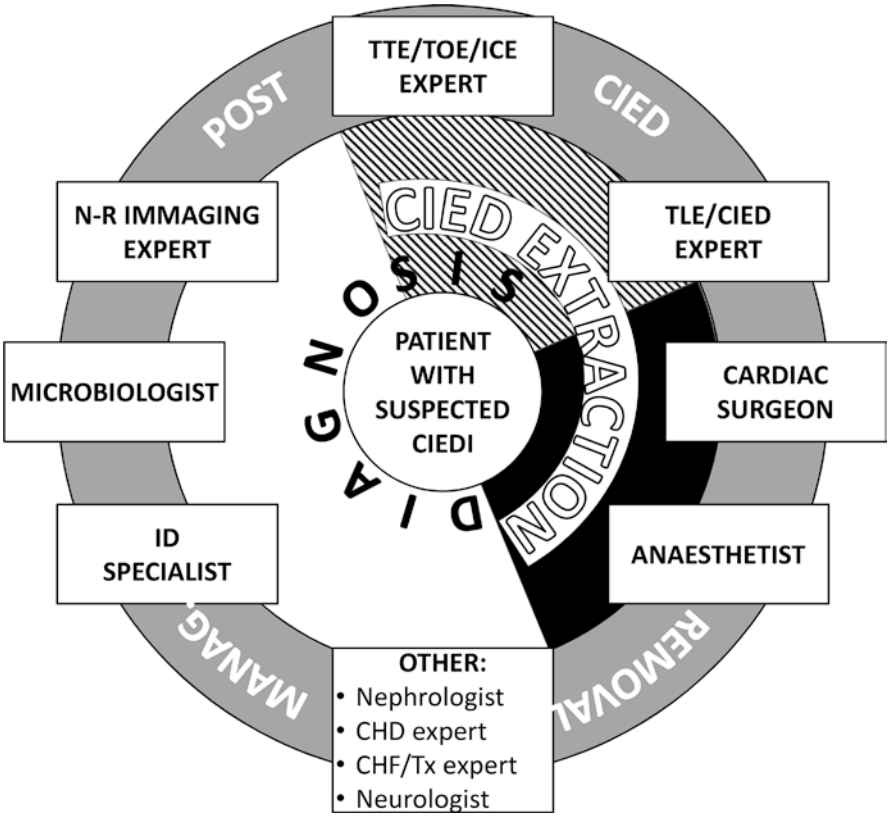


Fig. 4.4 The ideal "CIEDI-team". Representation of an ideal, multidisciplinary team for the management of patients with CIEDI. The diagnostic workup is the first step a patient with CIEDI should undergo, to confirm or to rule out diagnosis. This step requires a careful evaluation of the patient performed by experts in imaging, nuclear diagnostics, and microbiology; the need of further specialists (nephrologist, neurologist, etc.) should be tailored on the characteristics of the patient. The decision regarding percutaneous (dashed lines) or surgical lead extraction (black area) should be taken after an accurate evaluation of echocardiographic findings by a team with experience in lead extraction, consulting a cardiac surgeon and anesthetist when necessary. *CIEDI*, cardiac implantable electronic device infection; *CHD*, coronary heart disease; *CHF*, chronic heart failure; *ID*, imaging diagnostic; *N-R*, nuclear radiology; *TLE*, transvenous lead extraction; *TOE*, transoesophageal echocardiography; *TTE*, transthoracic echocardiography; *Tx*, cardiac transplantation

findings or complaints associated with a pocket site indicate infection. In many cases, signs and symptoms resolve without intervention, signifying normal wound healing or a local superficial reaction. In general non-CIEDI pocket reactions occur early after CIED pocket manipulation (<30 days) without any characteristic suggesting involvement of the deeper portion of CIED pocket or systemic diffusion (Fig. 4.5). Differences among the various documents are related to the strength of the suggestion to proceed to TLE in patients with native/prosthetic valve endocarditis or bacteremia in CIED carrier without a definite diagnosis of CIEDI. These cases are more challenging requiring a careful approach and patient information.

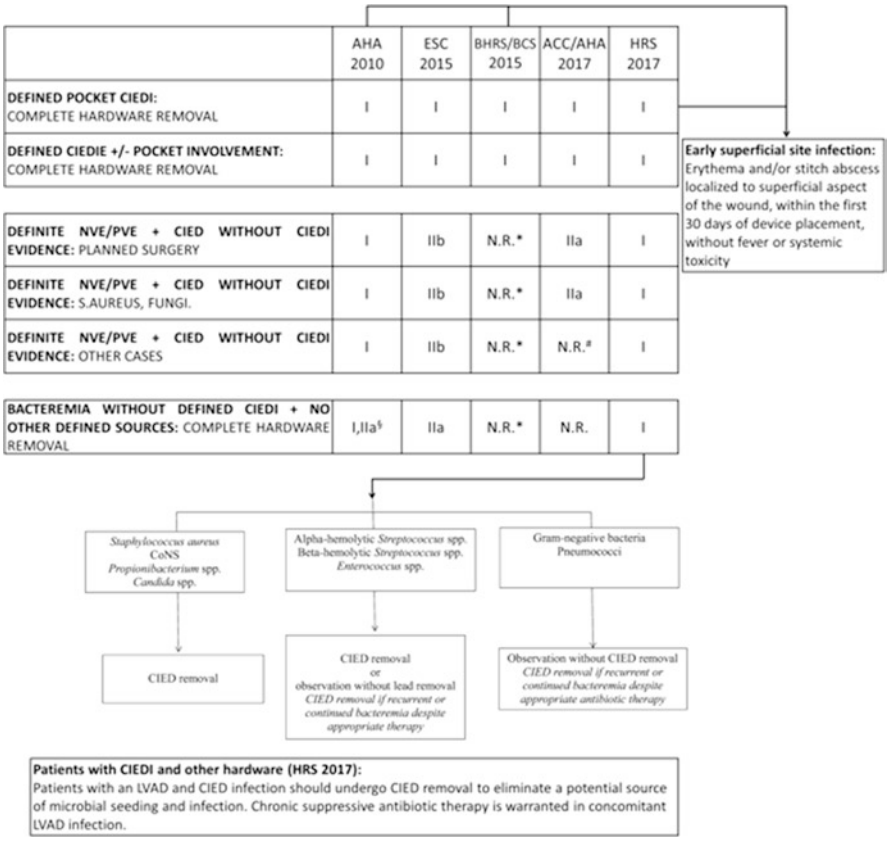


Fig. 4.5 Main guidelines on lead extraction [1, 19, 25–27]. *CIED(I)*, cardiac implantable electronic device infection; *N.R*, not reported; *NVE*, native valve endocarditis; *PVE*, prosthetic valve endocarditis

4.4 Transvenous Lead Extraction

CIEDI is associated with a risk of death up to 66%. This value is decreased to about 18% when infection is treated with prolonged i.v. antibiotic therapy and complete system extraction.

4.4.1 Safety and Efficacy

In the last 15 years many reports of single and multicenter transvenous lead extraction experiences were published (Table 4.2), but data about safety and efficacy supported by large studies were lacking. Two large multicenter prospective independent from industry observational studies of consecutive TLE procedures have been recently performed both in Europe and in North America: the ELECTRa and the LExICon registries.

Table 4.2 Overview of large prospective and retrospective studies for transvenous lead extraction

	Year of publication	Number of patients	Number of centers	Study design	Complete success rate (%)	Partial success rate (%)	Failure rate (%)	Major complication rate (%)
US database	1994	1299	64	Retrospective	86.8	7.5	5.7	2.5
US database	1996	2338	28	Prospective	93.0	5.0	2.3	1.4
Laser US total experience	1999	1684	50	Retrospective	90.0	3.0	7.0	1.9
LExICon study	2010	1449	47	Prospective	96.5	2.3	1.1	1.4
LEADER 2012 (Cook Vasc)	2012	2021	30	Prospective	93.3	4.2	2.5	1.4
ELECTRa registry	2017	3555	73	Prospective	95.7	2.8	1.5	1.6

Adapted from Auricchio et al. [33]

4.4.1.1 The ELECTRa Registry

In 2012 the European Heart Rhythm Association (EHRA) designed a large multicenter prospective registry of consecutive TLE procedures with the aim of identifying safety and efficacy of the current clinical practice about device extractions [34]. The registry enrolled, from November 2012 to May 2014, a total of 3555 consecutive patients of whom 3510 underwent TLE at 73 centers in 19 European countries. Primary endpoint was procedure safety, defined by pre-discharge major procedure-related complications, including death. Secondary endpoints included clinical and radiological success after TLE and all-cause in-hospital major complications; predictors of success and major complications were evaluated and outcomes were also compared between high-volume and low-volume centers, defined as ≥30 and <30 TLE procedures per year, respectively, according to the EHRA consensus document [35].

A total of 6493 leads, including 4917 pacing leads (75%) and 1576 ICD leads (25%), were targeted for extraction. Indications for TLE were infective in 52% (19% systemic infections and 33% local infections) and noninfective in 48% of the patients enrolled.

Primary endpoints: procedure-related major complications, including death, occurred in 58 patients (1.7%), 37 (1.1%) of which were intra-procedural and 21 (0.6%) were post-procedural. Seventeen patients (0.5%) died for procedure-related complications.

Secondary endpoints: all-cause in-hospital major complications occurred in 95 patients (2.7%) and all-cause in-hospital death occurred in 50 patients (1.4%). The overall radiological success rate, defined as complete removal of the leads (considered for each lead), was 95.7%, while the clinical success rate, defined as the absence of either a procedure-related major complication or a failure to achieve the clinical outcome for which the TLE was scheduled (considered for each patient), was 96.7%.

Nowadays the ELECTRa registry remains the largest registry available on current clinical practice of transvenous lead extraction. The strength of this study relies on the fact that is led by an independent scientific society. Among interesting aspects of this observational study the noninfective issues represented the main indication for extraction in almost a half of total procedures. The TLE efficacy, expressed as clinical (97%) and complete radiological (96%) success rate, was very high and confirmed the previous experiences.

4.4.1.2 The LExICon Registry

In 2010 another large multicenter prospective observational study was conducted in the USA and Canada. The aim of the study was to examine the safety and efficacy of laser-assisted lead extraction along with indications, outcomes, and risk factors in a series of 1449 consecutive patients enrolled from January 2004 to December 2007. The most common indication for extraction was infection, 57% of total with a 29.2% of systemic infections and 27.8% of pocket infections. Clinical success, defined as the ability to remove all lead material from the vascular space, was achieved in 97.7% of patients. The all-cause in-hospital mortality rate was 4.3% for

patients with device-related endocarditis, 1.7% for pocket infection, and 0.3% for all noninfected patients. The multivariate model indicated that failure to achieve clinical success was associated with patient BMI < 25 and when the extraction center volume was <60 cases over a period of 4 years.

4.4.2 Predictors of Adverse Short-Term Outcome

4.4.2.1 The ELECTRa Registry

Independent predictors of adverse outcome were also evaluated in the ELECTRa study. Procedure-related major complications and deaths were more common in female patients (OR 2.11), leads with a dwell time superior to 10 years (OR 3.54), the use of powered sheaths (OR 2.40), and a femoral approach (OR 3.60). Predictors of clinical failure were similar and included: low-volume centers (OR 2.23), female gender (OR 1.81), leads with a dwell time superior to 10 years (OR 4.00), three or more leads targeted for extraction (OR 2.47), the use of powered sheaths (OR 1.89), and a femoral approach (OR 3.93). Predictors of increased all-cause in-hospital mortality included low-volume centers (OR 2.02), age > 68 years (OR 2.42), NYHA class III or IV (OR 4.08), and presence of systemic infection (OR 4.93).

Predictors of outcome are multivariate and they can therefore be divided in two main categories: on one hand, not modifiable factors related to patient and lead profile, which may be used once recognized to stratify the procedural risk, and, on the other hand, those modifiable, related to the procedure, such as type of vascular approach (i.e., superior venous entry vs. transfemoral), the specific tool and technique used (i.e., mechanical vs. powered sheath), and the operator experience/center volume (high-volume vs. low-volume centers).

4.4.2.2 The LExICon Registry

In the LExICon study independent predictors of all-cause in-hospital mortality were renal insufficiency (defined as a serum creatinine >2 mg/dL), diabetes, BMI < 25, and presence of infection. No other risk factors were evaluated.

4.4.3 Predictors of Adverse Long-Term Outcome

Despite a great improvement in techniques and results of TLE procedures, the long-term survival after TLE for CIED infection is still poor [36]. The development of leadless pacing systems and entirely subcutaneous defibrillators as a possible approach for these patients could improve their prognosis, but at present it cannot satisfy the huge clinical demand and healthcare costs. For this reason more data about long-term risk stratification is needed in order to properly manage post-extraction patients and define the best reimplant strategy and optimize long-term follow-up.

Risk factors for development of CIED infection have been analyzed in a recent multicenter prospective observational study and have been found to be also

predictive of post-TLE mortality [37]. Overall mortality was 4.1% at 90 days and 12.5% at 1-year and 23.5% at 3-year follow-up (in line with previous, mainly retrospective, data). The presence of impaired renal function (eGFR <60 mL/min), chronic heart failure, diabetes mellitus, and anticoagulation therapy were significant predictive factors for mortality. In particular a Shariff score >3 [38] and the presence of vegetations at transesophageal echocardiography (TOE) were independent predictors of death for any cause [Fig. 4.6].

Another single center prospective observational study [39] showed that the modified Duke criteria for infective endocarditis provide a reliable estimate of long-term outcomes in patients undergoing TLE, despite the criticism about the lack of sensitivity in the diagnostic process.

No difference in long-term survival was recorded among patient with versus without post-TLE reimplant, while presence of post-TLE ghosts, eGFR <60 mL/min, and a closed CIED pocket were all independently associated with a worse

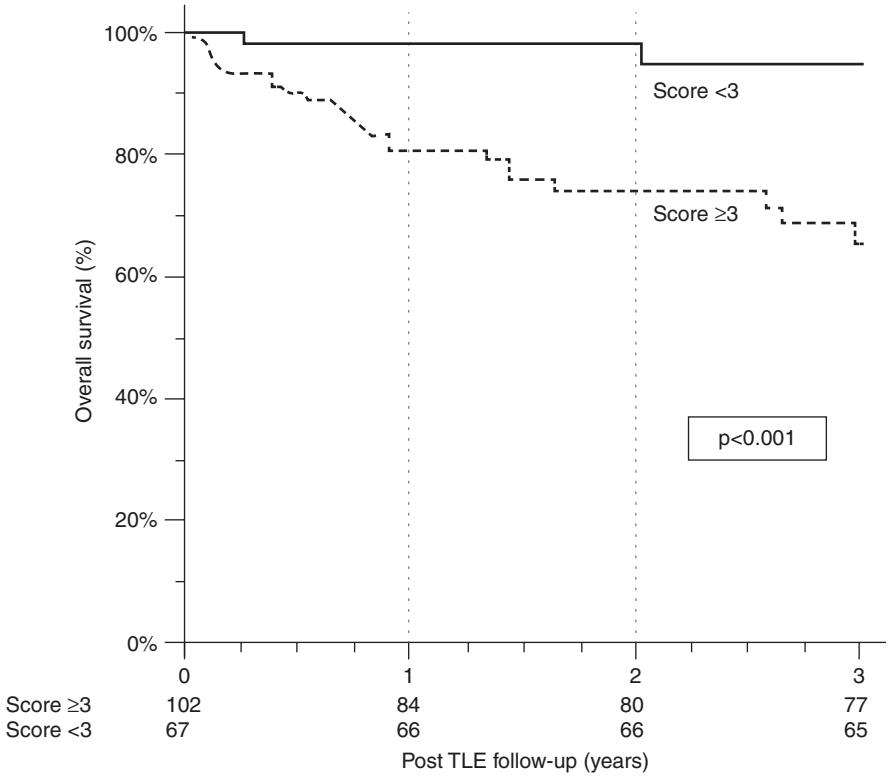


Fig. 4.6 Kaplan-Meier curves of patients according to "Shariff score". The graphic shows the comparison of survival of patients according to the presence of risk factors for infection at the moment of cardiac device implantation, as described by Shariff et al. [38]. A higher-risk score (equal or greater than 3) is related with a higher mortality rate. *TLE*, transvenous lead extraction. Image from Diemberger et al., 2017 [37]

prognosis in terms of death or infection relapse/recurrence. Several explanations have been proposed for this last risk factor: the presence of a skin lesion could enable early identification of CIED infection without delaying the extraction, while the possibility of obtaining pre-TLE swab samples from the pocket could impact on the reimplant procedure management and timing.

4.4.4 What About Abandoned Leads?

As the CIED population is growing, more patients undergo every year CIED pocket interventions for system changes, revisions, or upgrading procedures, increasing the number of a potentially complicating issue: lead abandonment. CIED re-interventions occur more frequently during patients' lifetime and represent known risk factors for infection; on the other hand lead abandonment could enhance the risk of developing infection (Fig. 4.7).

A large prospective registry of 1386 consecutive patients undergoing TLE for local or systemic CIED infection (323 of which with previously abandoned leads) has been published [40]. The primary clinical endpoint was complete procedural and clinical success defined as the successful removal of the device and all lead material from the vascular space, in the absence of a major complication. Failure to achieve the primary endpoint occurred more frequently in patients with abandoned leads (13% vs. 3.7%, $p < 0.0001$). This was primarily due to retention of lead material, which was associated with poor clinical outcomes including higher rates of short-term mortality (death at 1 month 7.4% vs. 3.5% in those without lead remnants). TLE procedures in patients with previously abandoned leads were also

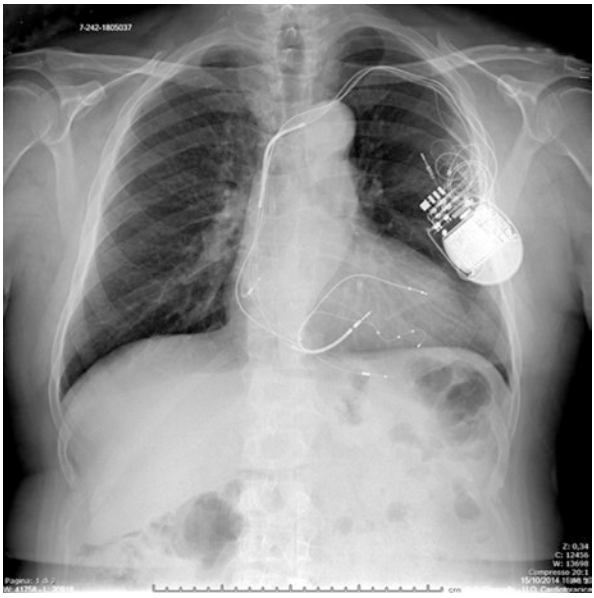


Fig. 4.7 Chest X-ray of a patient with multiple abandoned CIED leads. Abandoned leads are a common finding in patients who have been subjected to multiple procedure of CIED revision, and their presence is related with a higher risk of infections. This chest X-ray of a patient with an infected biventricular defibrillator shows abandoned right and left ventricular leads. After complete extraction, a contralateral biventricular defibrillator was reimplanted

longer, with longer fluoroscopy times and more likely to require specialized extraction tools or adjunctive rescue femoral workstations. Moreover procedural complications occurred more frequently in patients with previously abandoned leads (11.5% vs. 5.6%, $p < 0.0003$) for both major and minor complications.

4.4.5 Gray Areas

Despite the growing knowledge about infection diseases and their management, there are huge gaps in evidence. Although in case of infected devices a complete removal is mandatory, as seen before, the following points have to be addressed:

- **Standardization**
  Standardization of definitions and reporting of parameters are mandatory in order to analyze, compare, and pool data for scientific purposes. For this reason the European Heart Rhythm Association has commissioned an expert consensus statement to provide recommendations for designing scientific studies, reports, and registries relating to lead extractions [29].
- **Optimal Antibiotic Strategy**
  Type, duration, cost-effectiveness
- **Development of a Scoring System for Risk Stratification**
- **Reimplantation Strategy**
  - *Timing*
    Determine the safety of 1 stage contralateral device replacement compared with 1 stage epicardial or delayed device replacement guided by validated management algorithms in local and systemic infection
  - *Type of Device*
    Transvenous (one lead if possible?), epicardial, subcutaneous, leadless
    When considering device reimplantation after infections, there is poor evidence supporting management strategies. An ideal reimplant strategy would minimize the number of procedures and the amount of discomfort for the patient. The 2017 Heart Rhythm Society expert consensus on transvenous lead extraction suggested that all patients should have negative blood cultures for at least 72 h before reimplantation. There is a shy encouragement (C evidence level) to extend that interval to at least 14 days when there is evidence of valvular vegetations.
    Prior to reimplant, all patients should be thoroughly evaluated to reassess their need for a CIED. Reasons for not reimplanting devices include improved cardiac function, recovery of sinus function, and improvement of symptomatic bradycardia.
- **Dedicated Diagnostic Criteria for CIED Infection**
  Modified Duke criteria, role of additional diagnostic tools (PET, intracardiac echocardiography, etc.)
- **Shared Definition of High- and Low-Volume Centers**

4.5 Conclusions

CIED infection is an increasing problem due to rising absolute numbers of CIED procedures and increasing patient comorbidity. The key challenge in the management of CIED infections is clearly prevention. Careful prescription of CIED treatment and careful patient preparation before implantation is pivotal.

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Building Up the Diagnosis of Cardiac Device Infections: The Role of Imaging

5

Igor Diemberger, Stefano Lorenzetti, and Rachele Bonfiglioli

5.1 Introduction

Imaging represents only a part of the workup for the diagnosis of cardiac implantable electronic device (CIED) infection. Clinical examination, laboratory exams, blood cultures, and swabs all are mandatory steps for the diagnostic process, similarly to what occurs during diagnosis of endocarditis. However, since the diagnosis of CIED infection (CIEDI) may often be challenging, because signs and symptom may be mild or confusing [1], imaging has a key role in the management of a patient with suspect CIEDI, especially in patients without overt involvement of CIED pocket. Notably, the role of imaging techniques in CIEDI is not limited to rule out the diagnosis but also for the assessment of the extension of the infectious process, evaluation of presence of infective endocarditis, detection of complications of secondary localizations of infection and follow-up and as a help during transvenous lead extraction (TLE), and for planning CIED reimplantation. Echocardiography was the first of these imaging techniques introduced and it still represents the gold standard for detection of cardiac involvement in CIEDI, being echocardiographic positivity the only imaging data included as a standard major criteria for the assessment of endocarditis according to modified Duke criteria [2]. However other approaches, either anatomical like computed tomography or functional like nuclear imaging, are involved in a growing expanse of their indications and are currently included in guidelines [3].

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5.2 Echocardiography

Echocardiography, both transthoracic (TTE) and transesophageal (TEE), represents the gold standard for diagnosis of infective endocarditis [3], being the imaging technique of choice for the assessment of modified Duke criteria [2]. Standard TTE is an easy accessible methodic and should be always performed in patients with a suspicion of CIEDI during the initial evaluation; in addition, TEE should be considered in patients with possible CIEDI [3], given their complementary data.

5.2.1 Vegetations in Patients with CIEDI

Presence of vegetations is the most important findings provided by echocardiography when CIEDI is suspected (Fig. 5.1). Vegetations are defined as oscillating masses with motion independent from the heart, attached to a native cardiac valve, to endocardial surface, or to prosthetic material like prophetic valve or CIED leads [4]. When these characteristics are met this finding fulfills one of the major criteria for modified Duke criteria used for diagnosis of endocarditis (Table 5.1) [2]. In general vegetations can be identified in 20–25% of patients with CIEDI [5, 6].

The superior sensitivity of TEE vs. TTE for identification of infective vegetations, for the closer distance to involved structures without interposition of lungs, is well known. TEE sensitivity and specificity for the detection of tricuspid valve vegetations are 70% and 96% for native cardiac valves, while it is lower for prosthetic valves 50% and 92%, respectively [7]. For comparison, the reported sensitivity of

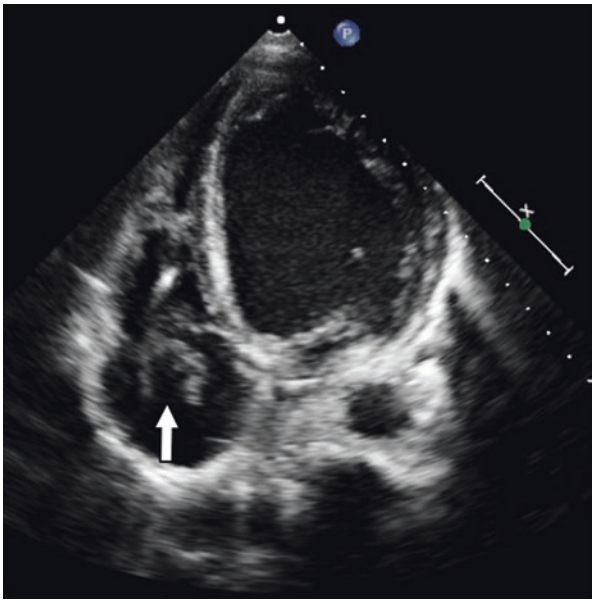

Fig. 5.1 Valvular vegetations in CIED-related endocarditis. Transthoracic echocardiogram in a patient with CIED infection, which shows a large vegetation (pointed by the arrow) attached to the atrial side of the tricuspid valve

Table 5.1 Modified Duke criteria for the diagnosis of endocarditis

Major Criteria
1. Positive blood cultures, either by: (a) Microorganism typical for IE (viridans streptococci, *Streptococcus gallolyticus*, HACEK group, *Staphylococcus aureus*, community-acquired enterococci), found in at least two separate BC (b) Microorganism consistent with IE from repeated positive blood cultures (at least two positive BC obtained with a time interval >12 h; all of three or the majority of four positive separated BC; a positive BC for *Coxiella burnetii* or antiphase I IgG antibody titer >1:800) 2. Evidence of cardiac involvement at imaging (a) Echocardiogram positive for IE (perform TEE if there is at least a "possible IE" according to clinical criteria, in patients with suspected complicated IE (i.e., paravalvular abscess) and in patients with prosthetic valves; TTE first in other cases)
Minor Criteria
1. Predisposition: predisposing heart condition or injection drug use 2. Fever as temperature >38 °C 3. Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysms, intracranial hemorrhage, conjunctival hemorrhages, Janeway's lesions 4. Immunological phenomena: glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor 5. Microbiological evidence: positive blood culture that does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with IE

A diagnosis of "definite" endocarditis requires two major criteria, or one major and three minor criteria, or five minor criteria [2]. If those criteria are not met, a diagnosis of "possible" endocarditis is performed with one major criterion and one minor criterion or three minor criteria. *BC*, blood cultures; *HACEK*, *Haemophilus parainfluenzae*, *H. aphrophilus*, *H. paraphrophilus*, *H. influenzae*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella kingae*, and *K. denitrificans*; *IE*, infective endocarditis; *Ig*, immunoglobulin; *TEE*, transesophageal echocardiography; *TTE*, transthoracic echocardiography

TTE is far lower (22–43%) [8]. For CIED infections, the detection of lead-related vegetations is also well performed by TEE with a reported sensitivity of 91–96% [9–11], while the sensitivity of TTE is lower at 22–30% [12] (Figs. 5.2 and 5.3). Another advantage of TEE over TTE is the possibility to visualize vegetations in atypical locations hardly visible to standard TTE such as: the right atrium, the proximal portion of the superior vena cava, and some portions of the right ventricle [7], even if it should be underlined that TEE accuracy may be lower in these cases [8] which in specific cases can be overcome by intracardiac echocardiography (ICE; see below) [13]. Notably, use of TEE is particularly relevant in planning CIED removal to rule out involvement of native/prosthetic valve beyond CIED hardware. It has been estimated that a similar event occurs in 13–30% of all CIEDI [9, 10, 14] [for additional information see also Chaps. 1, 2, and 4] [7] and a similar evidence may drive the choice of preference to a complete surgical reparation in spite of standard transvenous lead extraction (TLE). Cardiac abscess is another CIEDI-related echocardiographic finding (Fig. 5.4), which is better visualized using TEE (90% sensitivity of TEE vs. 50% sensitivity of TTE) [7].

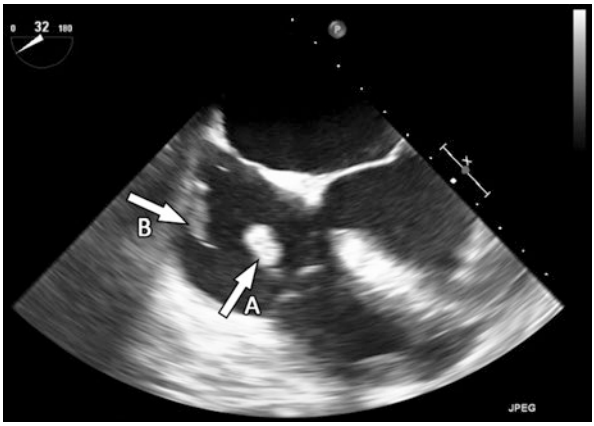

Fig. 5.2 Echocardiographic findings in CIED-related endocarditis. Transesophageal echocardiogram (TEE) provides a better visualization and a higher sensitivity for the detection of endocarditic vegetations. In this picture, TEE shows a large tricuspid valve vegetation (**a**) and also a vegetation attached to the right atrium wall (**b**)

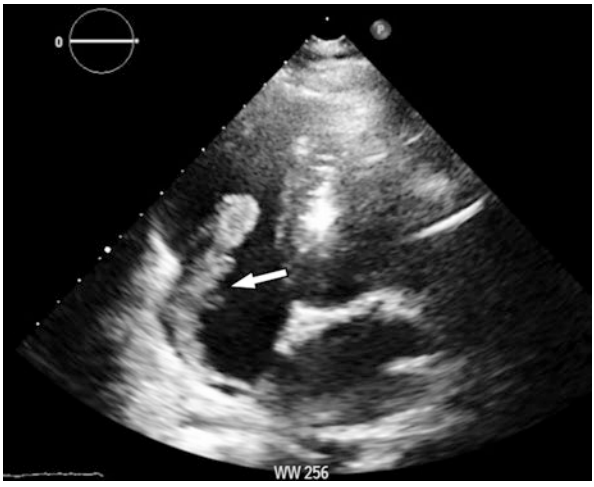

Fig. 5.3 Lead-related endocarditis. Transthoracic echocardiogram in a patient carrier of an infected CIED. The arrow points a large vegetation attached to the CIED lead

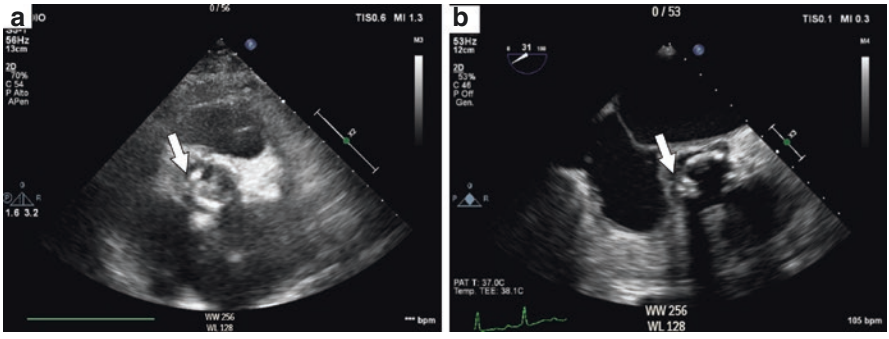

Fig. 5.4 Perivalvular abscess as an echocardiographic finding. Endocarditis-related abscess around aortic valve, visualized as an echogenic space in view of its liquid content. Both images have been obtained from the same patient, adopting transthoracic echocardiogram in (**a**) and transesophageal echocardiogram in (**b**)

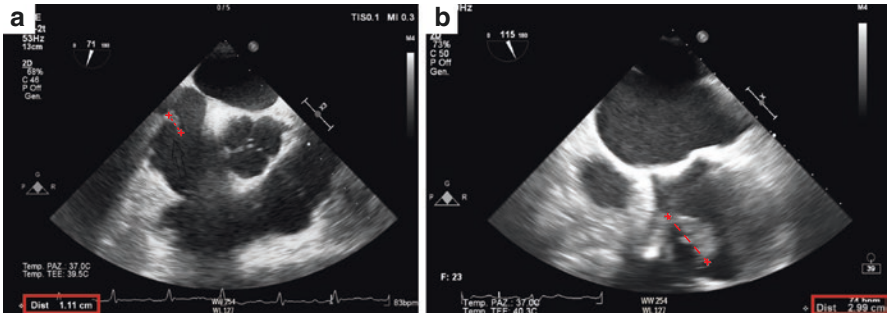

Fig. 5.5 Measurement of endocarditic vegetations. Echocardiography represents a useful tool for the measurement of endocarditic vegetations. Pictures **a** and **b**, obtained from transesophageal echocardiogram of two different patients with CIED infection, show vegetations of different size (highlighted in red)

Accurate visualization of infective vegetations is not only relevant for assessing the presence of CIEDI-related endocarditis but also to properly estimate their size, which is a factor of extreme relevance to plan CIED removal strategy (Fig. 5.5). Presence of vegetations in a patient with patent foramen ovale is a particular issue for the risk of paradoxical systemic embolization (e.g., risk of septic stroke) which is generally managed with surgical treatment [3]. The second major concern in patients candidate to TLE and vegetations is the risk of pulmonary embolism during TLE. In general during TLE it is expected to have limited pulmonary embolism from the thrombotic/infective material surrounding the leads; however it is really infrequent that this phenomenon is associated with relevant sequelae. Formerly, a cutoff of vegetation size >10 mm was proposed [11] to perform a surgical extraction, based on initial experience on complications after extraction. However, the same authors highlighted that while two of the five patients undergoing TLE with vegetations >10 mm presented scintigraphy evidence of embolism only one with a vegetation >40 mm presented nonlethal, hemodynamic consequences. On the opposite the four in-hospital deaths among 52 patients (7.6%) occurred either pre-extraction (two patients) or after surgical extraction (two patients with vegetation sizes of 14 and 20 mm, respectively). Subsequent studies demonstrated the safety of TLE even in patients with vegetations larger than 20 mm [15]. A retrospective review from Mayo Clinic [14] reported the absence of clinical relevant pulmonary embolism even in patients with large vegetations (range 0.3–7 cm). A consistent result was reported also in another retrospective study published by Baman et al. [16], in which the vegetation size and the presence of pulmonary embolism was not associated to patients' outcome. However, it should be underlined how in this study was reported a higher prevalence of patients with elevated (higher than 60 mmHg) right ventricular pressure and with pulmonary embolism among the death cohort. This may be due to the presence of a more severe disease in these patients, but another explanation is that these factors may represent the consequences of a prior embolization of larger vegetations. It should be noted, indeed, that the sizing of endocarditic vegetation depends by the timing in which echocardiogram is performed.

For all these considerations current guidelines do not provide a limitation in terms of vegetation size to proceed with percutaneous CIEDI removal, but they suggest to tailor the extraction strategy on an individual basis [17]. At this regard, it is important to consider the evolution of tools and techniques for CIED extraction that are providing additional approaches for challenging cases. In particular, the introduction of the AngioVac (AngioDynamics, Latham, NY) system has enabled experienced operators to free leads from vegetations by aspiration without the need for open-chest extracorporeal circulatory system and pulmonary bypass (*see below*).

A latter consideration is that TTE should not be disregarded in management of CIEDI since it is not inferior to TEE for general cardiovascular evaluation before TLE (left/right ventricular function, valvular dysfunction, etc.) but also after TLE. The easier repeatability of TTE makes it useful to monitor heart recovering and assess for some complications that can manifest/progress also later after TLE: left/right ventricular dysfunction, tricuspid regurgitation, pericardial effusion, and pulmonary artery pressure (which may increase in the presence of pulmonary septic embolism) [3, 7].

5.2.2 Limitations of Echocardiography for CIEDI Diagnosis

It should be underlined that a negative echocardiogram does not rule out CIEDI. Indeed, despite being the gold standard technique, TEE still presents a non-negligible rate of false negatives. The main reasons for the under detection of cardiac vegetations are as follows: (a) early use of TEE (during a stage in which vegetations are not present yet), (b) non-floating or atypically shaped vegetations (e.g., infective material along the course of the lead without a definite mass), (c) small vegetations, and (d) inadequate visualization (usually when intracardiac prosthetic material is present, causing a shadowing effect on echoes) [13]. Given the unsatisfactory negative predictive value, especially in patients with prosthetic material, if the clinical suspicious persists, a second imaging technique should be considered according to ESC guidelines [3].

Another reported limitation of echocardiography is the risk of false-positive results. This possibility rises from the intrinsic characteristics of echocardiography which in case of vegetations it provides information on size, shape, and movement. However, composition of the identified mass can only be speculated and differentiating sterile masses or thrombus from endocarditic vegetation may become a hard task [8]. This is especially frequent among CIED carrier, since the presence of strands and fibrous material is a common finding and may represent a confounding factor. Indeed, in a comparative study of TTE and TEE including both patients with an established diagnosis of CIEDI (n = 23) and controls (n = 70), TTE was positive in 7/23 vs. 21/23 with TEE. Notably, strands were visualized by TEE in 5/70 patients. The size of strands was lower (in general

1–2 mm wide and 3–5 mm long) and they were all localized in the right atrium [9]. In other reports incidental masses attached to CIED leads have been reported in up to 22% of the patients [9, 18, 19]. For this reason, Lo et al. performed a large retrospective study reviewing about 2000 consecutive TEE to identify patients with visible leads. Fifteen among the 125 exams with "explorable" CIED lead presented a mass and only 9/15 presented a pre-TEE suspect of CIEDI. The six patients with incidental mass were treated with medical therapy alone without sequelae [18]. Downey et al. performed a similar study analyzing 177 TEE from 153 candidates to TLE. They found lead-associated masses in 14% of them without any evidence of infective origin in about three quarters [19]. For these reasons, in patients without a clinical suspicion of CIEDI or with ongoing infection with other plausible sources, a second imaging technique, like positron emission tomography or white blood cell single-photon emission computed tomography, should be considered to define the nature of unclear masses.

5.2.3 Intracardiac Echocardiography

Intracardiac echocardiography (ICE) has been recently proposed as a further evolution of echocardiography with the potential to overcome some of the limitations of extravascular techniques, especially in CIEDI settings. This derives from a higher resolution and the possibility to closely study distant area (e.g., vena cava) (Fig. 5.6) [13]. A prospective study comparing the diagnostic accuracy of TEE and ICE was conducted by Narducci et al. [13] in 162 patients with a diagnosis of CIEDI and all referred for TLE. All patients underwent both TEE before TLE and ICE that was performed right before TLE and prosecuted during the procedure for monitoring possible complications. The authors also included a control group of patients referred to TLE for lead malfunction. ICE allowed higher sensitivity for vegetations (100% vs. 73% in patients with definite endocarditis), with no reported loss in specificity (all controls resulted negative for both techniques). The main advantages of ICE have been described in patients with intracardiac masses located in sites whose visualization at TEE is reduced, such as vegetations attached to the right ventricular lead, crossing the tricuspid valve. This is mostly due to the suboptimal visualization of the right ventricle with TEE, given the greater distance between the probe and this chamber, placed anteriorly [20]. Moreover, ICE allows detection of vegetations also in unusual sites like innominate vein [21]. The lower risk of shadowing artifacts from leads and other prosthetic materials also has a role [13], enabling the possibility to detect concentric masses around leads [8]. The main factor limiting a wider adoption of this methodic is the relatively high cost of the disposable devices and the need for the invasive nature of the procedure. For this reason, while it is clearly a helpful tool for monitoring patient during TLE, the indication for ICE in the diagnostic process of CIEDI have still to be defined.

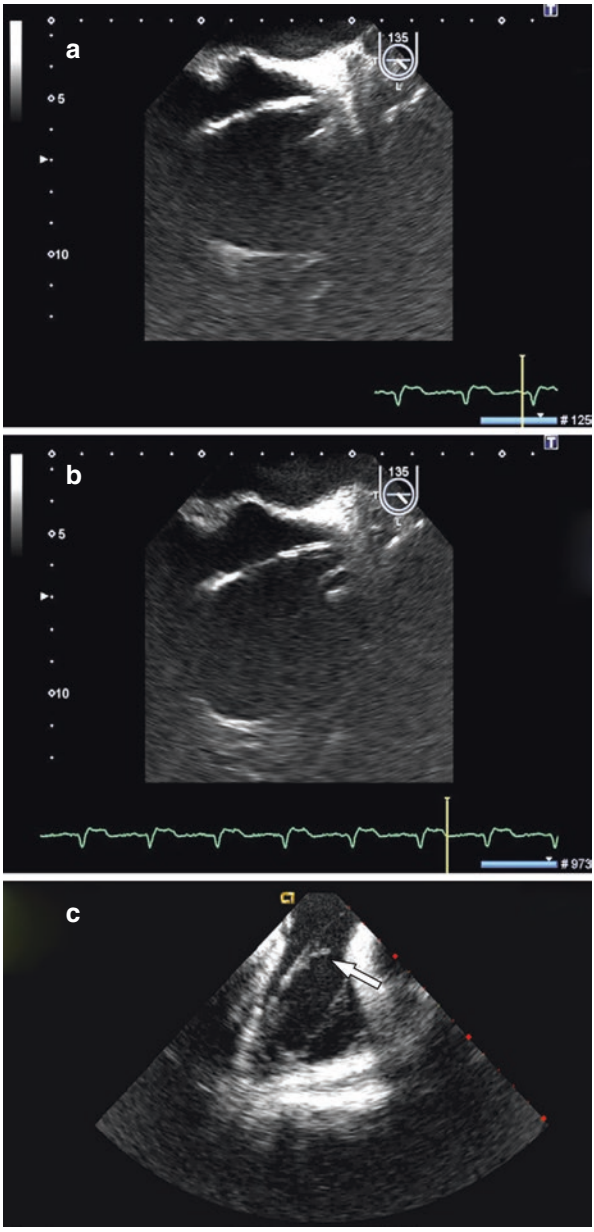

Fig. 5.6 Intracardiac echocardiography. Figures (**a**) and (**b**) show a transesophageal echocardiogram (TEE) of a patient with a suspect of CIED infection with no evidence of cardiac vegetations. The intracardiac echocardiography (**c**) shows a vegetation attached to the CIED lead, not visualized with TEE. (Reproduced from Narducci et al. [13] with permission)

5.2.4 Peri-/Postoperative Role of Echocardiography

As previously mentioned, echocardiogram plays also a role during TLE and for postoperative follow-up, to rule out possible complications [22]. In case of general anesthesia TEE is performed during TLE for a quick detection of vascular tears

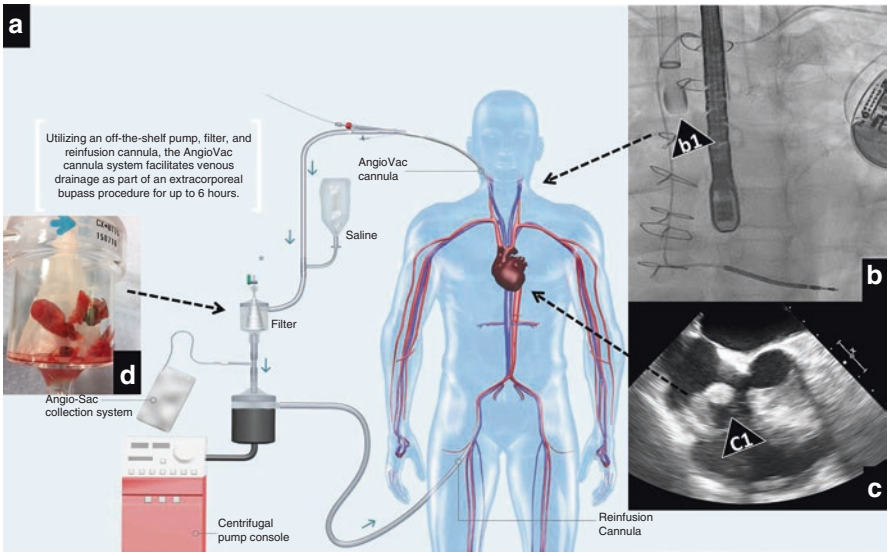

Fig. 5.7 Representation of the AngioVac system. AngioVac system (Panel **a**) (the image in the background is reproduced from Ram et al. [23] with permission). The AngioVac cannula (b1), inserted through the jugular vein under X-ray guidance (Panel **b**), drains the target vegetation (c1) under TEE guidance (Panel **c**), which is collected in the filter (Panel **d**). A reinfusion cannula is also inserted in the femoral vein to allow blood reinfusion

(with limited sensitivity), pericardial effusion, and embolization of vegetations. ICE, when available, represents an added value for improving detection of these findings but also for characterizing vascular obstruction and stenosis and the presence of fibrosis [8]. Moreover, ICE does not require general anesthesia to be used for monitoring during TLE, and this should be carefully considered when planning the procedure. A particular case is represented by candidates to percutaneous aspiration of vegetations. The AngioVac system is approved by The US Food and Drug Administration (FDA) "to remove fresh, soft thrombi or emboli during extracorporeal bypass for up to 6 h." It consists of a 22F suction cannula and is combined with a veno-venous bypass circuit and a reinfusion cannula through a filter canister, which traps any undesired material such as thrombus, before being reinfused into the patient via a reinfusion cannula (Fig. 5.7) [23]. Obviously to properly perform aspiration the procedure has to be performed under combined X-ray and echocardiography guide (TEE or ICE).

Notably, in patients who underwent TLE, aseptic residual tubular and mobile masses following the route of the extracted CIED lead have been found by echocardiogram (Figs. 5.8 and 5.9). One of the first reports of these was from Le Dolley who defined these images as "ghosts" [24]. The reported incidence for "ghosts" after TLE was 8% and authors observed a correlation between a diagnosis of CIED-related endocarditis and the detection of ghosts, which have never been observed in noninfected patients who underwent TLE. The proposed mechanism leading to

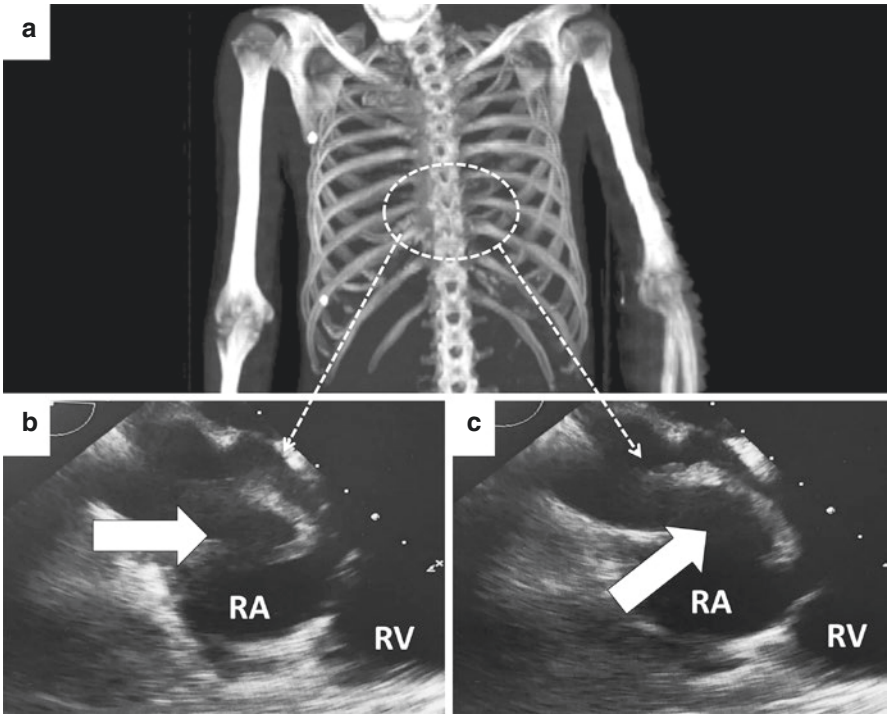

Fig. 5.8 "Ghost" found at echocardiogram. After complete extraction of all hardware (Panel **a**) the transesophageal echocardiogram shows a tubular mass fluctuating inside the right atrium, called "ghost" (Panels **b**, **c**; white arrows). *RA* right atrium, *RV* right ventricle

ghost formation after device extraction is the persistence, in patients with infection, of the fibrous sheath that surrounds the lead, with a possible overlap of vegetations. These findings should not be overlooked since the presence of "ghosts" has been associated with an over threefold increase in post-TLE mortality [25, 26].

5.3 Computed Tomography

The role of computed tomography in the diagnostic workup and risk stratification for endocarditis is a topic of growing interest during last years. When performed with ECG gating, computed tomographic angiography (CTA) demonstrated high performances for detection of morphological alterations and structural damage induced by the endocarditic process, like abscess, fluid collections, and vegetations [3, 27–29]. Technological progress allows very high levels of spatial resolution (<0.5 mm) and the ability to discriminate fast moving objects like hypermobile vegetations attached to valvular leaflets, with the possibility of tridimensional reconstruction of anatomical structures [28]. CTA findings may be helpful when performed in a patient with suspect endocarditis, but also have an added value even

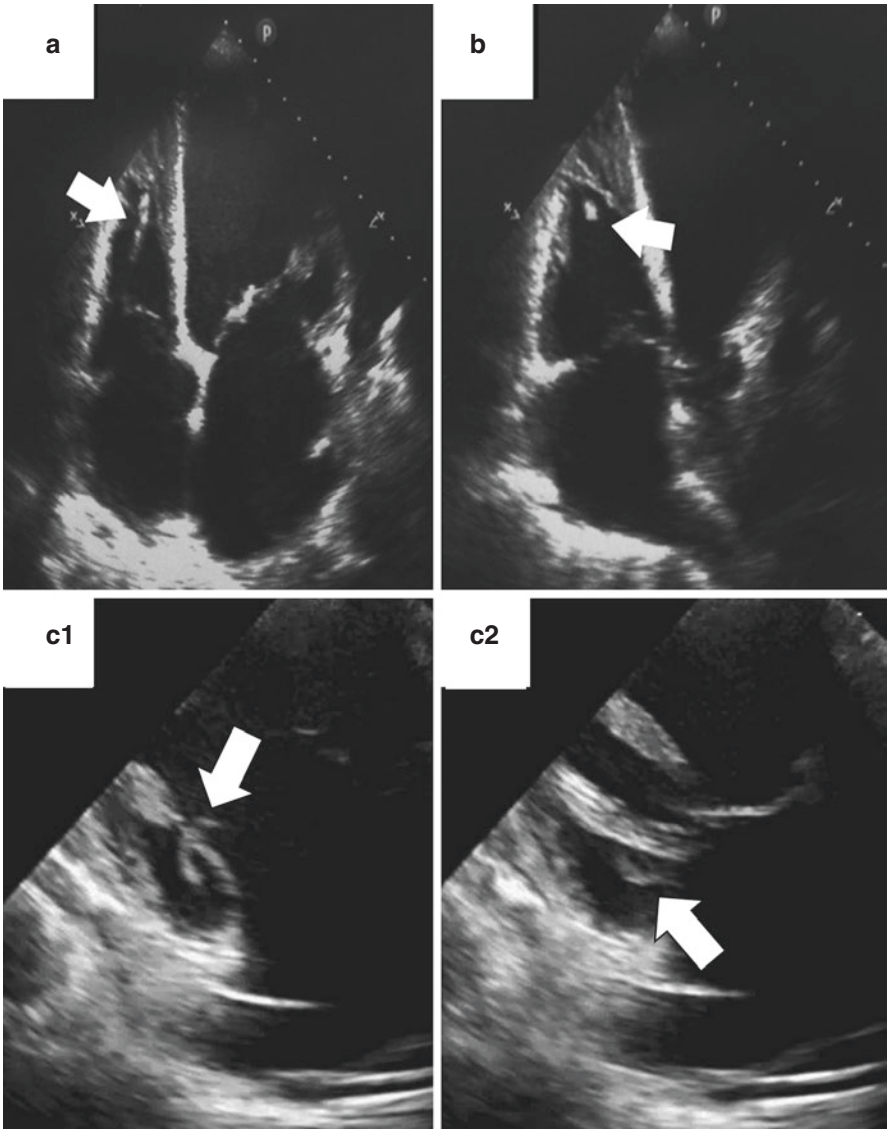

Fig. 5.9 Migration of a "ghost." Figure (**a**) is obtained from the transthoracic echocardiogram of a patient after the removal of an infected electronic device. A "ghost" is present (pointed by the arrow). Image (**b**) was recorded afterward from the same patient, showing the result of a spontaneous embolization of the "ghost" just below the tricuspid valve (**C1**, **C2**)

for those with an already established diagnosis, since it allows to detect most of endocarditic complications. CTA can detect cardiac vegetation and measure their size, thus stratifying the embolic risk, and if correctly set it is able to visualize valvular leaflet fissuration [28]. In addition, CTA has proven to be useful to assess the

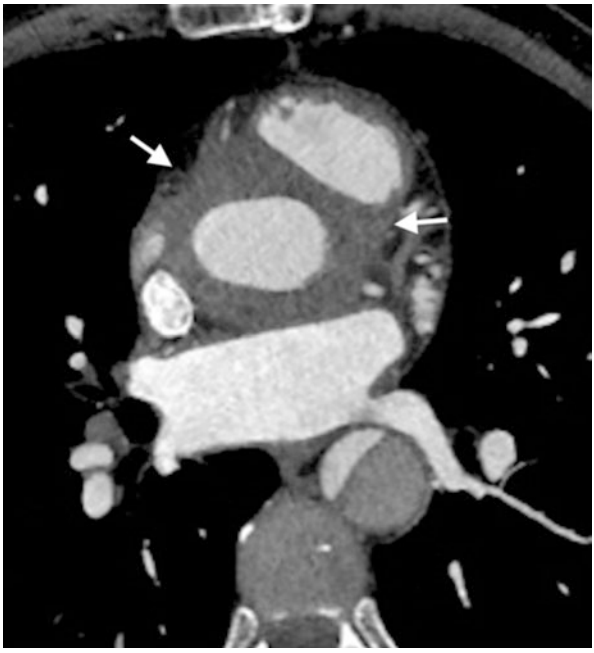

Fig. 5.10 Cardiac CT scan in endocarditis. ECG-gated computed tomography shows a para-aortic inflammatory fluid collection in a patient with endocarditis. (Reproduced from Hryniewieck et al. [30] with permission)

involvement of the perivalvular tissues by the infective process, showing high accuracy for the detection of perivalvular abscesses, pseudoaneurysms and valve dehiscence (Fig. 5.10) [30]. This information is of paramount importance since these complications represent one of the most frequent indications for cardiac surgery in patients with endocarditis [4, 31]. A comparison [32] between CTA and surgical findings reported very high rate of sensitivity and specificity for CTA in detecting paravalvular complications.

A limitation of CTA is the lower quality of images obtained in patients with irregular heart rhythms or tachycardia (a common condition in patients affected by endocarditis), that could obstacle the ECG-gating leading to the formation of artifacts. Another limitation of CTA is represented by the limited accuracy for small vegetations and small valvular perforation [28]. Moreover, metal artifacts could be present in patients who are carrier of intracardiac prosthetic material like CIED leads, which may further reduce the accuracy of CTA [27]. This is a well-known issue raised by previous studies on CIED carriers performing CTA scan showing a very high rate of reported "asymptomatic perforation" of cardiovascular structures [33]. However, the relatively low incidence of severe cardiovascular complications during TLE in current practice [34] seems to challenge these findings. Recently, first studies combining CTA with ^{18}F-FDG PET/CT have been published [35]. The key point of this new technique (PET/CTA) adding to the functional whole-body findings of ^{18}F-FDG PET/CT with a highly accurate chest CTA with ECG gating. The main goal is to obviate to the limited capacity of anatomical reconstruction for cardiac structures of the low-dose, not ECG-gated CT usually combined with PET scan, which cannot

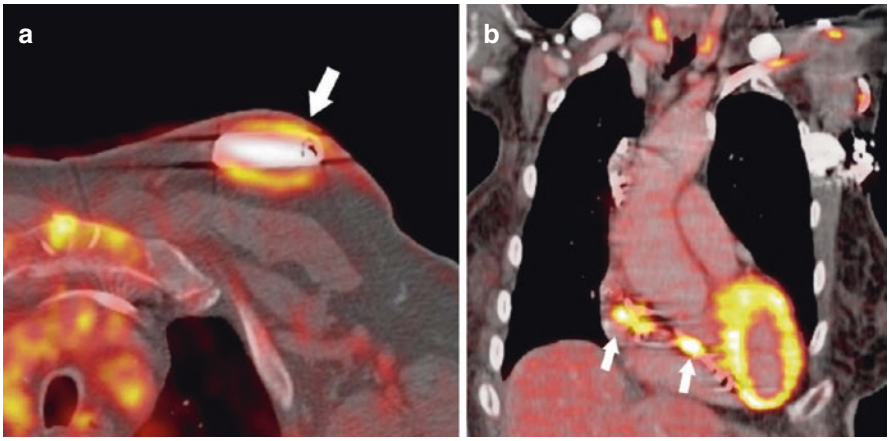

Fig. 5.11 PET/CTA. PET/CTA combines the high spatial resolution of ECG-gated computed tomography with the metabolic data provided by ^{18}F-FDG-PET. Image (**a**) shows an increased uptake of radiotracer around the CIED generator. Image (**b**): PET/CTA allowed to detect the involvement of CIED lead in a patient with infective endocarditis. (Reproduced from Pizzi et al. [35] with permission)

visualize images like valvular leaflets or vegetations [36] (Fig. 5.11) [35]. Evidence regarding the usefulness and the cost-effectiveness of this methodic is lacking, and it is not included in guidelines yet [3]. Pizzi et al. [35] reported higher sensitivity and specificity of PET/CTA compared to standard PET/CT for diagnosis of CIED and prosthetic valve-related endocarditis. Notably in that study, given the higher resolution of PET/CTA for cardiac anatomy, this technique allowed to detect a larger number of complications of endocarditis, more than PET/CT alone and also more than TEE. This is a striking fact since lots of the reported complications detected with PET/CTA (coronary artery involvement, pseudoaneurysms, fistulas) could have a surgical indication. As stated by authors further studies are needed to assess the role of this technique.

5.4 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) plays a little role in the management of patients with CIED infection. The detection of vegetations is limited by the low spatial resolution of MRI [37] and the evidence supporting the usefulness of this technique to detect endocarditis lesions comes from case reports and studies with a limited number of patients [38–40]. MRI could help in assessing perivalvular extension of endocarditis and the extent of valve regurgitation [37]. An added value of MRI is the high performance of this method in detecting secondary localizations of endocarditis in targeted sites. In particular, MRI offers high sensitivity for detection of brain embolism [41, 42].

However, focusing on CIED infections, it should be underlined that we lack of data regarding the usefulness of MRI in this context. The main determinants of this lack of evidence are represented by the aforementioned limitations of MRI and the impossibility to perform this imaging technique in a large number of carriers of older, non-MRI compatible CIED [43]. Given the larger diffusion of MRI-compatible devices nowadays, it cannot be excluded that the role of MRI for CIED infections may be further investigated in the future.

5.5 White Blood Cell Single-Photon Emission Computed Tomography/Computed Tomography

Radiolabeled white blood cell single-photon emission computed tomography/computed tomography (WBC SPECT/CT) is a nuclear medicine imaging technique that has been proposed for improving the diagnostic workup for CIEDI. Autologous leukocytes are collected and labeled in vitro with a radioisotope, either ^{111}In-oxine or ^{99}mTc-hexamethylpropyleneamine oxime (HMPAO). Labeled white blood cells are then reinjected through the bloodstream, spreading and accumulating preferentially in sites where inflammation and leukocyte migration is present [44]. Then images are acquired with a gamma camera from multiple angulations and fused with those produced by a low-dose computed tomography acquired at the same time; acquisition is performed usually 4 h after injection of radiolabeled leukocytes (Fig. 5.12) [45]. ^{111}In-oxine was the first isotope to be utilized and has progressively

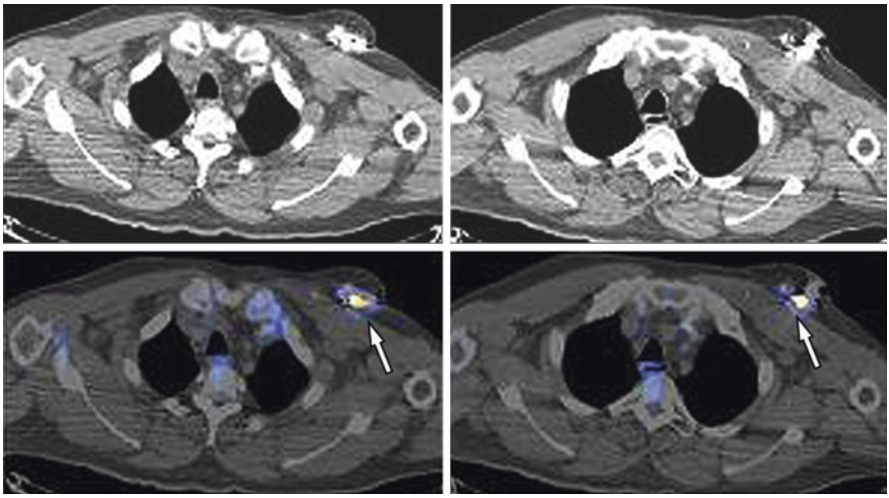

Fig. 5.12 Labeled white blood cell SPET/CT for CIEDI. Tecnetium-99 hexamethylpropyleneamine oxime-labeled autologous white blood cell (99mTc-HMPAO-WBC) scintigraphy in a patient with a suspect of CIED infection, which shows a localized pocket involvement at SPECT/CT fusion imaging (lower images; upper images show CT scan alone of the same patient). (Reproduced from Erba et al. [45] with permission)

been substituted by ^{99}mTc-HMPAO in view of the lower half-life and consequently radiation burden for the latter.

The sensitivity of WBC SPECT/CT is strictly dependent on the migration rate of labeled cells, which is influenced by the residual activity of marked leukocytes after the in vitro labeling process, the production of inflammatory mediators, the pathogenicity, and the concentration of microorganisms. Overall, WBC SPECT/CT presents low sensitivity but high specificity for infection [27]. This fact was confirmed by Rouzet et al. [46] in a small size study (39 patients) comparing WBC SPECT/CT with ^{18}F-FDG PET/CT for diagnostic accuracy for prosthetic valve endocarditis. ^{18}F-FDG PET/CT showed higher sensitivity (93% vs. 64%) but lower specificity (71% vs. 100%) compared to WBC SPECT/CT. Authors suggested that WBC SPECT/CT could be helpful after an inconclusive PET (in case of suspect of false positive) or in the immediate period after CIED implantation/cardiac surgery (when ^{18}F-FDG PET/CT utility is lowered by the high metabolism associated with the reparation process). Regarding the performance of WBC SPECT/CT for CIEDI, only one study with at least ten patients was performed [47]. Compared to a gold standard based on an integrated diagnosis with clinical and echocardiographic parameters and a 12-month follow-up, authors reported a high diagnostic accuracy for WBC SPECT/CT (94% sensitivity, 100% specificity).

5.6 Positron Emission Tomography

Being started to be adopted for clinical use during the 1990s [48], positron emission tomography (PET) with fluorodeoxyglucose marked by fluorine-18 (^{18}F-FDG) is a relatively novel imaging technique, able to provide information about the functional state of organs and tissue. PET scan reveals the pattern of utilization of glucose among body's tissues, giving to operators information about the presence of an increased metabolic activity among a particular body district, usually indicating neoplastic, inflammatory, or regenerative processes (Fig. 5.13).

5.6.1 Technical Aspects

^{18}F-FDG represents by far the most widely used tracer for PET. Fluorine-18 presents a half-life (given by radioactive decay) of 110 min and labels a molecule of fluorodeoxyglucose, an analog of glucose with similar metabolism [48]. Radioactive tracer thus is administered to the patient 45–60 min before acquiring PET scan, with an injection in blood circulation. During this period, marked fluorodeoxyglucose spreads throughout the body, being preferentially uptaken by tissues with higher glucose consumption. When transported inside cells it is metabolized to FDG-6-phosphate, a metabolite which (as opposite of normal glucose) cannot be further processed and remains trapped in cells [49]. ^{18}F-FDG accumulation is higher for neoplastic tissues, as a consequence of the higher expression of glucose transporter proteins due to increased anaerobic metabolism [50]. Moreover, some tissues

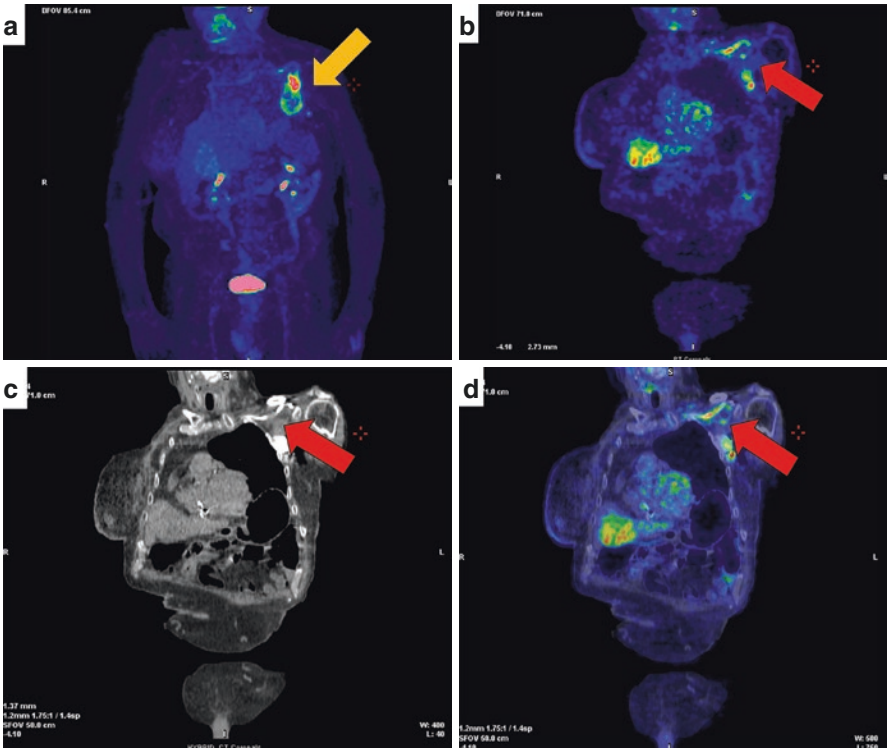

Fig. 5.13 PET/CT scan for the diagnosis of CIEDI. ^{18}F-FDG PET/CT performed in a patient with CIEDI. This scan clearly shows the increased FDG uptake at the pocket site (orange arrow in PET-only anteroposterior image, Panel **a**). The involvement of the CIED lead is evidenced after proper rotation in a trans-axial image, as evidenced by the red arrow (Panel **b**=PET-only image; Panel **c**=CT scan; Panel **d** = fusion PET/CT)

present a high rate of glucose uptake even in normal conditions, due to their intrinsically high metabolic demand, like brain, myocardium, brown adipose tissue, and urinary and gastrointestinal tract [51]. Finally, body sites where an increased concentration of cells is present, like inflammatory cell infiltration, infection site, or regenerative processes after a surgical intervention, also present an increased ^{18}F-FDG accumulation [48]. PET scan is clearly a whole body examination, usually not including the brain. The entire process (since radiotracer administration) requires usually less than 2 h [27], which represents a substantial advantage when compared to WBC SPECT/CT which takes several hours. ^{18}F-FDG undergoes beta decay with emission of positrons. After a very short distance, the issued positron meets an electron in the patient's tissue, thus developing the annihilation of both particles with release of a pair of 511-KeV photons which travel in opposite direction [48]. PET scanner detects this gamma radiation and it is able to compose the image, showing the distribution of radiolabeled FDG in the patient's body. After a first visual examination of PET images, semiquantitative evaluation is performed to establish the

maximal standardized uptake value (SUV_{max}). One of the most common pitfalls for ^{18}F-FDG PET scan is represented by the risk of false positives. ^{18}F-FDG PET is not specific for infections and/or cancers, as previously mentioned. To increase discrimination between pathologic and physiologic accumulation of the tracer, all patients should observe a fasting period of several hours, in order to reduce the concentration of insulin which contributes to alter results [48].

Whenever it is necessary to investigate the heart, as in the suspect of CIEDI, further precautions should be followed. Despite the preferential use of lipids as the primary substrate, myocardial cells have also a high glucose uptake which can conceal a lead vegetation/abscess. Thus, a fasting period >12 h preceded by one, or more, meal at high percentage of lipids and with strict limitation of carbohydrates should be considered since it can improve PET diagnostic accuracy by suppressing the native myocardial glucose uptake [52]. Unfractionated heparin has also been proposed to further reduce the physiological myocardial glucose uptake, but supportive data are more limited [53].

A known drawback of standard PET scan is the limited spatial resolution of this technique [51]. For this reason PET scan is usually combined with low-dose computed tomography (^{18}F-FDG PET/CT). This allows to correlate anatomical reconstruction and CT pathological findings with PET functional imaging, improving the sensitivity and specificity of PET scan alone [51]. An additional improvement of combining CT scan is the possibility to correct PET scan on the base of density of patient's tissues, thus providing more precise data. However, it has to be considered the possibility of generating new artifacts caused by overcorrection of attenuation for materials with high density (such as CIED leads), resulting in a false-positive increased ^{18}F-FDG uptake [27]. To preclude this, both attenuation-corrected and non-attenuation-corrected acquisitions should be evaluated when a focal positivity is observed in ^{18}F-FDG PET/CT [27].

5.6.2 ^{18}F-FDG PET/CT for Diagnosis of Infection

Every inflammatory process (either aseptic or infective) presents several characteristics favoring local FDG accumulation: (a) initially there is an increase of local perfusion combined with an increase of vascular permeability; (b) later there is a recruitment and migration of white blood cells promoted by chemotaxis; (c) finally, white blood cells, microbiological agents, and concomitant reparative process induce a higher FDG consumption [54]. All these factors contribute to the efficacy of ^{18}F-FDG PET/CT for supporting diagnosis of several challenging infectious/inflammatory processes, like fever of unknown origin [55], vasculitis [56, 57], sarcoidosis [58], and musculoskeletal infections [59]. As previously discussed, the diagnosis of infections involving the heart (i.e., CIEDI, endocarditis, prosthetic valve infection, mechanical circulatory support device infection) is particularly challenging, given the nonspecificity of symptoms and the presence of various limitations of the available diagnostic techniques. In addition, achieving an early

diagnosis of endocarditis is a mandatory task, since delay of treatment is usually associated with severe outcomes [1].

^{18}F-FDG PET/CT showed good performances in terms of sensitivity and specificity for detection of the endocarditic process. A recent meta-analysis by Mahmood et al. [60] reviewed 13 studies (for a total of 537 patients) investigating the usefulness of ^{18}F-FDG PET/CT in the contest of infective endocarditis in native or prosthetic cardiac valves and infected CIED. Authors examined all the available studies large enough to assess ^{18}F-FDG PET/CT sensitivity and specificity for diagnosis of possible infective endocarditis. The pooled sensitivity of ^{18}F-FDG PET/CT for diagnosis of endocarditis resulted 76.8% (95% CI 71.8–81.4%) and specificity 77.9% (95% CI 71.9–83.2) [60]. An ancillary but interesting fact reported by authors was a higher sensitivity found by studies with a more strict dietary control for suppression of myocardial glucose uptake before PET administration.

Consistent results were reported in a systematic review [29] where ^{18}F-FDG PET/CT reported good ability for detecting endocarditis in patients with prosthetic valves (73–100% sensitivity, 71–100% specificity, and 67–100%), whereas authors concluded that we lack data to assess performance of this methodic for detecting native valve endocarditis. Sensitivity and specificity rate increased when CT angiography was added [29].

5.6.3 Role of ^{18}F-FDG PET/CT for the Diagnosis of CIED Infection

The first report of detection of CIEDI by ^{18}F-FDG PET can probably be dated to 2006 [61]. Since then, several studies have been published on this topic, given the progressively increase of evidence supporting the usefulness of this methodic in this challenging disease both in the diagnostic and treatment process. However, we lack of large studies on ^{18}F-FDG PET/CT scan mainly because of organization issues (all available studies enrolled less than 100 patients). Table 5.2 [35, 62–71] reports the principal studies on this topic. Evidence regarding the performance of ^{18}F-FDG PET/CT for CIEDI infection comes primarily from meta-analysis and systematic reviews. The systematic review published by Gomes et al. (2016) [29] considered nine studies, mainly prospective and all of them assessing the usefulness of ^{18}F-FDG PET/CT for detecting CIEDI and finding potential extracardiac complications in patients with a suspect of CIEDI with/without endocarditis, diagnosed according to modified Duke criteria [2]. The reported sensitivity and specificity for diagnosis of CIEDI resulted high (80–89% sensitivity, 86–100% specificity, 94–100% positive and 85–88% negative predictive values). The diagnostic value was high for both lead involvement detection (24–100% sensitivity, 79–100% specificity, 66–100% positive and 73–100% negative predictive values) and pocket infection (87–91% sensitivity, 93–100% specificity, 97% positive and 81% negative predictive values). Interestingly, one of the included studies [68] compared the effectiveness of ^{18}F-FDG PET/CT performed with the standard delay of 1 h after radiotracer injection with a longer delay of 3 h; authors reported higher accuracy for 3-h delayed PET. In a more recent meta-analysis published in 2017 Juneau et al. [72] included 11 studies

Table 5.2 Main studies (more than 20 patients) assessing ^{18}F-FDG PET/CT diagnostic performance in CIED infection

Study	Year	Design	N.	Patient selection	Diagnostic gold standard	PET sensitivity-specificity (95% CI)[a]
Bensimhon et al. [63]	2011	Prospective, single center	21	Suspect of CIEDI	Culturing after device extraction or 6-month clinical follow-up	0.85 (0.55–0.98)1.00 (0.72–1.00)
Sarrazin et al. [70]	2012	Prospective, single center	42	Suspect of CIEDI	Culturing after device extraction or clinical follow-up	1.00 (0.89–1.00)0.90 (0.58–0.99)
Cautela et al. [64]	2013	Prospective, single center	21	Patients referred for CIEDI	Clinical, microbiological, and imaging criteria	0.70 (0.46–0.88)1.00 (0.03–1.00)
Graziosi et al. [67]	2014	Prospective, single center	27	Suspect of CIED-related endocarditis	Lead cultures after CIED extraction, clinical/instrumental reevaluation after at least 6 months	0.67 (0.35–0.90)0.87 (0.59–0.98)
Leccisotti et al. [68]	2014	Prospective, single center	27	Patients referred for device extraction	Culturing of extracted device	0.86 (0.65–0.97)1.00 (0.48–1.00)
Ahmed et al. [62]	2015	Prospective, single center	46	Suspect of CIEDI	Culturing after device extraction and/or clinical follow-up	1.00 (0.88–1.00)0.94 (0.71–1.00)
Pizzi et al. [35]	2015	Prospective, single center	28	Suspect of CIEDI	Multidisciplinary team and clinical/instrumental follow-up of at least 3 months	0.87 (0.62–0.98)1.00 (0.73–1.00)
Tlili et al. [71]	2015	Retrospective, single center	40	Suspect of CIEDI	Culturing data of explanted devices or clinical follow-up for at least 1 year	0.83 (0.58–0.96)0.96 (0.77–0.99)
Memmott et al. [69]	2016	Retrospective, single center	37	Suspect of CIEDI	Culturing data of explanted devices or clinical follow-up for at least 6 months	0.88 (0.69–0.97)1.00 (0.77–1.00)
Granados et al. [66]	2016	Retrospective, single center	29	Suspect of CIEDI/CIED-related endocarditis	Multidisciplinary team (clinical, echocardiographic, and microbiological findings)	1.00 (0.75–1.00)1.00 (0.79–1.00)
Diemberger et al. [65]	2019	Prospective, single center	105	Patients with a diagnosis of CIED	Multidisciplinary team (clinical, laboratoristic, culturing, and imaging data)	0.91 (0.84–0.96) N.A. (all with a definite diagnosis of CIEDI)

N, population size; *CIED*, cardiac electronic implantable device

[a]Sensitivity and specificity refer to original article when reported or reassessed on calculation based on reported data

(all single center, mostly prospective) enrolling a total of 331 patients with suspected CIEDI with/without endocarditis. The reported pooled sensitivity of ^{18}F-FDG PET/CT for the detection of CIEDI was 87% (95% CI, 82%–91%) and pooled specificity resulted 94% (95% CI, 88%–98%). Even if this results are consistent with the already mentioned data by Gomes et al. [29], it must be underlined that authors included also one study enrolling patients with infected left ventricular assist device. Regarding the diagnostic value of ^{18}F-FDG PET/CT for CIED-related endocarditis, the analysis of six studies resulted in a pooled sensitivity of 65% (95% CI, 53%–76%) and a pooled specificity of 88% (95% CI, 77%–94%). This result is quite lower than what has been reported for CIEDI (lead/pocket involvement). The more plausible explanation is the requirement for a good myocardial glucose uptake suppression to properly assess cardiac involvement in CIEDI, and many of the evaluated studies were not specifically designed to uniformly provide a similar patient preparation [72]. Two other factors have to be considered since they have been reported to affect sensitivity: (a) type/duration of antibiotic treatment before ^{18}F-FDG PET/CT scan and (b) presence of advanced heart failure with impossibility to modify heart metabolism [65]. A second meta-analysis on this topic was produced by Mahmood et al. [73] with 14 studies including 492 patients with a possible CIEDI undergoing ^{18}F-FDG PET/CT scan. The pooled sensitivity was 85% (95% CI, 80%–89%) and pooled specificity 90% (95% CI, 84%–94%). The subgroup analysis, performed including studies with a cohort of sufficient size, demonstrated again a high performance of ^{18}F-FDG PET/CT for detecting pocket infection (sensitivity 96%, 95% CI 86–99%; specificity 97%, 95% CI 86–99%) and a lower accuracy for lead infection (sensitivity 76%, 95% CI 65–85%; specificity 83%, 95% CI 72–90%). Notably, a higher sensitivity was reported in studies in which the protocol for preparation to PET (fasting, low carbohydrate diet, or heparin utilization) was clearly established [73].

Although not conclusive, available data suggest that ^{18}F-FDG PET/CT is a reliable methodic for diagnosis of CIEDI and CIED-related endocarditis. ^{18}F-FDG PET/CT has key advantages compared to the other imaging techniques available. Main strengths reported for ^{18}F-FDG PET/CT are confirmation of CIEDI when clinical presentation and/or other examinations are inconclusive, early diagnosis of endocarditis, and detection of extracardiac infectious foci (Fig. 5.14) [65].

5.6.3.1 Confirmation of a Diagnosis of CIEDI-Related Infection in Challenging Cases

^{18}F-FDG PET/CT scan may help confirming a suspect of CIEDI with/without related endocarditis in patients when other techniques are inconclusive, and it should be considered in all these patients. Since in absence of a lead and cardiac involvement the echocardiogram is usually negative, ^{18}F-FDG PET/CT may be useful to discriminate patients with true pocket infection. Ahmed et al. [62] compared a population of 46 patients with a suspect of CIED pocket infection with 40 controls without story of infection (patients who are CIED carriers undergoing ^{18}F-FDG PET/CT scan for other reasons such as cancer surveillance). Patients with suspect pocket infection were divided in two groups: definite pocket infection (erosion or

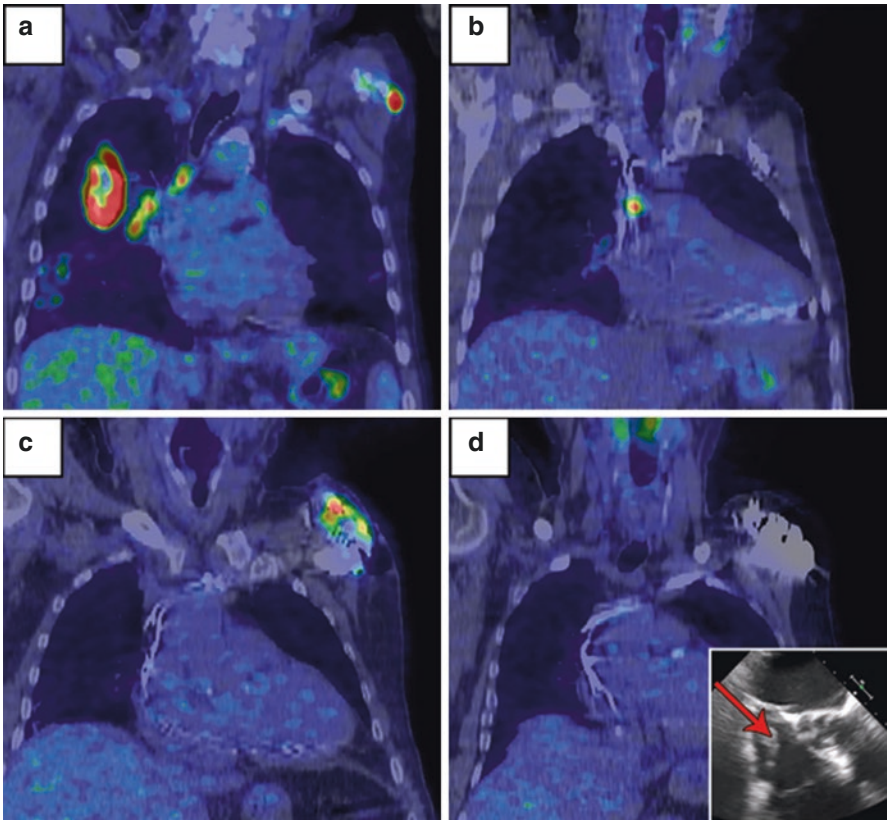

Fig. 5.14 ^{18}F-FDG PET/CT scan with different patterns in patients with CIEDI. Different presentations of patients affected by CIED infection at ^{18}F-FDG PET/CT scan. (**a**): pocket and lead involvement. (**b**): infection on the lead, negative pocket. (**c**): local infection (isolated pocket involvement). (**d**): false negative (negative PET in a patient with known endocarditis, as evidenced by echocardiogram). (Reproduced from Diemberger et al. [65] with permission)

dehiscence of the generator pocket, purulent discharge) or "possible" pocket infection (mild erythema or pain). ^{18}F-FDG PET/CT was administered to all patients, being positive in 17/20 of the patients with definite infection and negative in all controls. Strikingly, 13 of the 26 patients with only mild symptoms presented a positive ^{18}F-FDG PET/CT scan and the diagnosis of infection was subsequently confirmed for 11/13 (84.6%) of them. Authors concluded that ^{18}F-FDG PET/CT is a useful examination to classify and stratify the risk of these patients and it should be considered in all patients presenting with mild signs and symptoms like pocket erythema. After a standardized [3] diagnostic workup evidence for presence of CIED infection may be still limited and echocardiogram can difficulty discriminate the nature of a mass adherent to CIED leads [19] and some area cannot be explored due to presence of prosthetic material [29]. In these cases, if the clinical suspicious persists, ^{18}F-FDG PET/CT is an added value for the diagnosis of intravascular

CIEDI. Some authors also proposed to include ^{18}F-FDG PET/CT findings as a major criteria in modified Duke criteria, in order to increase the accuracy in diagnosis of CIED-related endocarditis. Pizzi et al. [35] in a prospective study enrolling 92 patients with CIED or prosthetic cardiac valves admitted for suspicious infective endocarditis, all undergoing ^{18}F-FDG PET/CT scan, compared standard modified Duke criteria (assessed at the admission) with Duke criteria including ^{18}F-FDG PET/CT findings as imaging criteria. According to results, ^{18}F-FDG PET/CT drastically improved the accuracy of the diagnosis of CIED infection. Reported sensitivity (compared to a final, multidisciplinary diagnosis of endocarditis made after a follow-up of 3 months, which was assumed as gold standard) was 90.7% (95% CI 79.7–96.9) for Duke criteria including PET versus 52% (95% CI 37.8–65.7) of standard modified Duke criteria. Sensitivity was slightly inferior for Duke criteria with PET (89.5%, 95% CI 75.2–97.1, versus 94.7, 95% CI 82.3–99.4). A potential concern regarding this data is the cost-effectiveness [66], since ^{18}F-FDG PET/CT scan was performed in all patients at admission, even those with rejected endocarditis at standard modified Duke criteria. Granados et al. [66] instead administered ^{18}F-FDG PET/CT to 80 consecutive patients with a diagnosis of possible endocarditis obtained with Duke criteria. After inclusion of ^{18}F-FDG PET/CT 90% of the patients were reclassified to both rejected or definite endocarditis (18 cases). Consistent findings have been also found in a more recent study [65] with 105 patients referred for TLE, where the adoption of ^{18}F-FDG PET/CT allowed to reclassify 23.8% of patients with 11 new diagnosis of endocarditis.

5.6.3.2 Early Diagnosis of Endocarditis

The functional nature of ^{18}F-FDG PET/CT, whose performances are related to metabolic process and may detect the presence of infection since from the first phases of the pathological process, allows the possibility to perform a diagnosis of CIED earlier than any other techniques, before the onset of morphological alterations and anatomical damage [27]. This point is of crucial importance since a delay in diagnosing CIED infection can result in a progression of the infective process, related to a worse outcome and to a higher risk of relapse [74].

5.6.3.3 Detection of Extracardiac Localizations of Infection

Extracardiac infections are a well-known complication of infective endocarditis, adding a further burden of mortality and morbidity to primary infection. CIED infection can spread either by direct embolization of vegetations (usually to lungs) or by hematogenous seeding, causing more frequently septic arthritis, osteomyelitis, and spondylitis [75]. Pulmonary embolization, especially in patients with larger vegetations, is a major concern and it is related with a higher mortality at 6 months (hazard ratio 3.76; 95% CI 1.25 to 11.30) [16]. They have been reported in 38.4% of patients with CIED-related endocarditis [11]. Spinal abscess represents another common secondary localization of CIED infection [75, 76]. The detection of secondary infectious site is often challenging, because they are often asymptomatic [11] or because related symptoms may be not specific and be masked by the primary infection.

MRI is often adopted as the preferred imaging technique for detection of spondylodiscitis [77] but it presents several limitations both in terms of feasibility (many patients with CIEDI have abandoned or damaged leads, which until now pose a contraindication for MRI [43]) and quality of obtained images (due to artifacts from implanted hardware [78]).

The main consequence of this is the risk of delaying or completely missing the diagnosis of septic embolism, despite the possibility of relevant consequences and the impossibility of adjusting antimicrobial therapy duration. Recently, the role of ^{18}F-FDG PET/CT for the detection of hidden infective localization of CIED infection has started being investigated, given the promising results in finding extracardiac complications of infective endocarditis (^{18}F-FDG PET/CT positive for extracardiac infection in a quarter of patients) [79, 80]. Furthermore, ^{18}F-FDG PET/CT allows to scan the whole body at once, providing the possibility to detect infection complications at distance from the primary site. No large study specific for this topic exists, comparing ^{18}F-FDG PET/CT with other imaging techniques, and all available studies exhibit a limited number of patients. In a 2016 prospective study by Amraoui et al. [76] ^{18}F-FDG PET/CT was administered to 35 patients before the execution of TLE, aiming to identify metastatic foci. They reported septic emboli in 29% of patients (seven spondylodiscitis, two septic pulmonary emboli, and one infected aortobifemoral vascular prosthesis). None of the cases of spondylodiscitis have been diagnosed prior to PET administration (patients resulted asymptomatic or other imaging exams resulted inconclusive). Thus, authors underlined the important contribution of ^{18}F-FDG PET/CT, which allowed to modify patient therapy according to scan results for all patients positive for secondary foci, either by prolonging antimicrobial therapy duration or administering nonpharmacological treatments.

A more recent, prospective, study [65] with a larger cohort size of 105 patients, aiming for investigating the prognostic value of the extension of CIED infection at ^{18}F-FDG PET/CT scan, reported that PET scan allowed to perform a first detection of septic emboli in 11.4% of patients. These findings allowed to adjust patient treatment and to optimize the timing of CIED reimplantation. Moreover, although not representing the main focus of imaging for CIED infection, ^{18}F-FDG PET/CT also allows to detect other pathological conditions, unrelated to CIED infection like neoplastic processes [73, 76], which may have a prognostic significance and may lead to a change of strategy in terms of treatment and assessment for reimplantation. Notably, systemic infections caused by some microbial agents have been related with presence of occult cancer [81]. Although not completely exhaustive, available data thus report a good performance of ^{18}F-FDG PET/CT in detecting occult metastatic infections and suggest that routine administration of ^{18}F-FDG PET/CT could improve patient management, at least in patients with proven endocarditis [29].

5.6.3.4 Prognostic Value of PET Findings

Several authors reported a worse survival rate for patients affected by systemic CIED infection than those with an infection limited to the site of the CIED pocket [82, 83]. Considering the ability of ^{18}F-FDG PET/CT to assess the localization and the extension of the infectious process and to discriminate a local versus a diffuse

infection, the possible role of ^{18}F-FDG PET/CT findings in predicting the outcome of patients with CIEDI has been investigated. A recent study by Diemberger et al. [65] enrolled 105 patients with an already established (by clinical criteria) diagnosis of CIEDI and referred for TLE, all of them undergoing ^{18}F-FDG PET/CT scan before procedure. Comparison was made between patients with pocket infection alone and those with systemic involvement at ^{18}F-FDG PET/CT scan (infection of endovascular trait of leads, cardiac valves, secondary localization). A trend toward a better survival for patients with local infection was reported, but it didn't reach statistical significance. However, the most relevant finding of this study was that a CIED pocket with a negative ^{18}F-FDG PET/CT scan and absence of signs of infection (*Cold Closed Pocket*, found in 24/105 patients) was a strong independent predictor of mortality (hazard ratio 2.84, 95% CI 1.37–5.89). Authors suggested that the PET scan negative for pocket infection, the longer period since last CIED implant/replacement, and the higher percentage of positive blood cultures in patients with *Cold Closed Pocket* may be related with a metastatic nature of the CIEDI in these patients, started elsewhere. This is a topic of interest, given that the actual strategies to reduce the risk of CIEDI are mainly focusing on surgical procedures.

5.6.3.5 Limitations of ^{18}F-FDG PET/CT: False Negatives and False Positives

Despite the good performance of ^{18}F-FDG PET/CT in terms of sensitivity and specificity, both false negative and false positive have been reported. Graziosi et al. [67], investigating the role of PET for the diagnosis of CIED-related endocarditis, reported 17 negative PET scans, four of them false negatives. Diemberger et al. [65] reported also nine false-negative PET in a sample of 105 patients. As underlined by authors, patients with false-negative ^{18}F-FDG PET/CT scan were usually treated with prolonged antimicrobial therapy, already started before PET administration. Long-lasting antibiotic therapy is a known cause of false-negative ^{18}F-FDG PET/CT scan [29]. A possible workaround to fix this is performing ^{18}F-FDG PET/CT early during the management of a patient with a suspicious of CIEDI, possibly before starting an antimicrobial therapy if allowed by patient's clinical conditions and PET availability, in order to maximize ^{18}F-FDG PET/CT sensitivity. Additional causes of false negatives are the possibility of little size vegetations, falling below the spatial resolution of ^{18}F-FDG PET/CT (4–5 mm) [29], and the insufficient suppression of myocardial glucose uptake (by inadequate dietary preparation of the patient before the administration of PET) which can mask the presence infection (Table 5.3) [84]. False-positive results are mostly caused by increased FDG uptake during noninfective processes, such as inflammatory diseases or cancer or inadequate glucose uptake suppression. An increased FDG uptake is often observed during first period after CIED implantation [73] and this should also be kept in mind before performing PET. Another cause of false positivity of ^{18}F-FDG PET/CT is artifact by overcorrection of attenuation in proximity of high density materials like CIED leads; for this reason a visual comparison between imaging obtained with attenuation correction and non-corrected images should always be performed.

5.6.3.6 Considerations About ^{18}F-FDG PET/CT Role in CIEDI Management

The growing interest on ^{18}F-FDG PET/CT role in diagnosis of CIEDI is motivated by the high diagnostic yield of this imaging technique. ^{18}F-FDG PET/CT provides high sensitivity and specificity and should have a role in the management of a CIEDI. Actually, ^{18}F-FDG PET/CT still has not an established role in guidelines of European Society of Cardiology regarding CIEDI [3], dated 2015, and available evidences suggest that this examination should deserve a more prominent role. Notably since reimplantation strategy is strongly affected by systemic involvement of CIEDI (for additional information see Chap. 7), it should be carefully considered to perform ^{18}F-FDG PET/CT also in patients with a defined diagnosis of CIEDI since about one quarter of the patients can be reclassified according to modified Duke criteria if ^{18}F-FDG PET/CT is systematically performed [65]. However, cost-effectiveness (no data are actually available on this topic) and the risk of false positive/negative still remains a concern (Table 5.4).

Table 5.3 Recommendations for the patients' preparation before administration of ^{18}F-FDG PET for cardiac structures

The patient should follow a low carbohydrate diet for 24 h prior to the PET/CT administration or at least a low-carbohydrate meal before starting the recommended fasting period before the study (6 h).
Patients must avoid strenuous exercise for at least 6 h before the FDG PET/CT study, and preferably for 24 h, in order to minimize the glucose uptake of skeletal muscles.
The patient should be able to lie still for the entire duration of the PET/CT scan (30–60 min).
If the patient has a blood glucose concentration higher than 11 mmol/L (200 mg/dL), the FDG PET/CT scan should be rescheduled or the patient excluded.
In patients affected by diabetes mellitus, FDG PET/CT study should be preferably performed in the late morning.

Recommendations from European Association of Nuclear Medicines Guidelines [84]

Table 5.4 Strengths and limitations of the discussed imaging techniques for CIED infection

Imaging techniques	Strengths	Limitations
Transthoracic echocardiogram (TTE)	• Easily available and low-cost technique • Identification and measurement of lead endocarditic vegetations • Detection of endocarditis-related complications (i.e., tricuspid valve regurgitation, other valve involvement)	• Limited to heart CIEDI involvement • Lower sensitivity (in general), especially if performed too early • Limited discrimination of cardiac masses • Accuracy limited by artifacts from prosthetic material
Transesophageal echocardiogram (TEE)	• Low costs • Higher sensitivity for vegetations • Better visualization vs. TTE • Detection of valvular and perivalvular extension of CIEDI • Gold standard for diagnosis of endocarditis • Allows perioperative monitoring	• Suboptimal visualization of some sites (right ventricle, extracardiac vessels) • Lower sensitivity if performed too early • Limited discrimination of cardiac masses • Accuracy limited by artifacts from prosthetic material

(continued)

Table 5.4 (continued)

Imaging techniques	Strengths	Limitations
Intracardiac echocardiography	• High sensitivity for vegetations • Better visualization of remote areas vs. TEE/TTE • Better discrimination of cardiac masses vs. TEE • Higher performance for perioperative monitoring	• High costs and limited availability • Requires an invasive access • Impractical for pure diagnostic purposes
ECG-gated computed tomography (CT)	• Very high performances in estimation of endocarditis extension (detection of paravalvular abscesses, fluid collection)	• Limited accuracy in tachycardia/rhythm disturbance • Low accuracy for detection of small vegetations • Presence of metal-induced artifacts in patients with CIED
WBC SPECT/CT	• Functional imaging • Allows detection of infection before the onset of anatomical damage • High specificity for infections, may be considered for confirmation of PET (+++ patients with recent procedure)	• Longer time required • Sensitivity inferior to PET/CT scan
^{18}F-FDG PET/CT	• Functional imaging • Allows detection of infection before the onset of anatomical damage • High sensitivity/specificity for CIEDI • Allows a whole body scan (excluding brain) to detect extracardiac complications of CIEDI • Shorter execution time compared to SPECT	• False positives in case of inadequate glucose suppression or recent cardiac surgery • False negatives in case of prolonged antimicrobial therapy • High costs and limited availability, even if progressively increasing

CIED cardiac electronic implantable device, *WBC SPECT/CT* white blood cell single-photon emission computed tomography/computed tomography, *^{18}F-FDG PET/CT* positron emission tomography (PET) with fluorodeoxyglucose marked by fluorine-18

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From Diagnosis of Cardiac Device Infection to Complete Extraction of the System

6

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6.1 Introduction

Infection of cardiac implantable electronic devices (CIED) is associated with high mortality [1]. The progressive increase in implantation of CIED together with increased comorbidity in patients receiving them has set the stage for higher rates of CIED infection (CIEDI) and infective endocarditis (IE) [2]. Currently, CIED infection is the most frequent indication for lead extraction, [3] having increased from nearly 30% of extractions in 2006 to 50% in 2012 [4].

6.2 Importance of Complete CIED Removal to Prevent Recurrence of Infection

Medical therapy has been associated with high mortality and risk of CIEDI recurrence (Fig. 6.1) [4–6]. In a large cohort study, a sevenfold increase in 30-day mortality was observed if the CIED was not removed; despite fatal complications related to CIED removal, the mortality associated with delayed removal was significantly higher [7]. Therefore, this risk of recurrent infection makes it essential to remove all hardware [8, 9].

Current guidelines recommend complete CIED removal in all cases of CIEDI, whether systemic or localized in the pocket, and even when occult infection is suspected, with no apparent source other than the device. The only exception to this rule is a minor incisional/suture abscess, not communicating with the pocket, that

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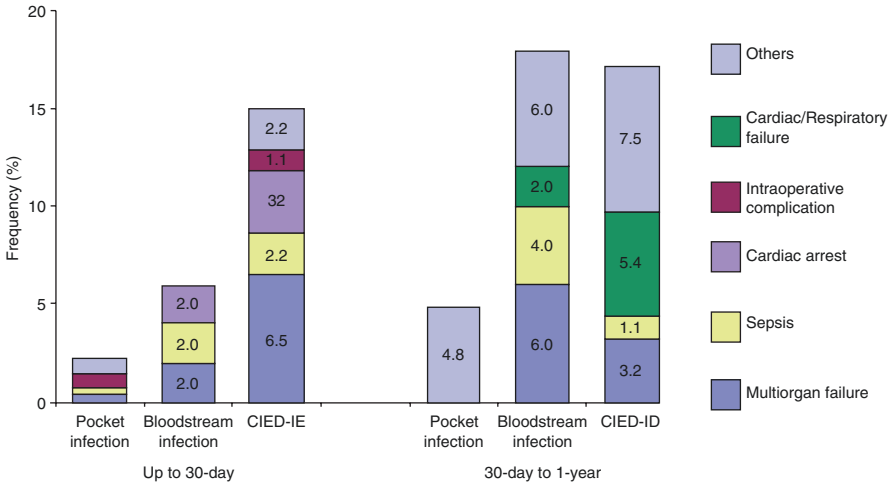


Fig. 6.1 Incidence and cause of death at 30 days and 1 year among three different clinical presentations of CIED infection (Reproduced from Lee et al. with permission) [4]. *CIED-IE*, infective endocarditis involving the CIED

occurs within a few days after implantation; this may be treated with antibiotics and careful follow-up [7] [see Chap. 4 for a complete discussion of this topic].

Considering the inherent risk of an open surgical procedure, transvenous lead extraction has become the preferred method [10]. In experienced centers, procedural mortality rates oscillate between 0.1% and 0.6%, with higher mortality rates associated with systemic infections [11].

Open extractions are generally favored in high-risk cases, in order to avoid life-threatening complications that can be encountered during percutaneous extractions. In general, open extractions are considered when the patient has epicardial leads, some other reason for cardiac surgery, or large lead masses (vegetation or thrombus >2.5 cm), or failed a prior extraction procedure [7, 10].

6.3 Definitions

The concept of "lead removal" includes a broad spectrum of procedures (Table 6.1). Distinction must be made between simple procedures that can be performed via the implant vein without specialized tools and removal of leads involving more complex procedures [10].

6.4 Perioperative Management for CIED Removal

After blood cultures are completed, i.e., antibiotics should be initiated before hardware removal. No clinical trial data are available to define the optimal duration of antimicrobial therapy. A plan for pre-, intra-, and postoperative antibiotic must be

Table 6.1 Definitions of lead removal procedures and outcomes

Lead removal	• Removal of a pacing or defibrillator lead using any technique
Lead explant	• Lead removal procedure where all leads are removed without tools or with implantation stylets and had been implanted for less than 1 year
Lead extraction	• Removal of a lead that has been implanted for more than 1 year • Removal of a lead, regardless of implant duration, requiring the assistance of specialized equipment that is not included as part of the typical implant
Complete procedural success	• Lead extraction procedure with removal of all targeted leads and all lead material from the vascular space, with the absence of any permanently disabling complication or procedure-related death
Clinical success	• Lead extraction procedures with removal of all targeted leads and lead material from the vascular space or retention of a small portion of the lead (<4 cm) that does not negatively impact the outcome goals of the procedure
Failure	• Lead extraction procedures in which complete procedural or clinical success cannot be achieved • Development of any permanently disabling complication or procedure-related death
Lead removal with clinical success	• Achieving removal of the entire lead from the body or with retention of a small portion of the lead material (<4 cm) that does not negatively impact the outcome goals of the procedure

formulated, including type and duration of the treatment, and will vary according to test results.

CIED removal may have serious and catastrophic life-threatening complications. Therefore, correct perioperative evaluation and patient management are essential to minimize the risk of procedure-related complications. Perioperative management can be divided into three phases: preoperative, procedure, and post-procedure.

6.4.1 Preoperative Phase

The aims of this phase are to confirm appropriate indications for lead extraction, assess procedure complexity, define extraction approach, and optimize the patient's clinical status in preparation for the procedure. This phase includes eight steps.

6.4.1.1 Medical History and Physical Examination

A comprehensive medical history is necessary, including a review of the patient's comorbidities that could worsen the prognosis of CIED extraction (Table 6.2), along with medical treatment, allergies, cardiac device history, CIED indication, and data of first implant. The pocket generator and device site also must be examined for signs of infection. Physical examination should identify signs of heart failure and assess chest wall venous collaterals suggesting venous occlusion or thrombosis.

6.4.1.2 CIED Interrogation

The cardiac device must be interrogated to obtain lead information and to assess pacemaker dependency. Patients who are not pacemaker dependent should have

Table 6.2 Factors associated with extraction procedure complications

Comorbidities	Associated risk
Age	1.05-fold greater mortality
Female sex	4.5-fold greater risk of major complications
BMI < 24	1.8-fold greater risk of 30-day mortality
Cerebrovascular accident	Twofold greater risk of major complications
Severe LV dysfunction	Twofold greater risk of major complication
Heart failure	1.3- to 8.5-fold greater risk of 30-day mortality and threefold greater mortality risk at 1 year
Renal dysfunction (ESRD)	4.8-fold greater risk of 30-day mortality Cr > 2.0 greater risk of in-hospital mortality and twofold greater risk of 1-year mortality
Diabetes mellitus	Increased in-hospital mortality 1.71-fold greater mortality
Low platelet count	Low platelet count: 1.7-fold greater risk of major complications
Coagulopathy	Elevated INR: 2.7-fold greater risk of major complications and 1.3-fold greater risk of 30-day mortality Anticoagulants: 1.8-fold greater 1-year mortality
Anemia	3.3-fold greater risk of 30-day mortality
Extraction for infection	2.7- to 30-fold greater risk of 30-day mortality 5- to 9.7-fold greater 1-year mortality risk

their device reprogrammed to backup pacing modes (VVI 40 bpm) prior to the procedure to confirm lack of dependency.

6.4.1.3 Chest X-Ray

Information regarding type of lead, position, and presence of abandoned leads can be obtained from posteroanterior and lateral chest radiography (X-ray). X-ray should rule out left-side lead implantation or extravascular lead course; otherwise, computed tomography (CT) may be necessary to characterize lead course and plan an appropriate procedural strategy (Fig. 6.2).

6.4.1.4 Venography with Fluoroscopy

Fluoroscopy is useful to identify regions of venous stenosis or occlusion in venography (Fig. 6.3). In two reports, about 20% of patients had a complete occlusion at the venous entry site [12, 13]. The presence of severe venous stenosis or occlusion increases the complexity of extraction. Moreover, if a new device must be implanted, other vascular access should be evaluated.

6.4.1.5 Transesophageal Echocardiography

In cases of CIEDI, transesophageal echocardiography (TEE) is mandatory prior to CIED removal (Fig. 6.3). TEE evaluates the presence, size, shape, and location of vegetations as well as their relationship with cardiac structures. These results determine the most appropriate approach (transvenous or open surgical) for the

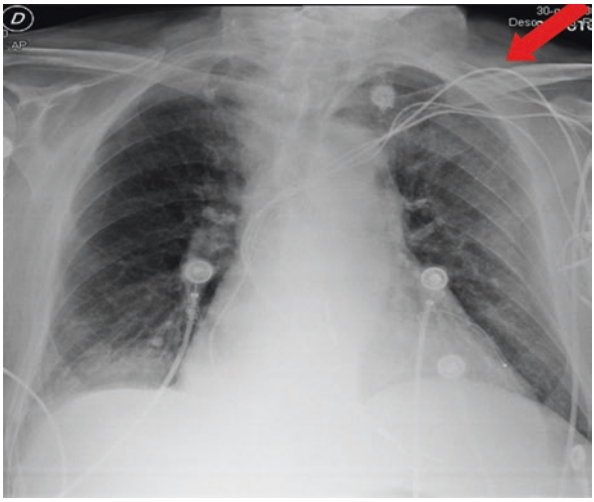


Fig. 6.2 Posteroanterior chest X-ray showing a dual chamber system plus an abandoned unipolar passive fixation PM lead implanted through left jugular vein (red arrow). Leads implanted through atypical accesses should be considered carefully for the increased risk or vein damage

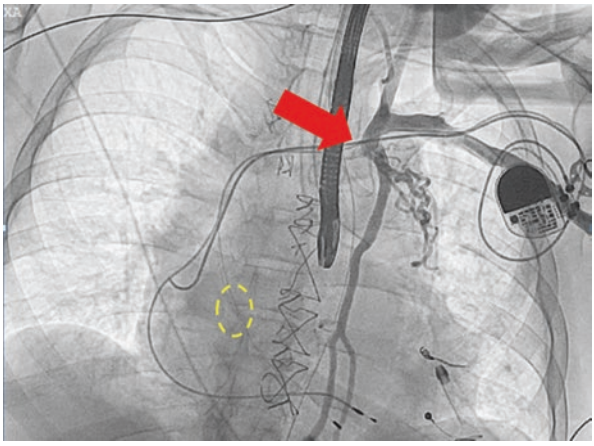


Fig. 6.3 Venography showing complete occlusion of the innominate vein in a GUCH patient (red arrow) with a previously failed lead extraction (dashed yellow circle) and systemic CIEDI

extraction [14, 15]. Decisions regarding percutaneous versus surgical removal of leads with large vegetations (>2.5 cm) should be individualized [10, 16]. Other imaging techniques (e.g., CT scan, ^{18}F-FDG PET/CT), when available, should be considered to properly identify systemic involvement of CIEDI [for a detailed description of imaging techniques applied to CIEDI see also Chap. 5].

6.4.1.6 Perioperative Management of Oral Anticoagulation

Observational studies have shown an increased risk of major complications and death in patients with an elevated international normalized ratio (INR) at the time of lead extraction (Table 6.2). Therefore, oral anticoagulation should be stopped and normal INR values should be achieved on the day of the intervention; the peri-procedural anticoagulation strategies should be individualized according to the patient's thromboembolic risk during non-protected periods [10].

6.4.1.7 CIED Reimplant

Previous to CIED removal, it is necessary to re-evaluate the indication for CIED reimplant. Over time, changes in clinical indications and the patient's clinical status may render CIED therapy unnecessary. About one-third of patients did not have devices implanted after undergoing system extraction for CIEDI [17] [see Chap. 7 for a detailed discussion of post-extraction reimplantation indication and strategies].

6.4.1.8 Informed Consent

A review of the case, including alternatives to extraction and potentially life-threatening complications, should be discussed with the patient and his or her family members and clearly documented in the patient's chart [10]. Surgical approach should be discussed as well as possible conversion to surgical approach in case of complications or failed percutaneous extraction. Also alternative approaches for CIED reimplantation should be discussed with the patient.

6.4.2 Procedure Phase

6.4.2.1 Patient Preparation

Routine preoperative blood work, including complete blood counts and metabolic and coagulation panels, should be obtained, along with the type and cross for 2–4 units of packed red blood cells, which should be available in the procedure room.

Patients should receive sterile preparation for possible emergent sternotomy, creating a sterile field that covers the entire anterior chest and bilateral groin areas. An arterial line should be placed to permit continuous invasive blood pressure monitoring and pulse oximetry to monitor oxygenation. Venous access to permit rapid infusion of fluid, vasopressors, and blood products should be placed in the femoral veins.

External patches that permit transcutaneous pacing and defibrillation should be placed outside of the sterile working field. Once the patient is connected to a cardiac monitor, the CIED may be reprogrammed to inactivate tachycardia therapies and/or asynchronous pacing when appropriate.

CIED removal can be performed under general anesthesia or local anesthesia with sedation. The use of general anesthesia minimizes the patient's discomfort and allows a quick rescue surgery in case of complication.

For transient rate support, temporary pacing using the femoral approach is generally preferred when a superior extraction approach is planned. This will minimize interaction between the temporary pacing catheter and extraction tools. If longer periods of temporary pacing are required after the lead extraction procedure, an external pacemaker (or in selected cases defibrillator) is used, typically placing active fixation leads via the homolateral superior veins (Fig. 6.4) [18].

6.4.2.2 Intraprocedural Imaging

Transesophageal Electrocardiography

Transesophageal electrocardiography (TEE) is helpful for characterizing lead vegetation, evaluating tricuspid valve function, and documenting pericardial effusions

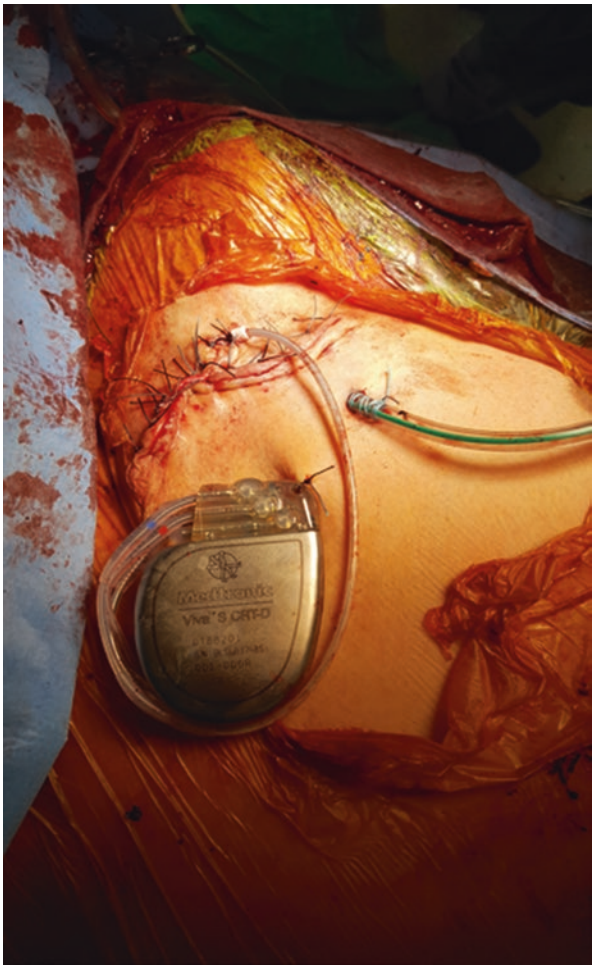


Fig. 6.4 After lead extraction for systemic CEDI this patient received a homolateral dual coil active fixation lead connected to an externalized ICD (after disabling can form shock vectors) to provide both continuous pacing (PM-dependent patient) and backup shock. This approach was in line with a previous report [18]

during lead extraction [19]. TEE allows a prompt identification of cardiovascular causes of hemodynamic instability during lead extraction [20].

Intracardiac Echocardiography

Intracardiac echocardiography (ICE) is more sensitive than TEE to detect vegetations in patients with endocarditis. ICE offers an excellent visualization of cardiac leads and related areas of adherence and may improve the efficacy and safety of the procedure [21, 22].

6.4.2.3 Techniques and Tools for CIED Extraction

The major obstacle to lead removal is the inflammatory and fibrotic response of the body to an intravascular foreign object. Within a few months postimplantation, the lead is surrounded by fibrous tissue. The fibrous lead encapsulation increases over time. The binding is most likely to be present at the point of lead insertion at the

Table 6.3 Tools for CIED lead extraction

Simple traction	• Non-locking stylets • Fixation screw retraction clips
Non-powered extraction tools	• Locking stylets • Snares • Mechanical dilator sheaths composed of metal, Teflon, polypropylene, or other materials that require manual advancement over the lead and rely on the mechanical properties of the sheath to disrupt fibrotic attachments
Powered extraction tools	• Laser sheaths • Electrosurgical dissection sheaths • Rotating threaded tip sheaths

subclavian vein, the junction between innominate vein and superior vena cava (SVC), right atrium, the lead tip, and, in ventricular leads, the tricuspid valve [10].

Extractions can be successfully completed using a variety of tools designed to disrupt fibrous adhesions (Table 6.3, Fig. 6.5). Optimal tool selection is based on factors such as lead-tissue interface, characteristics of the lead, characteristics of the fibrotic lesions, lead dwell time, and operator experience. To date, no unique tool is available to disrupt all types of fibrous adhesions during lead extraction, often requiring the operator to switch between extraction tools and approaches.

Femoral snares and telescoping sheaths tend to fail in the presence of densely fibrotic or severely calcified lesions. Laser sheaths are very effective against fibrous lesions but less effective with severely calcified lesions; however, mechanical cutters more efficiently traverse these lesions [23].

6.4.2.4 Approaches for Lead Removal

CIED leads are most commonly extracted through the original implantation site, where they are connected to the pulse generator. At times, the lead breaks or is free-floating, becoming inaccessible from the original implantation site. In such cases, extraction is performed from a remote site, such as via the femoral vein or the internal jugular vein [24].

Most operators begin the procedure using the venous entry approach and switch to femoral or jugular if necessary. Clinical success has been increased by applying approaches other than the superior approach for CIED extraction [24–26].

6.4.2.5 Lead Preparation

An incision is made over the device and, in cases of pocket infection, the device is dissected out in its entirety before proceeding with lead extraction. This avoids introducing infected material into the intravascular space. The lead must be free all the way to the venous entry site. In case of active fixation leads, the tip must be unscrewed.

6.4.2.6 Techniques for Lead Extraction

Simple Traction

After lead exposure and control, an attempt to withdraw the active fixation mechanism is undertaken, followed by gentle manual traction (pulling) of the lead,

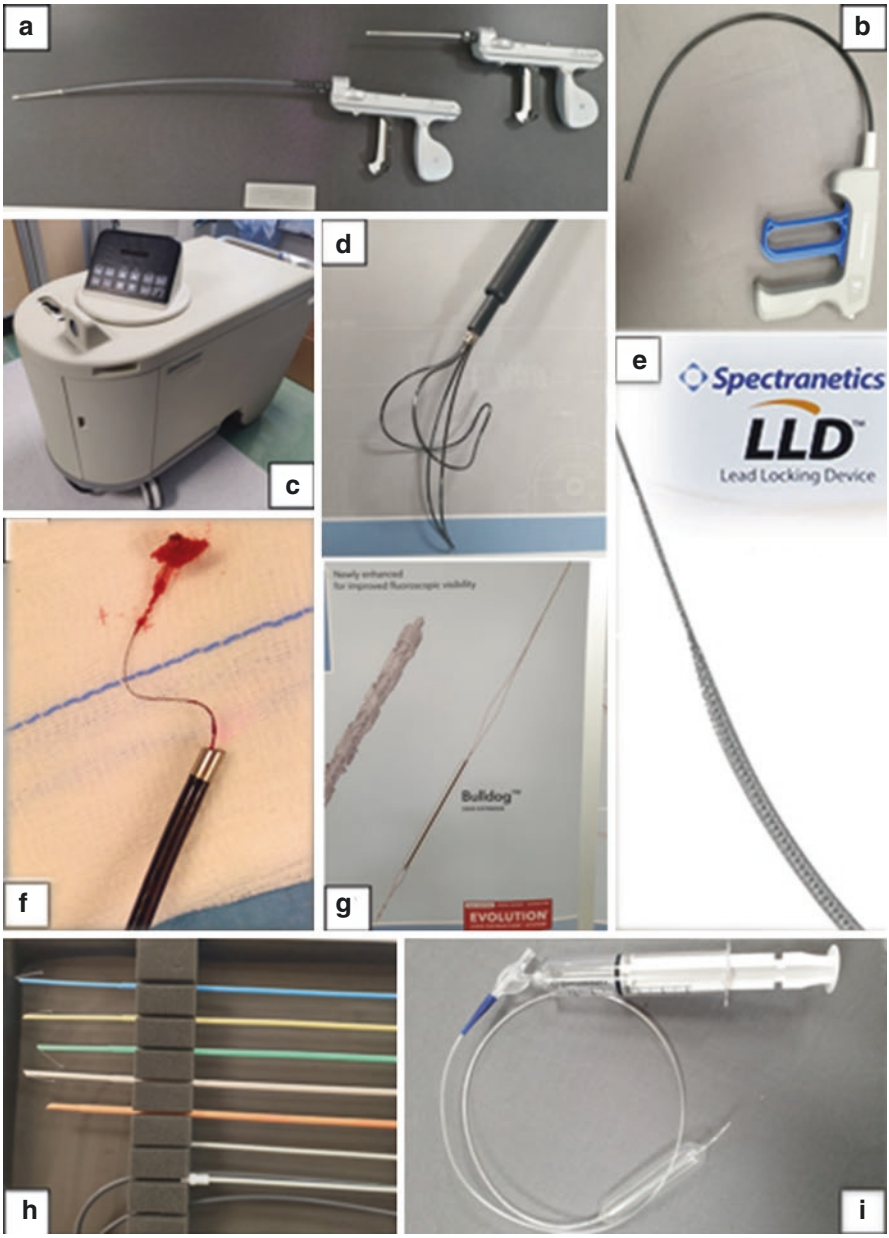


Fig. 6.5 Principal tools for lead extraction. Mechanical rotational sheaths: Evolution RL™ (Panel **a**; Cook Medical, USA) and TightRail™ (Panel **b**; Spectranetics Corp., USA); laser generator and laser-powered sheath (Panel **c** and **f**; Spectranetics Corp., USA); the Needle's Eye retrieval tool for either femoral or superior approach (Panel **d**; Cook Medical, USA); locking stylets to provide a stable support to advance extraction sheaths, LLD™ (Panel **e**; Spectranetics Corp., USA) and Bulldog™ (Panel **g**; Cook Medical, USA); standard Teflon mechanical sheaths (Panel **h**); the Bridge Balloon™ to be inflated in case of upper vein damage to decrease bleeding during the beginning of surgical backup (Panel **h**; Spectranetics Corp., USA)

combined with the use of tools typically supplied for lead implantation. Some authors suggest adding five to ten lead rotations to increase the effectiveness of the simultaneous gentle traction [27]. The success rate of transvenous lead extraction by simple traction ranges from 9% to 31% (19%) of patients and 28% of leads [28]. Most of these leads have a short dwell time. Despite a low success rate, simple traction could be performed as a first step for lead removal. However, when applying traction to chronically implanted leads, force will be distributed over the fibrotic binding sites and weakened at the distal end of the lead and may facilitate the elongation and fracture of the lead.

Counterpressure and Countertraction

If manual traction is unsuccessful, more advanced tools allowing counterpressure or countertraction are required to direct the force of traction along the length or at the distal end of the lead or to disrupt and dilate the encapsulating fibrotic tissue (Fig. 6.5). The locking stylet is advanced until reaching the tip of the lead. The different lead components are secured to the locking stylet with suture ties or a compression coil (One-tie; Cook Vascular Inc. USA) to convert all these components into one unit, allowing use of the lead as a "rail" for dissection by powered or non-powered extraction sheaths.

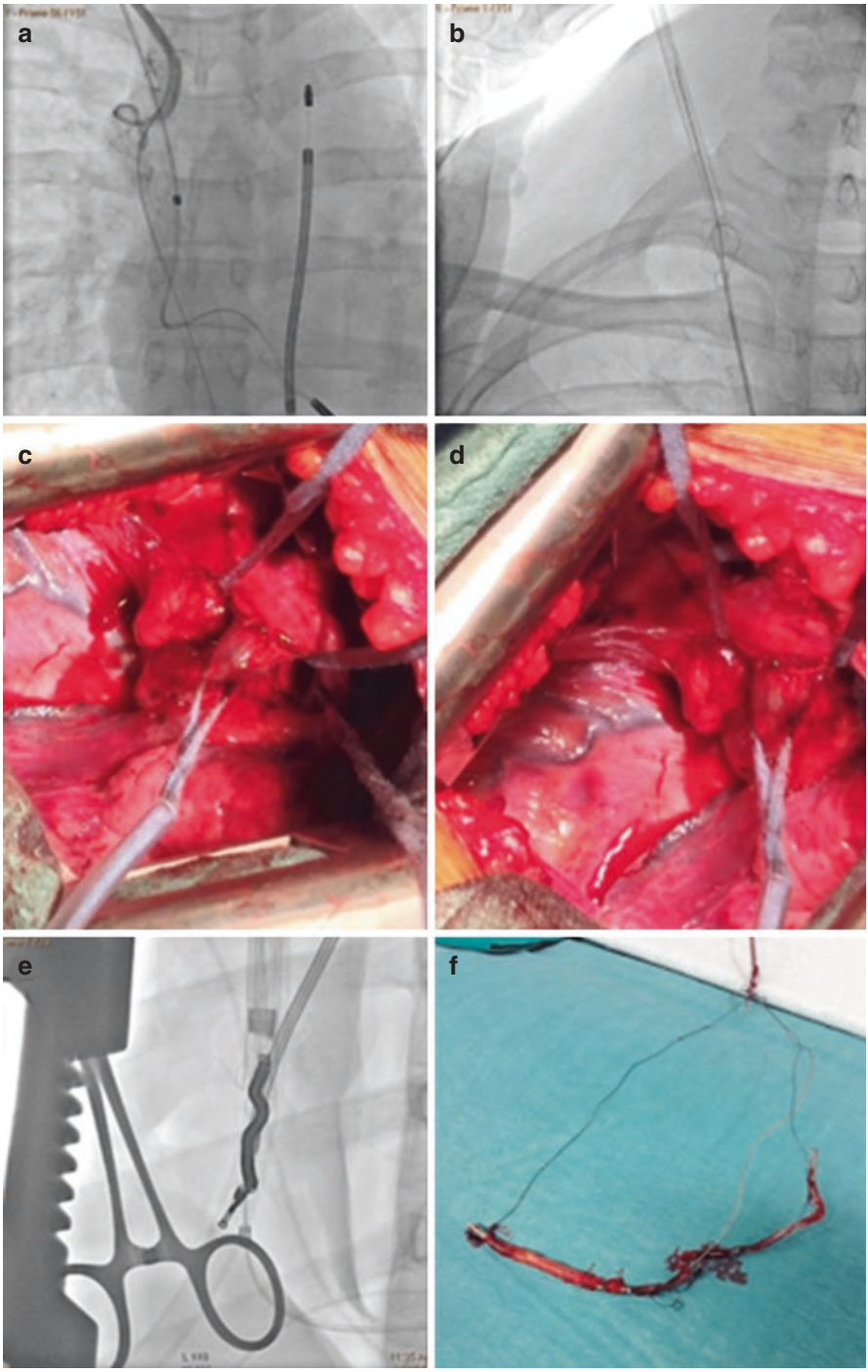
Counterpressure is the application of a forward pressure to the sheath and traction to the lead. These two forces must be balanced to avoid complications. Countertraction occurs when the traction applied on the lead is opposed and counterbalanced by pushing the overlie sheath on the endocardium, thus limiting myocardial invagination or avulsion.

In cases of failure of the superior approach or if the position of the targeted lead is completely intravascular, alternative approaches such as femoral or jugular can be applied [10]. In these cases, a snare is used to grasp the leads, usually in the right atrium. Once the lead is snared, it is pulled into the sheath, which is advanced over the leads to free them, until the tip is reached.

Additionally, in case of failure of a percutaneous approach even with advanced tools, cardiac surgery with sternotomy may be avoided adopting a hybrid approach with minimally invasive surgical access for completion of the procedure (Fig. 6.6) [28].

A stepwise extraction approach results in clinical success in up to 100% of CIED extractions, with a relatively low risk of procedure-related mortality and complications [29].

Fig. 6.6 "Hybrid" approach for lead extraction. (**a**) Fluoroscopy at the start of the procedure. (**b**) Advancement of the sheath (transjugular approach). (**c**) and (**d**) Surgical exposition of the venous vessels with minimally invasive approach. (**e**) Completion of lead extraction by percutaneous approach. (**f**) The lead after extraction. (Reproduced with permission from Bontempi et al. with permission) [28]


a
b
c
d
e
f

6.4.3 Post-Procedure Phase

The main goal is to monitor the patient for post-procedure complications. Hemothorax or pneumothorax after CIED extraction can be ruled out by a thorax X-ray. Transthoracic echocardiogram is useful to detect adverse events such as tricuspid valve injury or pericardial effusion or to document remaining intracardiac masses (either retained fragments or so-called ghosts), which are most commonly observed in patients with CIED endocarditis or positive blood cultures. Although the presence of ghosts was associated with high mortality, no specific therapy is indicated for these patients, [30].

In CIED infection the post-procedure phase also is focused on wound care, selection and duration of antibiotics and appropriate timing for device reimplantation [10].

6.5 Reimplantation

The new device should be implanted on the contralateral side. There is no clear recommendation concerning the optimal timing of reimplantation. Factors such as persistent bacteremia, persistent vegetation, and pacemaker or implantable cardioverter defibrillator dependency should be considered and the decision adapted to the individual patient.

Immediate reimplantation should generally be avoided, owing to the risk of new infection. Blood cultures should be negative for at least 72 h before placement of a new device. In cases of evidence of remnant valvular infection, implantation should be delayed for at least 14 days [7]. New devices like subcutaneous ICD (s-ICD) or transcatheter pacemaker may be a good option for these patients [see Chap. 7 for detailed discussion of different approaches for CIED reimplant after extraction].

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"Re-Implantation Strategy After Lead Extraction for Cardiac Device Infection"

7

Christian Butter and Alberto Tosetti

7.1 Introduction

Cardiac implantable electrical device infections (CIEDI) are one of the most important complications associated with patient outcome and healthcare costs. Due to expanding CIED indications and increasing comorbidities such as diabetes and chronic kidney disease, the burden of infections associated with cardiac devices is increasing over time. The rate of CIED infections has been estimated at 0.5% with primary implants and 1–7% with secondary interventions [1, 2]. This trend leads to high financial costs and prolonged hospital stay [3, 4]. Nowadays the clinical standard treatments is based on the full extraction of the cardiac device (TLE) that is proved to be possible in more than 95% of these patients, with a low incidence of complications related to the procedure (1.7%) [5]. It is interesting to note that, although lead extraction is successful in more than 95%, the mortality remains high in this population. Still, during the past decades the mortality decreased from around 66% using conservative techniques to 12.5% in the first year of follow-up after introduction of extraction [4]. CIEDI management is complicated, from diagnosis to extraction to re-implantation. Each individual case should be managed with an "hub-and-spoke" organization, including referral centers and a centralized unit, requiring a team of expert operators from the beginning [6]. Although the literature supports the use of antibiotic therapy and device extraction, there are still doubts regarding the need of a re-implantation and even more regarding optimal timing, technique, and device selection. Considering a strong indication for the CIED, there

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are studies reporting on the association between re-implantation and major risk of complication such as infection, whereas other studies could not confirm these findings [7]. We have to consider the possibility that a new implantation, whether temporary or permanent, may be a carrier of new microorganisms or may perpetuate the first one. One of the possible choices to face the complication is a temporary device, although in literature it is proved to be a risk factor for new complications and infections [8–11]. Another consideration is not to perform a re-implantation. The main reason is that patients no longer meet device indication. The rate of re-implantation after extraction varies from 48% to 87% [12–15]. However, growing evidence suggests that re-implantation of a new device is not required in about 20% of patients [16–18]. Also, data indicate that patients without re-implantation have a significantly lower survival rate compared to patients being re-implanted, even though the main cause of higher mortality is related to comorbidities and device-associated complications, rarely to arrhythmia [16].

These points are most relevant, interesting, and controversial in both acute and chronic patient management. Until validate data exists, one should consider this topic as controversial. As such, clinicians need to consider all options available in the clinical decision making of re-implantation after lead extraction.

7.2 Considerations and Examinations Before Lead Extraction and Device Removal

In order to achieve the best outcome for the patients intending to eradicate the infection, to verify the need for re-implantation, to optimize the timing of re-implantation, to choose the best site for re-implantation, and to select the best device, several questions have to be answered step by step (Box 1).

Box 1 The following questions have to be answered prior to re-implantation

- What is the extent of infection? Early or late pocket infection, lead involving infection, bacteremia, endocarditis, septicemia?
- What is the expected duration of antimicrobial treatment?
- What was the initial indication and is there still an indication for the PM, CRT(D), or ICD after extraction?
- Is the patient pacemaker dependent and do we need a bridging strategy?
- Do we have venous access ipsilateral and/or contralateral for temporary/permanent pacing confirmed by venography?
- Does the size and localization of vegetations allow an interventional approach?
- Will we intent a simultaneous extraction and (temporary/permanent) re-implantation strategy?
- What is the overall prognosis of the patient and what are his/her expectations in life? Considering these facts is an extraction (and re-implantation) justified at all?

These questions vary whether a pacemaker has to be removed, a resynchronization system or a defibrillator, or the combination of both. A clear concept has to be discussed and finally agreed between interventional cardiologists, electrophysiologists, and cardiac surgeons before the initial lead extraction can be scheduled. Integrating experts in the field of infective diseases and antimicrobial chemotherapy might help to improve outcome.

7.3 Evaluating the Need of Re-implantation in PM, CRT, and ICD Patients

For all CIED patients facing a lead extraction and device removal due to an infection, it might be very helpful to go back into the patient history and try to figure out what was the initial indication for the CIED implantation.

If the patient had a history of repetitive dizziness, syncope, AV block III, resuscitation, and heart failure, the initial indication seemed to be valid and with the utmost probability the need for re-implantation is high.

If the implantations have taken place in a temporal context or directly after other interventions, it remains questionable whether the necessity persists. We have demonstrated that the need for permanent pacing after TAVR declines after time and in 45% of patients AV node conduction recovers after reprogramming [19].

Guidelines have changed and CIED may have been implanted for a relative rather than absolute indication such as chronotropic incompetence or bradyarrhythmia. In such cases, re-implanting a device after a device-related infection may carry more harm than benefit for patients. Nevertheless the emotional impact on patients and their families of a denied re-implantation even when clinically justified should not be underestimated and needs convincing explanations.

Interrogating the PM and reprogramming clearly identifies pacemaker-dependent patients with a need for a bridging therapy or a delayed re-implantation. If the pacing rate is very low (<10%) it is unlikely that a re-implant is necessary. If patients are continuously paced a down programming to initially 40 bpm should be performed and if there is still a relevant proportion of pacing the pacing rate can be further reduced to 30 bpm next day. This strategy allows a slow recovery of sinus node and AV node function in order to minimize the need of temporary pacing. The implantation of a pacemaker prior to or simultaneously with the extraction procedure is mandatory if a sufficient heart rate cannot be established under this minimal pacing rate.

Besides the electrical understanding, the evaluation of the left (and right) ventricular function and valvular morphology by TTE and/or TOE is required. It offers an immediate impression whether a patient is at very high risk for the extraction procedure itself and for developing immediate heart failure afterward. Long-term mortality is highest under CRT removal with a more than threefold increased mortality rate [20]. This might be caused by loss of biventricular pacing or even temporary or prolonged right ventricular pacing when a delayed CRT re-implantation is indicated. Those patients have to be followed closely.

In patients initially implanted with an ICD for primary prevention of sudden cardiac death, the interrogation of the device, underlying cardiac disease and left ventricular function will determine the need of re-implantation. If never ever any appropriate VT or VF therapy has been documented, the reduced left ventricular ejection fraction is of nonischemic origin, and/or the ejection fraction has increased above 35%, a re-implantation might be justified. Often general health has deteriorated over years and increasing comorbidities might overweight the potential benefit of an ICD. In some patients heart failure has approached an end-stage situation and the avoidance of a re-implantation will offer the opportunity to die suddenly and unexpectedly. These scenarios have to be discussed with the patients and his/her relatives and not seldom the perspective of dying immediately cannot be accepted and leads to the wish of re-implantation.

Also, additional therapy options have to be evaluated as they might influence left ventricular function and the occurrence of arrhythmias. For example, sacubitril/valsartan has shown to improve left ventricular function and reduce sudden cardiac death and overall mortality. Initiation and/or uptitration of such a guideline-directed medical therapy—if prescribed for at least 3 months—will reduce the need for re-implanting an ICD. The ablation of monomorphic ventricular tachycardia has improved since years.

7.4 Strategies to Maintain Pacing in Pacemaker-Dependent Patients

Generally several options exist to secure heart rhythm during or post lead extraction and device removal in pacemaker-dependent patients. Which one is preferred is mainly influenced and determined by tradition, experience, interaction between departments and personal disposition as well as financial resources.

As long as no randomized trials exist which prospectively evaluate the differences in safety, complications, reoccurrence of infection, and mortality, no strategy can be favored or ultimately recommended. There are PROs and CONs for every approach.

Table 7.1 gives an overview of the technique, advantages, and disadvantages.

The epicardial procedure with a subxiphoid access and epicardial suture on or screw in lead secures safe pacing during endovascular and endocardial maneuvers and can be performed prior or during the extraction. It allows a complete removal of all transvenous material and a period of antibiotic treatment without additional temporary lead material intravenously.

Figure 7.1 shows the surgical access and epicardial implant technique and Fig. 7.2 the X-ray with the location of lead and device.

Also, it preserves the contralateral venous system for a delayed re-implantation and might even be used in complete venous occlusion of the upper body. An epicardial pacemaker can be a temporary solution or even a final answer allowing immediate mobilization.

Table 7.1 Strategies to secure pacing during and post lead extraction in pacemaker-dependent patients

Strategy	Description of procedure	PROs	CONs	Lit.
Epicardial RV permanent subxiphoidal	Approximately 5–7 cm subxiphoidal incision preparation down to pericardium, opening and epicardial electrical testing either bipolar suture on or unipolar screw in leads used tunneling into the pocket beneath the anterior rectus sheath; fixation of the generator can be done prior explantation or in same intervention	No cardiopulmonary bypass, at beating heart Small incision If done in same session already access to the pericardium in case of tamponade No remaining intravascular material Avoidance of contralateral venous stenosis/occlusion Safe, no dislodgement during extraction and potentially permanent after clinical reevaluation Immediate mobilization of patient Shorter duration of in hospital stay	Needs more surgical skills Difficult in obese patients Mainly RV apical pacing threshold sometimes increases over time	Amraoui et al. Heart Rhythm 2015 Amraoui et al. J Thorac Cardiovasc Surg 2013 Burger et al. Thorac Cardiovasc Surg 2012 Deharo et al. Heart 2012
Epicardial left/ biventricular permanent	Subxiphoidal access as described above and additional left lateral thoracotomy for atrial lead right parasternal additional access tunneling of all leads preferably into pocket beneath anterior rectus sheath, fixation generator	Might be considered as final solution in patients requiring CRT and complex or inaccessible CS Other PROs as described above	Complex implantation especially in patients with prior cardiac surgery and/or obesity Potential problems with threshold and intrinsic signals	Haight et al. Interactive CardioVascular and Thoracic Surgery 2018 Rickard et al. JACC Heart Failure 2013
Same-day contralateral transvenous permanent implantation	Explantation/extraction with pocket debridement as usual Standard transvenous reimplantation on the contralateral site	Full care in one session Immediate mobilization of patient Shorter duration of in-hospital stay	(maybe) only in isolated pocket infection under protection of a transvenous temporary pacing lead	Mountantonakis et al. Europace 2014

(continued)

Table 7.1 (continued)

Strategy	Description of procedure	PROs	CONs	Lit.
Externalized temporary transvenous lead via v.jug. int. v.subclavia, (v.fem.)	(Contralateral) venous access by puncture (mainly V. jug. int.) placement of a permanent screw in lead in RV used temporarily fixed with sleeve at venous exit connected to a (mainly resterilized) conventional permanent pacemaker taped on the skin	Stable position and safe pacing with an active fixation lead Maintenance of pacing up to 45 days Cost effective	Still endovascular material in a potentially infected area Might support ongoing infection Transitioning at least a part of the new transvenous access path for the permanent reimplantation Risk of thrombosis No final solution	Maciag et al. Kardiologia Polska 2015 Kawata et al. Europace 2013

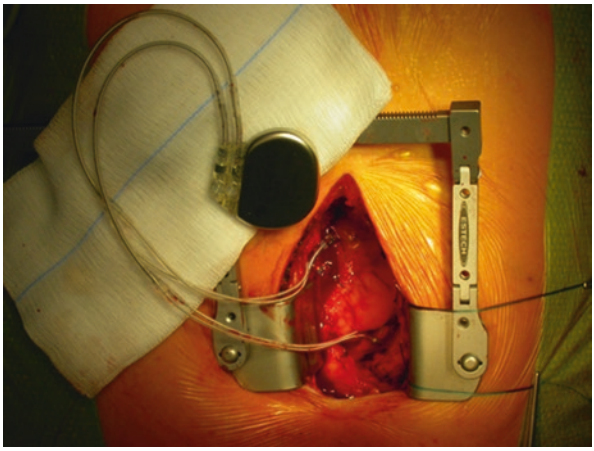

Fig. 7.1 Epicardial dual-chamber pacemaker with two bipolar sutures on leads in subxiphoidal access

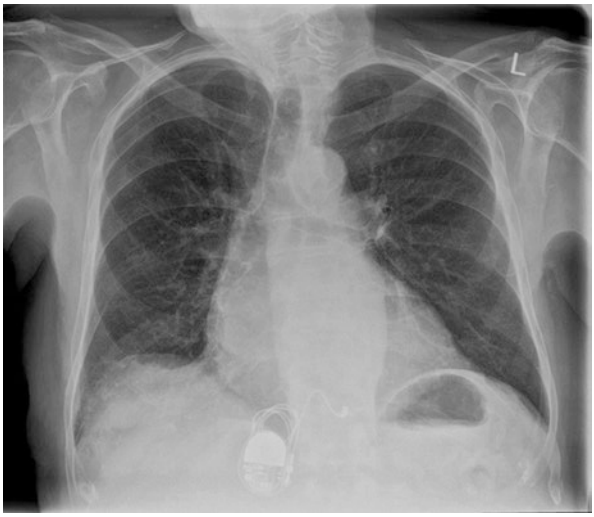

Fig. 7.2 Chest X-ray showing epicardial single-chamber PM with unipolar screw in lead

Alternatively standard transvenous screw in leads delivered via contralateral internal jugular vein or subclavian vein will be externalized and connected to a resterilized pacemaker, which will be tapered on the skin. This is a temporary solution for several days, might be unstable and risky during the transvenous extraction, might damage the vascular access which is needed as permanent access for the final implant, and might prolong the process of eradicating the infection. Nevertheless this strategy is commonly used as a cost-effective bridging alternative.

7.5 Strategies to Prevent Sudden Cardiac Death During Reevaluation

In order to protect the patient after ICD removal from sudden cardiac death, two general strategies can be chosen based on the individual situation.

If the indication for SCD protection is still existing a wearable cardioverter defibrillator (LifeVest®—Zoll) can be prescribed and has to be worn continuously until re-implantation. The heart rhythm is continuously derived by epidermal patches and monitored. In case of life-threatening arrhythmias an alert occurs, which allows the patient to react, sit down, and even suppress the shock delivery until he/she will lose consciousness. If artifacts or non-life-threatening arrhythmias will cause the alert, the patient can withhold the shock and avoid inappropriate therapy. Patient compliance is essential and has been a matter of concern. The use of wearable cardioverter defibrillator (WCD) can be easily monitored online. WCD therapy has been used after lead extraction and has shown to be effective and cost saving [21–23].

All components of a wearable cardioverter defibrillator are shown in Fig. 7.3.

Alternatively, a subcutaneous ICD can be chosen, not as a temporary bridging, but as a final solution. The implantation might be performed earlier compared to the re-implantation of a transvenous system because it does not require the insertion of any leads into the cardiovascular system and the subcutaneous lead and pocket placement are generally far away from previously infected pockets which are in the pectoral region. This will allow optimal healing of the intravascular and intracardiac infection. Compared to a transvenous system the S-ICD neither offers a permanent pacing opportunity nor an antitachycardiac pacing. The discrimination of supraventricular arrhythmias is worse compared to TV-ICDs. Nevertheless an

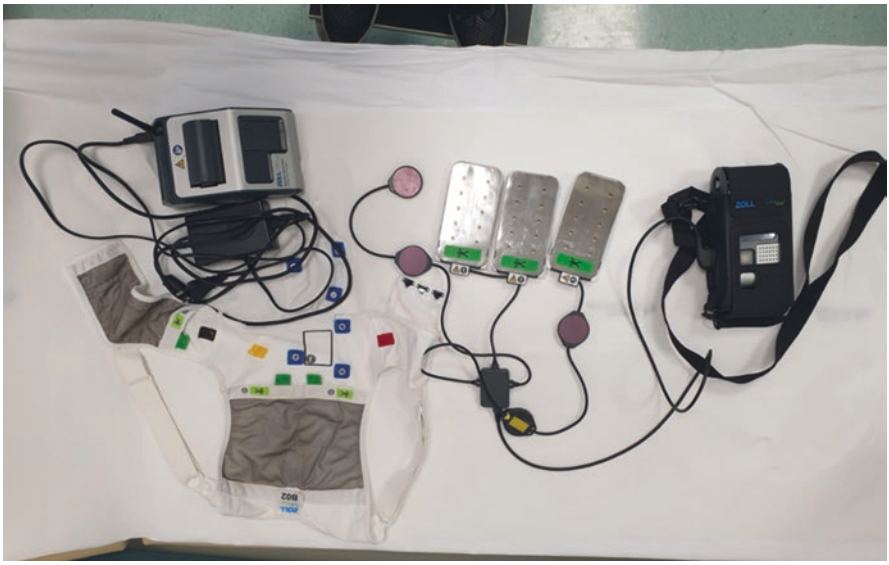

Fig. 7.3 All components of a LifeVest® (Zoll)—wearable cardioverter defibrillator—before applied to a patient

analysis of current clinical practice in Italy has shown an increase of S-ICD use after lead extraction from 9% in 2011 to 85% in 2017 preferably in younger patients. The implantation technique using an intra- or submuscular access for the pocket is important to minimize complications [24].

The S-ICD can be combined with an epicardial pacemaker in case of missing venous access or in order to avoid any intravascular material. In the near future leadless intracardiac pacemaker will communicate with the S-ICD, delivering intracardiac signals and allowing antitachycardiac pacing. This option might be extended to AV synchronous and/or endocardial biventricular pacing.

7.6 Duration of Antibiotic Treatment and Timing of Re-implantation and Envelope

As previously discussed, approximately 20–30% of patients do not need a re-implantation because the indication or clinical situation has changed. Besides the group of pacemaker-dependent patients who are simultaneously extracted and permanently implanted the remaining patients can be treated at a later date. The optimal time for re-implantation is a matter of discussion and clear guideline recommendations still do not exist.

Timing of re-implantation depends on type and extent of infection, response to (antibiotic) treatment, suppression of inflammatory marker, and negative blood cultures (Fig. 7.4).

A noneffective antibiotic treatment either due to duration or to choice of drug will not only prolong the course of infection, but delay the re-implantation. There are no trials comparing different durations of antimicrobial therapy, the eradication

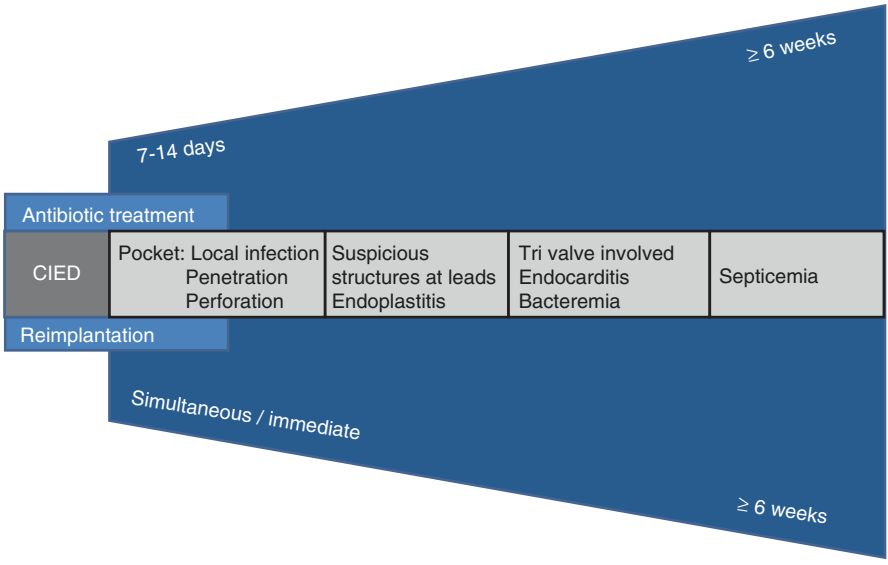

Fig. 7.4 Duration of antibiotic treatment and timing of re-implantation

of infection, and the reoccurrence of infection. After the initiation of antimicrobial treatment the infected device and leads should be removed immediately. Antimicrobials should be continued depending on the initial clinical situation.

Unfortunately in many publications generator pocket infections, CIED-infective endocarditis, and CIED-lead infections are amalgamated, which somehow reflect the clinical challenge. If small floating fibrotic structures are found in TOE in combination with a suspicious pocket, the severity might be extended to CIED-LI or the structures are just judged as normal fibrotic tissue treating the patient as "pocket infection." There is more or less agreement in the literature that pocket infections have to be treated between 10 and 14 days. There is less agreement according the duration in CIED-LI and CIED-IE ranging from 4 to 6 weeks. Sometimes it is difficult to see whether masses attached to a lead passing the tricuspid valve involved the tricuspid valve itself leading to the diagnosis "infective endocarditis." As soon as left-sided valves are definitely affected therapy duration of at least 6 weeks is recommended.

Wherever possible, re-implantation should be avoided or delayed until symptoms and signs of systemic and local infection have resolved. No data exist to answer the question whether it is safe to re-implant under ongoing antibiotic treatment (advocated 7–10 days after device removal) or whether it has to be finished first and blood cultures have to be negative for at least 72 h (if initially positive) [25].

When considering the best site for re-implantation venous access should be preferably performed in the contralateral side such as internal jugular, subclavian, axillary, or cephalic vein. As already discussed an epicardial lead placement with a pocket behind the anterior rectus sheath is a safe and elegant option avoiding any intravascular material. If just a defibrillation without pacing option is need, a subcutaneous ICD should be used. If the ipsilateral side has to be used again (due to venous occlusion contralateral or other anatomic limitations), preparation of the new pocket has to be done cautiously; a deeper tissue layer as in the previous pocket should be prepared since a rigorous debridement during the initial explantation has been performed.

Based on the currently published WRAP-IT trial in all re-implantations, an absorbable, antibiotic-eluting envelope can be recommended in order to reduce the reinfection rate [26].

7.7 Relevance of "Ghosts" and Remaining Unclear Intracardiac Structures

In 8–14% small residual strands, tubular structures or masses remain within the RA or SVC following lead extraction and can be visualized in TOE. These so-called ghosts are most commonly observed in patients with positive blood cultures, CIED infection, or infective endocarditis and have a negative impact on survival and CIED recurrence or relapse [27–29]. The echocardiographic appearance does not distinguish between pure fibrotic remnants, thrombus formation, and endocarditis which make the therapy uncertain. If a combination of antibiotic therapy and

anticoagulation given for at least 2–4 weeks reduces the size of the suspicious structure and eliminates all signs of a systemic infection, a re-implantation might be considered. If a permanent suppression or cure of the infection is not possible and even a growth of the structure can be detected by echocardiography, a vacuum-based device (AngioVac®) can be used for debulking and consequently enhancing the efficacy of antibiotics. In some cases the open surgical removal of the masses is the last remaining option.

In general, remaining postextraction suspicious intravascular or intracardiac structures should be followed closely by TOE and re-implantation considered if any signs of infection have disappeared and blood cultures have been negative repetitively.

7.8 Device Selection for Re-implantation

After complete removal of pacing, defibrillation, or resynchronization system with transvenous leads, the clinical future of a patient is substantially determined by the optimal choice of the device, its functional capabilities, and its access and technical limitations [see also Chaps. 10 and 12 for additional hints on available and future technologies].

First, it has to be clarified whether the patient has still accessible veins of the upper body best at the contralateral side of the removed device. If the venous system is undamaged, not critically stenosed, or not occluded, this access side should be preferred. Using this approach all currently available transvenous systems can be implanted ranging from a simple single-chamber pacemaker or ICD to a complex CRT pacemaker or ICD assuming that the superior vena cava is open and posterolateral tributaries of the coronary sinus system are accessible after TLE. Thus full functionality can be achieved. If the coronary venous system is damaged or occluded, a dual-chamber ICD might be implanted transvenously and be combined with ultrasound-based, LV endocardial pacing triggered by a conventional right ventricular pacing spike from a co-implant.

The WiSE System® ("Wireless stimulation endocardial system"; EBR Systems Sunnyvale, CA, USA) delivers ultrasound energy via a small USB stick-like transducer placed in the intercostal space to a tiny LV endocardial electrode, which is implanted through a guiding catheter retrograde passing the aortic valve, where the ultrasound energy is transferred into electrical energy, which stimulates the left ventricular posterolateral wall and resynchronizes the heart [see Chap. 10]. Among others effectiveness and safety has been shown in CRT nonresponders [30–33].

Alternatively an epicardial lead might be implanted surgically at the posterolateral left ventricular wall. This transvenous and epicardial combination will also allow full CRT-P or CRT-D function and can also be considered in selected patients as an established option.

Recently HIS bundle pacing experiences a rebirth and is seen as a more physiologic pacing than RV pacing. Technical implant success has improved with new shaped guiding catheters, but clinical data showing a comparable success rate as CRT are still lacking [34–36].

Once having the opportunity to reconsider a CRT-D implantation a change in comorbidities, life expectancy, left ventricular function, or patient attitude toward sudden peaceful death might open up a discussion about "simplifying or downgrading" the new device. This means that pacemaker (or CRT-P) is implanted instead of the previously explanted ICD (or CRT-D). This step has to be discussed with the patient and her/his relatives extensively highlighting the consequence of an immediate unexpected and unpredictable death.

Real "leadless" pacemaker like the Micra® (Medtronic) delivered via a guiding catheter through the femoral vein and implanted in the apico-septal region of the right ventricle is particularly attractive for younger patients with previous pocket problems who have been freed from all transvenous electrodes and/or venous access problem of the upper body. Furthermore the leadless pacemaker is of potential interest for patients who are physically very active or have a job, which will not allow stress on a "device pocket." The widespread use of this technology is limited by the currently available VVI-R pacing mode which mainly justifies its use in rare episodes of sinus node dysfunction or sinus node arrest, very rare episodes of symptomatic AV block III, or symptomatic bradyarrhythmias.

This single-chamber leadless pacemaker should not be used in indications where continuous AV synchronicity is required like AV block. Currently the combination and communication between two leadless PM implanted in different chambers of the heart is under investigation and might be an option in the future. A further concern is the concept after battery depletion which will either discuss the extraction or just the additional implantation of the next capsule [37, 38].

If the need for an ICD re-implantation is validated two options can be discussed in general, the transvenous and the subcutaneous implantation.

Re-implantation with a standard single- or dual-chamber ICD might be performed using the conventional transvenous route predominantly from the contralateral side. If pocket problems occurred in the past, special care should be taken on the subfascial of submuscular preparation of the pocket and the sufficient coverage of the sleeves at the entrance site.

The subcutaneous ICD (S-ICD) is a meanwhile accepted alternative predominantly in younger patients with primary prevention indication and no need for antibradycardiac or antitachycardiac (ATP) pacing. This technology with a subcutaneous parasternal lead keeps the vascular and intracardiac space free from any leads and allows an easy risk-free extraction. Furthermore the tricuspid valve is not touched by any lead which might avoid tricuspid regurgitation. Initial investigations show that a communication between a S-ICD and a "leadless PM" is feasible and promising offering the opportunity to use the intracardiac signal and the intracardiac pacing for ATP f.e (Fig. 7.5) [24].

Whether a newly demonstrated leadless ICD, the so-called string defibrillator, is more attractive has to be demonstrated by research in the future (Fig. 7.6) [39].

Table 7.2 summarizes the existing guidelines and recommendations regarding the re-implantation [3, 25, 40–43].

Table 7.3 supports the device selection in case of re-implantation and the combination of different technologies.

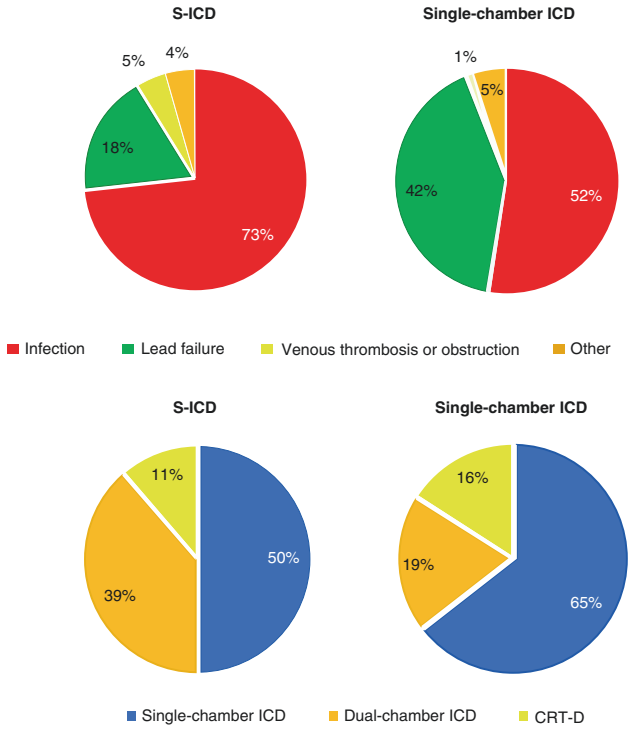

Fig. 7.5 Comparison of the use of S-ICD and conventional single-chamber ICD in re-implantation after lead extraction in a multicenter registry both in terms of indication to extraction (top 2 pies) or previous implanted ICD system (in the bottom) (Reproduced from Viani et al. [24] with permission)

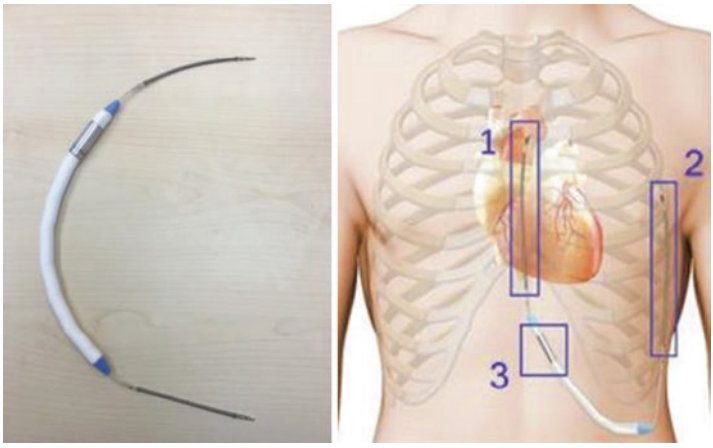

Fig. 7.6 The string ICD. The figure represents the device, composed of a 10-cm-long, 5-mm diameter sternal coil (1); a 10-cm-long, 3-mm diameter side coil (2); and a 4-cm-long, 1.5-cm diameter cylindrical metal tube called the "active segment" (3). (Reproduced from Petr Neuzil [39] with permission)

Table 7.2 Current international recommendations and guidelines regarding re-implantation after lead extraction due to infection

Guidelines:		AHA 2010	ESC 2015 Endoc	BHRS/BCS 2015	ESC 2015 V. Arrhythmias	ACC/AHA/ HRS 2017	HRS 2017
Reassessment:		Yes (I C)	Raccommended (I C)	Raccommended (I B)	n.a.	n.a.	"Imperative"
Timing	Pocket Infection	Negative blood cultures for 72h (IIIa C)	Postponed, to allow antibiotic therapy (IIa C)	Delayed until symptoms and signs of infection have resolved (B)	n.a.	n.a.	Same day if isolated pocket infection
	Lead Infection				n.a.	n.a.	Negative blood cultures for 72 h
	Valvular infection	Delayed 14 days (IIa C)	Delayed 14 days		n.a.	n.a.	
Location:		Contralateral, Iliac, Epicardial (I C)	Contralateral	Not ipsilateral to extraction side (C) [a]	n.a.	n.a.	Not ipsilateral to extraction side [a]
PM dependet patient: (Temporary pacing)		Active lead E-PM is an option.	ipsilateral active fixation (I C) No routine use (III C)	Active fixation lead connected to external CIED is an option	n.a.	n.a.	Required (Semi-permanent pacing)
If ICD required:		n.a.	n.a.	n.a.	S-ICD is a useful alternative (IIB C)	-S-ICD (I B-NR)- Wearable ICD (IIa B-NR) [b]	Wearable defibrillator

[a]Alternative: contralateral side, iliac vein, epicardial or subcutaneous approaches

[b]for prevention of SCD when removal of the ICD is required (IIB B-NR) and in patient who are not inelegible for an ICD and with systemic infection (IIB B-NR)

Table 7.3 Options for device choice and combinations considering re-implantation

ICD	PM	Need for pacing			
		OOO	VVI	DDD	CRT
Need for ICD backup	Yes	• S-ICD • T-ICD (Contr.) • EPIC. ICD[a]	• T-ICD (Contr.) • S-ICD + LEADLESS PM • S-ICD + EPIC. PM (subx.) • EPIC. ICD+PM[a]	• T-ICD (Contr.)[b] • S-ICD + EPIC. PM • EPIC ICD/PM[a] [*S-ICD+AV LEADLESS PM*]	• T-CRTD (Contr.) • T-ICD[b] + EBR • EPIC. CRTD[a] • S-ICD + EPIC PM [*CRTD LEADLESS*]
	No	No reimplantation	• T-PM (Contr.) • EPIC. PM (subx.) • Leadless Patient-specific choice	• T-PM (Contr.) • EPIC. PM [*AV LEADLESS PM*]	• T-CRTP • EPIC. CRTP[a] • (AAT + EBR) [*CRTP LEADLESS*]

000 no pacing needed, *AAT* atrial pacemaker with triggering function, *Contr.* contralateral, *CRTD* defibrillator with resynchronization therapy, CRTP pacemaker for cardia resynchronization, *EBR* leadless left ventricular pacing, EPIC epicardial, *ICD* implantable defibrillator, *PM* pacemaker, S-ICD subcutaneous ICD, *subx* subxiphoid, *T-ICD* transvenous ICD, *T-PM* transvenous PM

[a]Consider in any case of conversion to surgery

[b]Consider VDD single lead ICD system (Biotronik); [*option*] = *possible future options*

7.9 Summary

The infection of a CIED is not a rare, but serious and life-threatening, complication which is often overseen and treated lately especially when the device pocket is not suspiciously affected. Keeping this potential complication in mind and initiating necessary investigation to verify or exclude this complication is the first step to a timely treatment.

Only in a minority of patients characterized by very old age, high comorbidity, reduced general condition or life expectancy, as well as a very high procedural risk for extraction, a continuous antibiotic treatment for a long time period might be considered.

In all other patients the complete extraction and removal of all extra- and intravascular components is mandatory accompanied by an adopted antimicrobial therapy.

When this decision is made an immediate strategic planning of the procedure and the time afterward involving the interdisciplinary team has to be initiated to avoid any intraprocedural surprise and choose the best approach afterward to secure the best individual pacing and defibrillation strategy in order to avoid any early and late reinfection. This discussion needs the involvement and her/his relatives as well.

Device interrogation, TOE, infection parameters, blood cultures, and the clinical appearance will determine whether a bridging device to maintain rhythm and/or to prevent sudden cardiac death is needed. The duration of antibiotic treatment, follow-up imaging, and the timing and site of re-implantation as well as the choice of the new device are crucial to achieve long-lasting infection-free results for the patient's future.

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Follow-Up and Prognosis After System Removal for Cardiac Device Infection

8

Dominic A. Theuns, Sing-Chien Yap, and Tamas Szili-Torok

8.1 Reimplantation

Complete device removal is a class I recommendation in all cases of pocket infection and endocarditis, regardless of whether there is definitive evidence of device involvement [1]. When considering device reimplantation after infection, there is a variety of reimplantation strategies. The vast majority of patients who underwent CIED extraction undergo device reimplantation. However, up to 40% of patients do not require reimplantation as reported in several series [2–6]. The Multicenter Electrophysiologic Device Infection Cohort (MEDIC) prospective registry enrolled 434 patients with device infections [3]. Of these, device removal was completed in 381 patients (88%) and 53 patients (12%) did not undergo device removal due to various physician justifications. Among the 381 patients who had device removal, 220 (58%) underwent reimplantation and 161 (42%) did not require reimplantation. Reasons for not reimplanting devices include improved ejection fraction, recovery of sinus function and improvement of symptomatic bradycardia. The study by Al-Hijji et al. reported that approximately 14% of patients do not receive CIED reimplant after extraction [2]. Approximately 70% of the patients without reimplant either did not meet any indication for ongoing device therapy or their device was not indicated at the index implantation according to current guidelines. During follow-up, the mortality rate was higher in the no-reimplant group compared to the reimplant group. However, the higher mortality rate was mainly driven by noncardiac comorbidity, device complications and infection (Fig. 8.1).

The timing and approach to reimplant devices are major concerns in managing CIEDI. The 2017 HRS expert consensus report on transvenous lead extraction (TLE) recommends new device implantation in patients treated by antimicrobial therapy for 3 to 14 days after extraction [1]. In fact, new CIED implantation can

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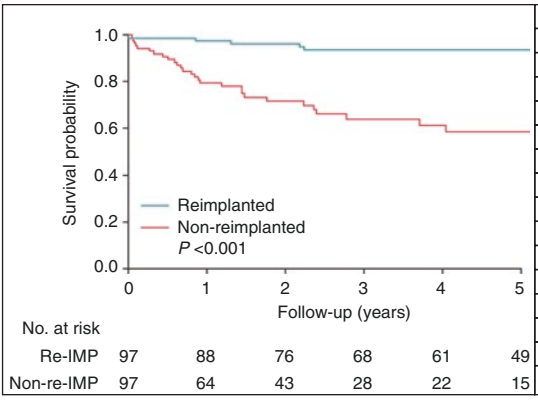

DEATHS	31,96%
Cardiac causes	5,15%
End-stage cardiomyopathy	3,09%
Myocardial infarction	1,03%
Arrhythmia	1,03%
Noncardiac causes	23,71%
Cancer	5,15%
Cerebrovascular accident	5,15%
Respiratory failure	3,09%
End-stage renal disease	4,12%
Sepsis	5,15%
Suicide	1,03%
Unknown	3,09%
MULTIVARIATE ANALYSIS	
Unresolved device complications	HR 4.79
TLE for infection	HR 2.69

Fig. 8.1 Survival and cause of death of reimplanted versus not reimplanted patients after TLE for CIEDI (Kaplan-Meier curve figure reproduced from Al-Hijji et al [2] with permission). The table on the right shows the cause of deaths reported by authors and the result of multivariate analysis as reported in the paper (main independent predictors of mortality were CIED-related complication and extraction for infective cause). Legend: HR, hazard ratio; TLE, transvenous lead extraction

reasonably be postponed until blood cultures are negative for 3 days. The timing of reimplantation in the MEDIC registry varied considerably among the study population [3]. The median time was 10 days, interquartile range of 6 to 19 days; in all, 70% of patients were reimplanted within 2 weeks. As suggested by existing guidelines, patients were treated differently when they had confirmed infective endocarditis (IE). Patients with IE were reimplanted at a median of 13 days, while those without IE were treated at a median of 8 days. Considering the potential gravity of prosthetic material infections, CIED should be reimplanted while taking the greatest precautions to prevent recurrent infections. [For additional information on CIED reimplant approaches see Chap. 7.]

8.2 Recurrent Infection After Transvenous Lead Extraction

The true incidence of recurrent infection after TLE for infection is hampered due to limited data on long-term outcome after TLE [7–9]. Reported data are primarily based on single-centre studies (Fig. 8.2). A recent single-centre study demonstrated an overall repeat TLE rate of 6% (including all indications) during a mean follow-up of 5.5 years [9]. Of the patients who underwent initial TLE for infection, the incidence of recurrent infection requiring TLE was 4% (15 of 419 patients). Maytin et al. demonstrated an incidence of recurrent infection requiring TLE of 2% (10 of 520 patients) during a mean follow-up of 3.7 years [7]. Patients underwent the repeat TLE procedure for infection at a mean of 21 months (range 1–53 months) after the initial procedure. It is important to realize that not all patients experiencing a CIED recurrent infection undergo TLE due to poor candidacy (e.g., elderly patients with multiple comorbidities) or patient refusal. Therefore, the true

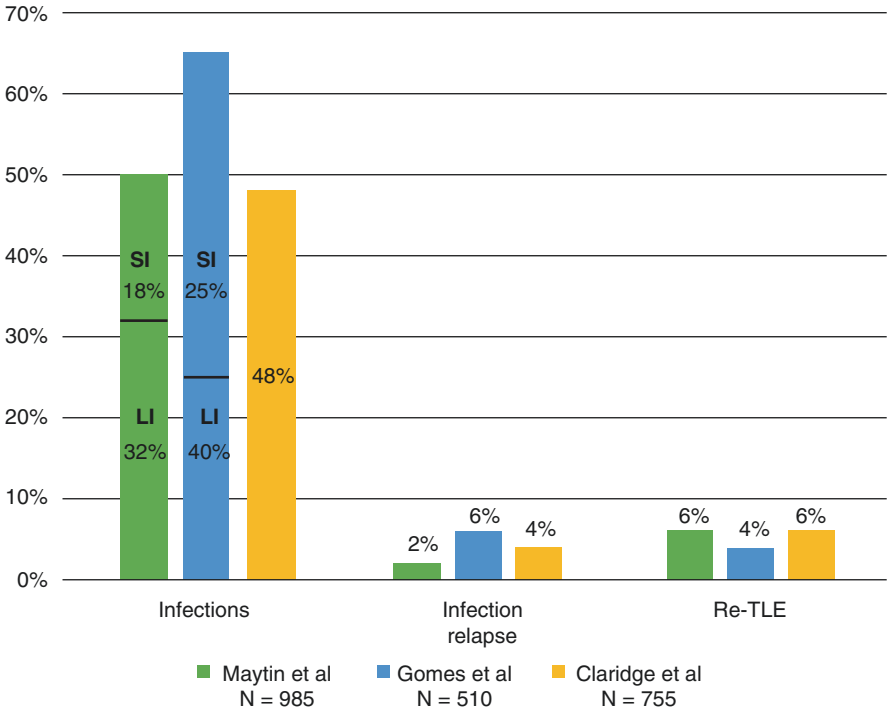

Fig. 8.2 Main studies on follow-up after TLE. Main studies on long-term follow-up for reinfection after TLE [7–9]. The graphic reports the size of the cohort, the rate of patients with an indication of TLE for infection (splitted by local or systemic infection when data were provided from the paper), the rate of relapse (among those admitted for infection) and the percentage of patients who repeated TLE. Legend: LI, local infections; N, number of patients; SI, systemic infections; TLE, transvenous lead extraction

incidence of CIED recurrent infection post-TLE may be higher. This is demonstrated by a single-centre study from Australia [8]. In this study, the incidence of recurrent device infection was 6% (20 of 331 patients) post-TLE for infection. Of the patients with recurrent device infection, 7 (35%) were medically managed and 13 (65%) underwent repeat TLE (thus 4% repeat TLE rate for infection). Based on above-mentioned data from high-volume centres, the incidence of CIED recurrent infection post-TLE is estimated at 6% and the CIED reinfection rate requiring repeat TLE is around 2–4%.

Considering the risk of recurrent infection, one may wonder whether this is due to an ongoing (latent) infection despite initial TLE. In a retrospective single-centre study, five patients had positive microbiology at initial and repeat TLE of which the same organism was identified at initial and repeat TLE in the same individual in only two cases (coagulase-negative staphylococcus in both cases) [9]. Thus, it is more likely that patients have a predisposition to infection even if there is apparent sterilization at the initial procedure [9, 10]. There are several clinical and procedural

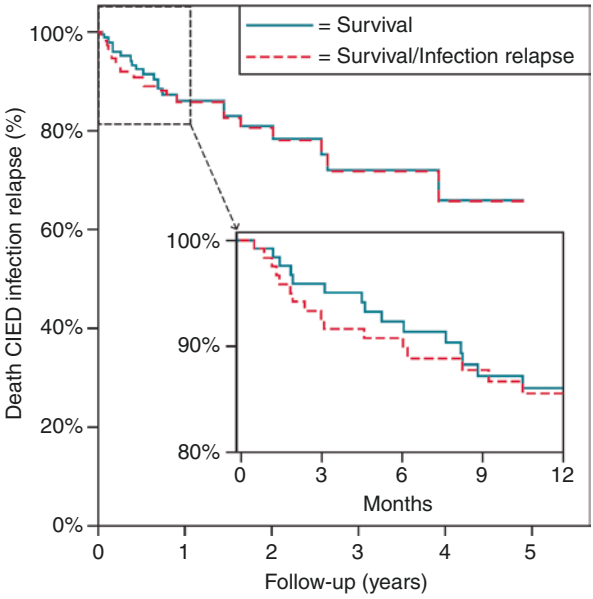

Fig. 8.3 Comparison of survival from death alone or the composite endpoint of death or CIED infection in a prospective cohort of patients undergoing TLE for CIEDI. No statistic difference was shown at the long-rank test between these two curves at any timepoint: 30, 60, 90, 180 and 365 days or complete follow-up. (Reproduced from Diemberger et al. [13] with permission)

factors associated with CIEDI, including end-stage renal disease, diabetes mellitus, chronic obstructive pulmonary disease, use of immunosuppressive drugs, older age, pocket hematoma and longer procedure duration [11, 12]. It is likely that these risk factors are also important for reinfection after TLE for infection. With regard to the TLE procedure, it is important to aim for complete lead removal. Retained lead fragments have been associated with a higher reinfection rate [3, 8].

The occurrence of reinfection requiring TLE seems to be associated with a poorer outcome (Fig. 8.3) [13]. In a single-centre study, all-cause mortality was 36% for those who underwent repeat TLE for infection compared to 5% in those where repeat TLE was indicated for lead problems [9]. The 36% mortality rate was also higher when compared with patients who had undergone a single TLE for infection (23%, P = 0.02). In addition, multiple studies have shown a higher all-cause mortality in patients undergoing initial TLE for infectious indications in comparison to patients undergoing TLE for other indications [3, 7, 8]. Thus, the prognosis of patients undergoing a repeat TLE for infection is poor. Every effort should be taken to lower the risk of recurrent infection. This could be achieved with early diagnosis of CIEDI and performing complete device and lead removal within a relatively short time after diagnosis.

8.3 Mortality After Transvenous Lead Extraction

Transvenous lead extraction has been associated with a risk of major adverse events, including vascular laceration, cardiac avulsion, pericardial effusion, hemothorax and death [1]. Recently, data of 11,304 extraction procedures from the National

Cardiovascular Data Registry ICD Registry were analysed [14]. In-hospital mortality during TLE was observed in 98 (0.9%) patients. Among these, 44 (44%) patients underwent TLE for CIEDI. Urgent cardiac surgery was required in 41 (0.36%) patients, of which 14 died either during surgery or immediately post-op. The European Lead Extraction ConTRolled Registry (ELECTRa) reported on the outcomes of 3555 patients who underwent TLE [15]. The in-hospital procedure-related major complication rate was 1.7% including a mortality rate of 0.5%. Major conclusions of both registries were high success rates and low major procedure-related complications. Most importantly, it was clearly demonstrated that procedure-related complication and peri-procedural mortality rates are the lowest among high-volume and experienced centres.

Data concerning short- and long-term outcomes is steadily increasing. In a retrospective cohort analysis of 176 patients who required TLE, mortality rates of 3.4% at 30 days and 8.5% at 1 year were reported [16]. Among patients who required TLE because of CIED systemic infection, mortality rates increased to 19% at 30 days, 32% at 1 year and 39% during long-term follow-up, as compared with a long-term mortality of only 12% in patients who required TLE for other reasons. In a similar study, Maytin et al. also demonstrated an increased risk of mortality associated with CIEDI [7]. In their cohort, mortality at 1 year was nearly 25% among patients with systemic infection compared to less than 10% among those with local infection. Henrikson et al. reported the outcomes of 67 patients undergoing TLE because of infective indications [17]. The overall mortality rate of patients with systemic infection was 44%. Considering the data from NCDR ICD registry and ELECTRa, mortality risk directly related to the TLE procedure is relatively low (<1%), but 1-year mortality rate as observed in single-centre studies is high, particularly in patients with systemic infection. Risk assessment in patients undergoing TLE is underestimated and may be related to the focus on procedural risk. A few studies focused on predictors for long-term outcome after TLE.

Tarakji et al. evaluated risk factors for 1-year mortality among patients with CIEDI and examined the association between the type of infection and the mortality risk [18]. Data of 502 consecutive patients who underwent CIED removal for the indication of device-related infection were analysed. A total of 102 (20.3%) patients died within the first year after CIED removal. Risk factors for 1-year mortality among patients with CIEDI undergoing system removal include dementia, renal insufficiency, worse functional class, use of anticoagulation, bleeding requiring transfusion and CIED-related systemic infection as opposed to pocket infection. Higher mortality risk among patients with systemic infection seems unrelated to the presence of vegetations on TEE. Habib et al. evaluated data of 415 patients with CIEDI in order to identify risk factors associated with short-term (30 days) and long-term (>30 days) mortality [19]. Factors associated with long-term mortality included patient age, heart failure, metastatic malignancy, corticosteroid therapy, renal failure and CIED-related systemic infection. Another study found the presence of chronic kidney disease, increased numbers of leads to extract, lower ejection fraction and procedural failure as predictors of mortality [20]. Caution must be taken as in this study, the majority of patients underwent TLE particularly for

non-infectious reasons. Taken the studies together, the data suggest that the development of CIED-related systemic infection and the presence of co-morbid conditions are associated with short- and long-term mortality in patients with CIEDI (Table 8.1) [7, 13, 16–21].

When most risk factors are taken into account such as in the IKAR risk score model, mortality can be predicted with a reasonable accuracy [21]. The IKAR risk score was derived in a single-centre cohort of 130 patients; the abbreviation of IKAR stands for: I, infectious; K, kidney; A, age; and R, removal of high-voltage leads. Patients with IKAR score ≥3 points were characterized by 79% mortality as compared to 16% for those with a score of 1–2 points. The proposed risk score may be helpful in making individual statements on mortality risk prior to TLE. However, the proposed risk should not disqualify patients from the TLE procedure. To determine the performance of this score, analysis in a larger multicentre series is warranted.

8.4 Strategies to Minimize the Risk of Adverse Outcomes

In clinical practice, CIED removal is often delayed in favour of initial trials of antimicrobial therapy alone. The consequences of sustained infection despite appropriate antimicrobial therapy and recurrent infection are well recognized. Early diagnosis of CIED-related infection and performing TLE within 3 days of diagnosis has been associated with lower in-hospital mortality. Based on this, early and complete CIED removal is critical in the management of CIED-related infection, regardless of the timing of the start of antimicrobial therapy.

Patients requiring TLE should be referred to dedicated centres with appropriate training and experience. Optimal cardiothoracic surgical backup at centres performing is imperative as a 16% incidence of requiring urgent cardiac surgery with a high mortality rate among these patients was observed in the NCDR ICD registry.

After CIED removal, reassessment of the need for a new CIED is imperative. Some patients may no longer meet guideline indications for permanent bradycardia pacing, ICD or CRT, and some patients might not wish to receive a new device. A new CIED implantation can reasonable be postponed until blood cultures are negative for 3 days. Reimplantation should be performed in an alternative location such as the contralateral side or using epicardial or subcutaneous implantation. Patients without the indication for bradycardia pacing, antitachycardia pacing or CRT are eligible for a subcutaneous ICD (S-ICD) system. The S-ICD involves no hardware exposed to the intravascular system, which reduces the risk of systemic infection. In a sub-analysis of the EFFORTLESS registry (Fig. 8.4), the S-ICD is a viable alternative for patients who underwent removal of a transvenous ICD system [22]. The risk of recurrent infection remains low even in patients whose devices were removed because of infection. [For additional information on new CIED devices to minimize CIEDI see Chap. 10.]

Table 8.1 Main studies assessing the survival after transvenous lead extraction

Study	N	Design	Localinfection (%)	Systemicinfection (%)	30-daymortality (%)	1-yearmortality (%)	Risk factors
Maytin et al. [7]	985	RET	33.9%	18.9%	2.1%	8.4%	CIEDI (both local and systemic), device system upgrade, diabetes mellitus, increasing age, kidney failure
Diemberger et al. [13]	121	PRO	54.5%	45.5%	0.83%	14.2%	Renal failure, presence of ghosts post-TLE, infection non-involving CIED pocket
Deckx et al. [16]	176	RET	34.7%	17.6%	3.4%	8.5%	Systemic CIEDI, lower haemoglobin level, higher level of urea
Henrikson et al. [17]	67	RET	49.3%	50.7%	7.0%	20.9%	NR
Tarakji et al. [18]	502	RET	57.6%	42.4%	5.8%	20.3%	Endovascular infection, renal failure, worse functional class and bleeding requiring transfusion
Habib et al. [19]	415	RET	51.6%	48.4%	5.6%	15.0%	Heart failure, corticosteroidtherapy, CIED-related endocarditis, age, renal failure
Merchant et al. [20]	508	RET	NR	NR	5.6%	11.8%	Procedural failure, chronic kidney disease, increased number of leads requiring extraction, lower ejection fraction
Oszczygieł et al. [21]	130	RET	18.5%	40.5%	NR	28.0%	Age ≥ 56 years, indication for CIEDI, kidney dysfunction, removal of high-voltage lead

When provided in the paper, the table reports the percentage of patients with local or systemic infection, mortality at 30 days and 1 year, and the reported statistically significative risk factors. *CIEDI*, cardiovascular electronic implantable device infection; *N*, number of patients; *NR*, not reported; *PRO*, prospective; *RET* retrospective

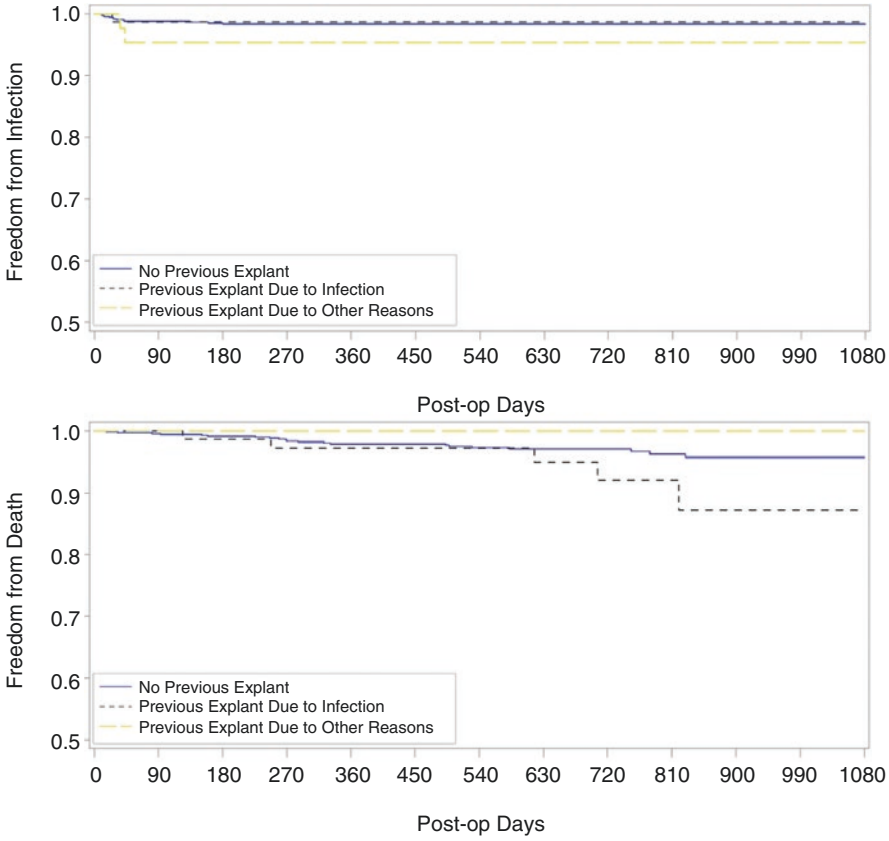

Fig. 8.4 Subcutaneous implantable defibrillator (S-ICD) represents a safe option for reimplantation of patients after transvenous lead extraction. Kaplan-Meier curves for freedom from infection and for mortality show a favourable outcome in patients implanted with S-ICD after a lead extraction for infection (blue line). From Boersma et al [22] (Reproduced with permission)

A method to reduce recurrent infection after TLE may be the use of antibacterial envelope (TYRX™) in patients at high risk for mortality. Data from non-randomized cohort studies have indicated that the use of an antibacterial envelope can reduce the incidence of CIEDI by more than 80% in high-risk patients. Data from the Worldwide Randomized Antibiotic Envelope Infection Prevention Trial (WRAP-IT) demonstrated that the use of an antibacterial envelope resulted in a 40% lower incidence of CIEDI compared to standard-of-care infection prevention strategies alone [23]. However, the antibacterial envelope was used at initial implant, replacement, or upgrade. Data regarding implantation after TLE is lacking. [For additional information see Chap. 11.]

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9 Management of Infected Implantable Cardiac Devices: Hub and Spoke Perspective

M. Rav-Acha and M. Glikson

9.1 General Perspective

As of today, lead extraction is an inherent part of cardiac implantable electronic device (CIED) lead management. Given the increased proportion of elderly population in developed countries with growing demand for CIED implantation, there is an accompanying increased need for CIED lead revision due to infections, lead failure, and lead advisory safety alerts [1]. As for CIED-related infections, there are numerous data revealing significantly increased mortality with antibiotic treatment alone without CIED lead extraction [2, 3]. Thus, CIED lead extraction is a must in most if not all CIED lead infections. Nevertheless, lead extraction is a challenging procedure associated with a non-negligible complications and mortality. Accordingly, the clinical considerations for every case should include the level of indication to pursue this procedure as well as the procedure-related risk in the individual patient, with a special emphasis on the local team expertise with this procedure. In the presence of a strong indication for lead extraction, as lead infection (Fig. 9.1) which is considered an absolute indication for extraction, and absence of a skilled operator, the patient must be transferred to a highly skilled center. Moreover, there are multiple relative indications for lead extraction, as extraction of an old RV pacemaker lead upon upgrading a pacemaker to an ICD device to prevent "lead burden" or extraction of specific leads upon company recalls [4, 5], which are recommended only in presence of highly experienced operators to ensure high success rate and minimum complications.

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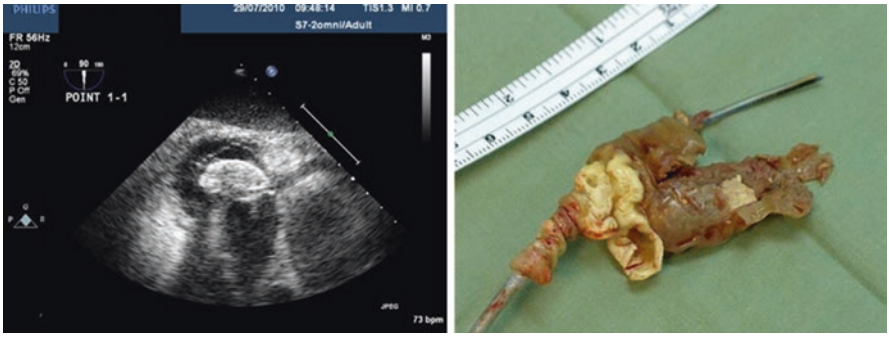

Fig. 9.1 Infected CIED lead with huge mobile vegetation attached, as seen on TEE (left) and post-extraction (right)

Analysis of lead extraction outcomes suggests that the frequency of complete procedural success improves dramatically after the first 10–20 procedures have been performed [4, 6]. Moreover, studies have shown a steep decline in extraction-related complications over the first 30 cases [4, 6]. Finally, there is a need to keep a fair number of extractions on a yearly basis in order to maintain expertise (Fig. 9.2) [7]. Indeed, even physicians with many years of experience with lead extractions have a reduced frequency of complete procedural success when 60 of fewer laser-assisted lead extraction procedures were accomplished over the prior 4 years [4]. Given the clear relation between lead extraction experience and their efficacy and safety, the HRS consensus document on lead extraction [4] recommends that physicians being trained in this procedure should extract a minimum of 40 leads as primary operator under a direct supervision of a qualified training physician and thereafter maintain a minimal volume of 20 lead extractions annually. Similar recommendations were adopted by the European Heart Rhythm Association as well [8]. Apart from a well-qualified operator, there is a need for a cardiothoracic surgeon, who is knowledgeable about the potential complications of lead extraction and understands the required surgical approach to each anatomic injury which may occur. This surgeon should be aware of the procedure and be immediately available if any of these complications should occur (Table 9.1). Notably, the major complications characteristic of lead extraction procedures are vascular avulsions, typically at the innominate vein-SVC level or the SVC-RA junction, cardiac avulsion or tear, pulmonary emboli, respiratory arrest, or other anesthesia-related complication. Many of the above complications, especially SVC tear or cardiac avulsion, may lead to exsanguination and death within minutes [4, 9, 10] and, thus, necessitate an immediate surgical intervention to prevent mortality. Accordingly, lead extraction centers must have a protocol for an emergency response when such a complication occurs including the need for performing an emergency cardiothoracic surgery. Indeed, some centers perform lead extraction in a hybrid EP surgical room and others perform the procedure within a cardiothoracic operating room, enabling an almost immediate surgical intervention if needed.

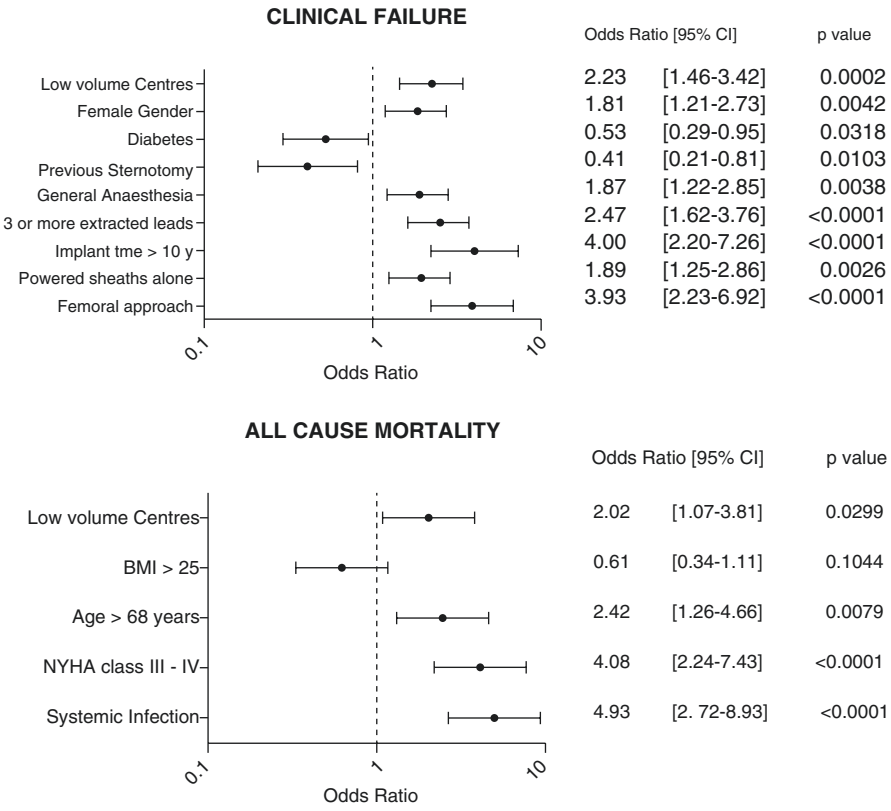

Fig. 9.2 Results from the ELECTRa prospective multicenter registry on lead extraction showing the impact of center volume on clinical outcomes (low-volume means <30/year) (Reproduced from Bongiorni rt. al [7]. with permission)

Given the need to maintain a minimal volume of lead extractions and the challenging requirements, both medically and logistically, to ensure an efficacious and safe extraction, many hospitals are not able to fulfill these requirements. Accordingly, we as many others advocate a "hub and spoke" arrangement, in which a central lead extraction center ("hub") serves many other hospitals around him ("spokes"). In this manner, instead of having several small centers performing small amount of lead extraction, there is a single center in each territory which performs significant amount of extractions, enabling its operators to maintain good procedure volume, well above the qualification requirements. Furthermore, this center has an established and experienced surgical backup to deal with the various complications associated with this procedure. The surrounding "spoke" centers refer patients to this experienced "hub" center, without the need and cost of maintaining the logistic and medical infrastructure needed for extraction procedures.

Table 9.1 Main complications of transvenous lead extraction and their incidence, according to the last Consensus of Heart Rhythm Society [4]

Complications	Incidence (%)	Treatment
Major	0.19%–1.80%	
Death	0.19%–1.20%	
Cardiac avulsion	0.19%–0.96%	Surgical
Vascular laceration	0.16%–0.41%	Surgical
Respiratory arrest	0.20%	Medical/interventional
Cerebrovascular accident	0.07%–0.08%	Medical/interventional
Pericardial effusion requiringintervention	0.23%–0.59%	Surgical or medical/ interventional
Hemothorax requiring intervention	0.07%–0.20%	Surgical or medical/ interventional
Cardiac arrest	0.07%	Medical/interventional
Thromboembolism requiring intervention	0 0.07%	Medical/interventional
Flail tricuspid valve leaflet requiring intervention	0.03%	Surgical
Massive pulmonary embolism	0.08%	Surgical or medical/ interventional
Minor	0.60%–6.20%	
Pericardial effusion without intervention	0.07%–0.16%	Monitoring
Hematoma requiring evacuation	0.90%–1.60%	Medical/interventional
Venous thrombosis requiring medical intervention	0.10%–0.21%	Medical/interventional
Vascular repair at venous entry site	0.07%–0.13%	Surgical
Migrated lead fragment without sequelae	0.20%	Monitoring
Bleeding requiring blood transfusion	0.08%–1.00%	Medical/interventional
AV fistula requiring intervention	0.16%	Surgical
Coronary sinus dissection	0.13%	Surgical or medical/ interventional
Pneumothorax requiring chest tube	1.10%	Surgical
Worsening tricuspid valve function	0.32%–0.59%	Monitoring
Pulmonary embolism	0.24%–0.59%	Medical/interventional

The table also reports the usual treatment approach for each complications

9.2 Diagnosis

CIED infection (CIEDI) typically manifest as two distinct presentations, namely, CIED generator pocket infection and a systemic infection with CIED lead infection or CIED-related endocarditis. Generator pocket infection may manifest via cellulites affecting the pocket site, incision site purulent exudate, wound dehiscence, or erosion through the skin of the generator or leads. CIED lead infection is usually defined by the presence of symptoms and signs of systemic infection with echocardiographic evidence of lead vegetation and presence of major Duke microbiological criteria [11]. CIED-related endocarditis is defined by definite endocarditis via duke criteria with echocardiographic evidence of valve involvement in a patient with CIED in situ [9].

The diagnosis of CIED lead infection is not always straightforward, with a broad spectrum of clinical manifestations ranging from none to a minimal pain in the pocket without any other infectious manifestations to a full-blown sepsis with continuous bacteremia, lead and/or valve vegetation, and septic emboli. Regardless of the clinical severity, once a CIED lead infection is definitely diagnosed, it becomes an absolute class I indication for complete extraction of all leads and device material as well as extensive debridement of the infectious tissue within the device pocket [1, 4, 12]. The importance of complete removal of all infected tissue including all lead materials, without having any remnant leads, was shown in the Cleveland Clinic infected CIED case series [13]. In this series, including 123 patients with CIEDI who underwent lead extraction, a post-extraction recurrent CIEDI developed only in 4/123 patients and these were the same patients in whom a complete extraction was not achieved [13]. Thus, even a small part of a remaining infected lead could be the source of a continued infection despite extensive and prolonged duration of an appropriate antibiotic treatment. This might be understood by the fact that some of CIEDI characteristic bacteria, as *Staphylococcus aureus*, can form a protective biofilm which adheres to the metal components of the device and leads, resulting in an antibiotic-resistant biofilm [14].

Positive blood cultures are pivotal for the diagnosis of CIED systemic infection, but quite often these cultures might be falsely negative in spite of a systemic infection. This may occur due to prior antibiotic treatment (without obtaining cultures, a mistake which is unfortunately often made) or due to unusual bacteria which do not grow in normal cultures. Notably, even cases with staphylococcal-related pacemaker endocarditis were shown to have negative blood cultures in previous studies [4, 12, 15]. Accordingly, one should not rely on negative blood cultures to rule out a systemic infection if other signs of device infection are present. This concept was further emphasized by the fact that 72% of patients presenting with infectious manifestations strictly limited to the pacemaker pocket were found to have systemic infection revealed by cultures of the extracted intravascular CIED leads [16]. Nevertheless, one should be aware of the possibility of false-positive extracted lead cultures due to contamination, especially when extracted percutaneously via the infected CIED pocket [2]. The other spectrum of CIED lead infection diagnosis is shown by cases with persistent bacteremia, namely, positive cultures obtained at different times, without any clinical evidence of an overt device pocket or systemic infection and in the absence of other potential infection sources upon completion of a thorough evaluation. This is especially true for persistent gram-positive bacteremia, which is considered another class I indication for complete CIED removal [4].

As mentioned above CIED infection (CIEDI) diagnosis may be challenging at times, especially when there are no gross infectious manifestations in the device pocket or when there are clues for a systemic infection among CIED recipients but with a negative blood cultures and/or no definite findings as lead or valve vegetations on TEE. During the last decade, PET-FDG has been increasingly used for those challenging scenarios, revealing high sensitivity and specificity for CIEDI diagnosis [12–19]. In a meta-analysis of trials using PET for diagnosis of CIEDI, PET was found to have a sensitivity and specificity of 85% and 90%, respectively,

for diagnosis of CIEDI [18]. The importance of improving diagnostic certainty of CIEDI is crucial given the need to remove all device components with the non-negligible risk associated with this removal. Thus, one should use all efforts in order to rule out or rule in a CIEDI, and PET-FDG appears as one of the powerful tools for this purpose [17, 18]. Moreover, at times PET may aid earlier diagnosis of CIEDI resulting in its earlier removal, reducing the risk for infection relapse and related mortality [2, 19]. Indeed, there seems to be data suggesting prognostic importance of early device extraction in cases of CIED-related endocarditis [2, 13]. Although PET/CT is a costly examination, its aid in clarifying CIEDI diagnosis at an earlier stage may be financially advantageous as it could minimize repeat testing, unnecessary device extractions, or prolonged antibiotic therapy. Nevertheless, it is important to remember that PET-FDG may at times be false positive, especially during the early period post CIED implantation [11, 17, 18] and its use is still advocated for cases with diagnosis uncertainty and not as a routine [9, 11].

9.3 Pre- and Post-Extraction Management

As stated previously, lead extraction is only part of infected CIED lead management as a whole. Thus, once a clear diagnosis of lead infection or lead-related infectious endocarditis is present, there is an absolute indication for lead extraction but extraction per se is insufficient. Prior to undertaking an extraction procedure several considerations should be made, preoperatively and intra- and postoperatively (Table 9.2). First, a clear plan for pre- and post-extraction antibiotics should be made. Notably, in most cases extraction is done only after the patient is already on antibiotic therapy appropriate for the specific bacteria found on cultures or on some empiric regimen, which is specific for every area, according to the common bacteria responsible for lead infections in that region [4, 9].

Another element in the preoperative evaluation is transesophageal echocardiography. The importance of this evaluation includes the identification of high-risk situations such as large vegetations, right to left shunts that may increase the risk of paradoxical embolism during extraction, and valve involvement of the infectious process. The findings of such evaluation may influence the decision to extend the duration of antibiotic therapy following extraction or to proceed with a surgical rather than transvenous lead extraction in case of a huge vegetation or infectious valvular involvement [9]. This is obvious for valve endocarditis and should be strongly considered upon presence of huge lead vegetations to prevent septic pulmonary emboli resulting from vegetation spreading during transvenous lead extraction and to enable wide surgical debridement of the infected tissue [1, 4, 9]. Regarding vegetation size above which a surgical approach should be considered, we tend to recommend surgery only for huge vegetations above 40 mm (Fig. 9.1), whereas old series have quoted much smaller vegetation sizes around 20–30 mm [4, 9].

The pacing status of the patient is of crucial importance in planning extraction. One needs to determine if the patient is pacer dependent before going for the procedure. Pacemaker-dependent patients should have a temporary wire placed prior to

Table 9.2 Pre-, intra-, and postoperative considerations in CIED lead extraction

Preoperative	
Diagnostic evaluation	Clinical assessment of device pocket and symptoms of systemic infection
	CBC, ERS, CRP, blood cultures
	TTE + TEE (lead and/or valve vegetation, myocardial abscess)
Antimicrobial therapy	Empiric therapy initially to be modified by culture results
CIED lead materials	CIED lead types (passive/active) Prior abandoned leads Access and route of implantation
Pacing status	Yes/no pacer dependent Re-evaluate initial indication of CIED and decide on need for reimplantation
Hx of appropriate device shocks	Plan the need for a life vest to protect from ventricular arrhythmias s/p defibrillator extraction
Surgical backup	Immediate availability surgical team Prophylactic sterile draining
General	Assessment and stabilization of comorbidities (renal failure, COPD, etc.) Allergy review Blood type, renal and liver function, coagulation status
Intraoperative	
Hemodynamic monitoring	Arterial line Continuous end-tidal CO_2 monitoring
Pacing	Venous catheter for temporary pacing wire
Bridge to surgery in case of SVC tear	Venous catheter and use of a bridging occlusion balloon
Postoperative	
Hemodynamic monitoring	Continued monitoring for at least 24 h post-extraction Attention to delayed shock phenomenon
Antibiotic therapy and meanwhile pacing/defibrillation protection	Consider duration of antibiotic therapy (IV or PO) Use of active fixation lead implanted via a jugular approach for pacer-dependent patients or early surgical intervention with epicardial lead implant Wearable defibrillator for patients in need for defibrillation protection but not pacer dependent
CIED reimplantation	Consider the need for CIED reimplantation Timing of reimplantation Device type: implantable, leadless PPM and subcutaneous defibrillator

extraction, and the temporary wire must be readily accessible during the procedure because it may dislodge and require rapid repositioning. Regardless of pre-extraction pacing status, patients who are not pacemaker dependent prior to extraction may become so during the procedure. Accordingly, it is recommended in non-pacer-dependent patients that their device be reprogrammed to a pacing rate below the patient's intrinsic rate, to enable immediate detection of the patient becoming pacer dependent. For this purpose, a venous sheath should always be ready to rapidly

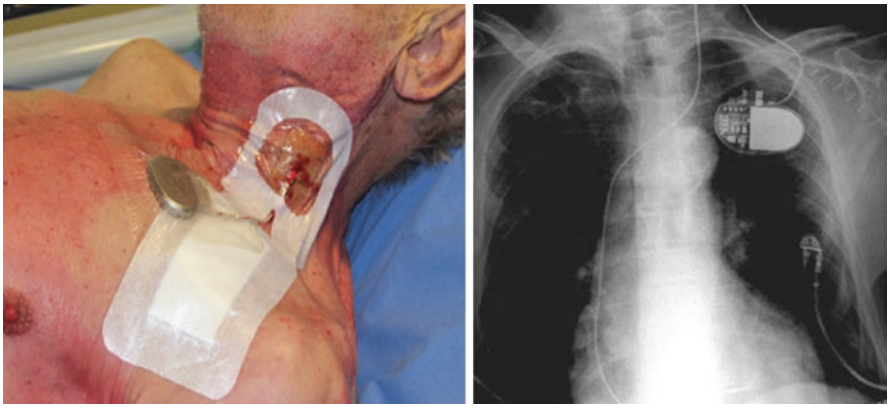

Fig. 9.3 Active fixation ventricular lead inserted via a jugular vein to bridge the period between infected device extraction and new device implantation in a pacer-dependent patient

deploy a pacing wire. Usually, pacer-dependent patients will leave the extraction room with a permanent pacemaker taped on the neck, connected to a permanent lead inserted percutaneously via the jugular vein. This is aimed to provide safety while enabling patient mobilization during the period post-extraction until reimplantation (Fig. 9.3).

In patients with infected defibrillators planned for device extraction, one needs to review all device prior interrogations to evaluate the arrhythmic history. In patients with multiple ventricular arrhythmia necessitating device interventions (ATP and shocks), a use of wearable defibrillator (LifeVest) should be advocated to protect the patient from recurrent life-threatening arrhythmias during the "bridge" period between prior infected device extraction and new device implantation [20, 21]. Given the bureaucratic arrangements associated with approval of LifeVest in different countries, it would be prudent to determine the need prior to the extraction procedure.

The operator should be aware of all device and lead hardware present. A thorough history and review of prior operative reports as well as pre-extraction CXR to determine number and location of leads is mandatory. Knowing the exact type of each lead and whether it is active or passive is important, as some active fixation leads may require special fixation stylets. Moreover, knowing the access by which each lead was implanted is critical. Some leads may have been implanted via a patent foramen ovale, ASD, or VSD usually unintentionally into the left ventricle. A mistake in this regard may end in a fatal complication. Also in this regard, one should be aware of the possibility of venous stenosis dilatation during the initial implantation or prior upgrade procedure, which is not uncommonly performed. In rare instances this may be accompanied by implanting a stent, in which case the lead may be entrapped between the stent and the vessel wall, precluding the advancement of extraction sheaths. For the sake of all the above issues, as well as to detect calcifications and extravascular course of the lead, a pre-procedural CXR should be

examined and if there is any doubt regarding the placement or access of a lead, a complimentary TEE and/or CT should be considered. One should do all necessary effort to obtain the maximal data regarding the various lead types, implantation date, route of implantation, and unusual location of leads to prevent catastrophic consequences of mistake.

All comorbidities of extraction candidates should be approached prior to extraction in order to attenuate procedure and anesthesia risks, which are not negligible even in otherwise "healthy" candidates.

Prior to the procedure, blood typing and crossmatch should be routinely performed. Also required is a full blood count, coagulation profile, electrolytes, liver and renal function, virology screen for hepatitis B and C, and HIV. Young females should undergo a pregnancy screen due to high radiation exposure during this procedure [4, 22].

Last but not least regarding the preoperative arrangements, there is a need for a thorough plan for surgical backup in case any complication occurs. Notably, the major and most serious complications characteristic of transvenous lead extraction are vascular avulsion or tear and cardiac tear. The vascular tears occur usually at the SVC-RA junction, due to fibrotic and at times calcified adhesions of CIED leads to the vessel wall in this area, necessitating pulling a significant force on the sheath during the extraction and applying laser energy at that location. Alternately, cardiac tear may occur due to adhesions of CIED leads to the RA and RV insertion sites [1, 4, 23]. The rate of major complications associated with CIED extraction and especially SVC tears during extractions vary in different studies in the range of 0.5–2% of cases, depending on expertise and type of sheath used for the extraction [1, 23]. The above tear may result in brisk exsanguination or cardiac tamponade and need an immediate response. Accordingly, there is a need for readily available surgical backup in these procedures, including a cardiothoracic surgeon who is knowledgeable of the procedure characteristic complications and the surgical approaches to intervene in case these occur, including a right thoracotomy approach for SVC tear to enable rapid control of the bleeding and enable repair of the vessel tear. Despite all of the above preparations and even with the most experienced surgeons, surgical control of bleeding might take several minutes. For this purpose the "Bridge® occlusion balloon" was recently developed (Fig. 9.4). This balloon could be inserted via a femoral venous catheter and expanded in the tear area to achieve an almost immediate sealing of bleeding as a bridge maneuver until a definite surgical control is achieved [21, 22]. Notably, many operators advocate prophylactic use of this balloon in high-risk procedures, by inserting it into the IVC with the ability to advance and expand it around the SVC tear area within seconds [24].

In accordance with the above paragraph, the intraoperative management should include a general anesthesia with a large central venous catheter to enable rapid fluid and blood transfusion and an arterial line for monitoring blood pressure and early recognition of any major complication jeopardizing hemodynamic status. Transesophageal echo should be readily available for rapid detection of tamponade or preferably inserted at the beginning of the procedure. For the sake of rapid surgical intervention, one needs to have a sterile preparation and draping of the chest

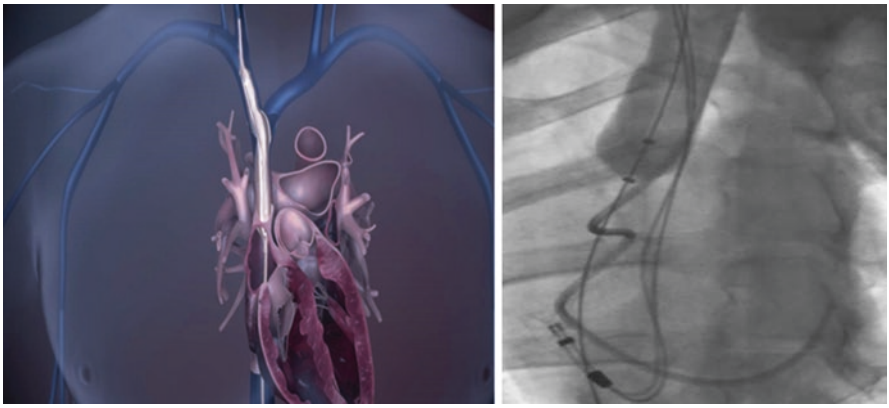

Fig. 9.4 Bridge occlusion balloon for rapid sealing of vascular tear during extraction procedures, as a bridge to definite surgical intervention

(and not only around the CIED site) and have all surgical equipment readily available including the bypass machine. In cases of increased risk (i.e., old dual-coil ICD leads or evidence of calcific adhesions on imaging) we recommend to have all surgical equipment already in the operation room. Indeed, many advocate performing such procedures in hybrid EP surgical rooms or in the cardiothoracic surgical room as a routine. We and others recommend insertion of at least two large femoral venous catheters to enable rapid insertion of a pacing wire and a bridge occlusion balloon for the case of need for immediate pacing or an SVC tear, respectively. Another venous catheter (usually jugular) is used by the anesthesiologist for fluid, blood, and ionotropic transfusion when necessary. Importantly, an extraction risk score was previously published to help guide the decision whether to perform CIED lead extraction in the EP suit or in the operating room [25]. This score was established by reviewing the outcomes associated with above 1000 lead extractions, revealing a significant association between lead duration and procedure major complications. According to this risk score, pacemaker leads above 10-year duration or ICD leads of more than 5-year duration were associated with increased risk for vascular tear, suggesting these high-risk extractions should be done in an operating room or a hybrid room [25].

There are few considerations which need to be taken postoperatively. First, an intensive care monitoring is recommended during the 24 h post-extraction. This is especially true given a "delayed shock" (Fig. 9.5) phenomenon which we described in post-extraction patients [26]. This phenomenon was found to be due to proven sepsis in some and suspected systemic inflammatory response in others, necessitating prompt management and resulting in high long-term mortality [26]. Second, the need and duration of post-extraction antibiotic therapy should be considered along with the timing of CIED reimplantation and CIED type. The duration of antimicrobial therapy varies from 10 to 14 days post CIED extraction in cases of generator pocket infection with negative blood cultures and no evidence of lead or valve

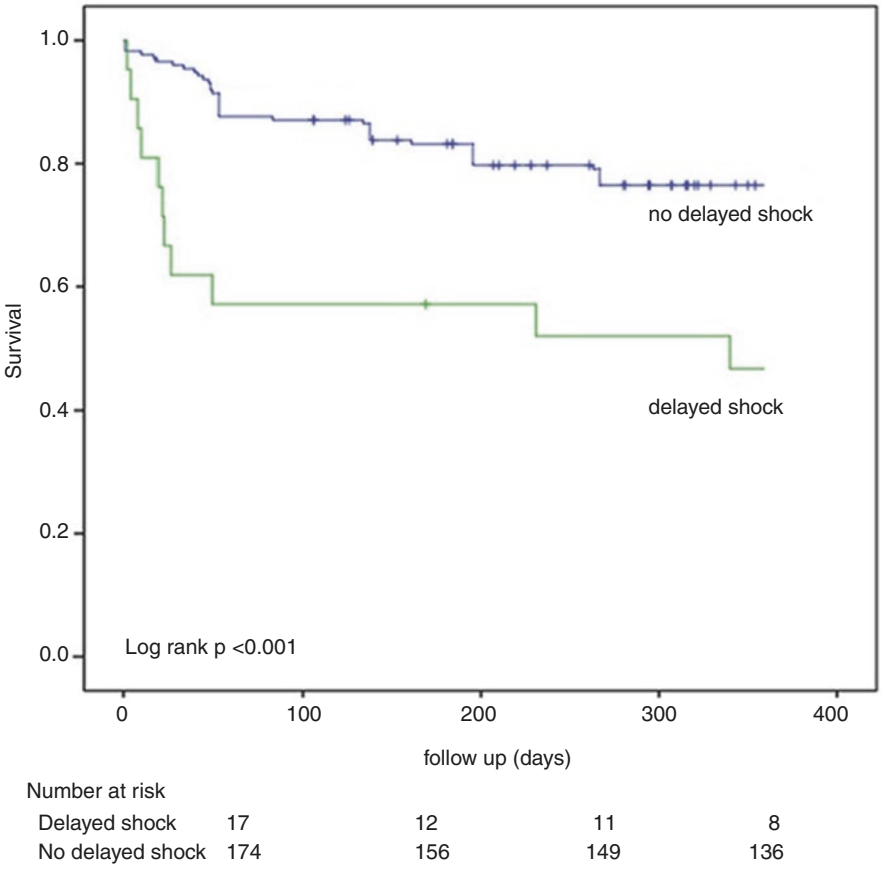

Fig. 9.5 Impact of "delayed shock" phenomenon on post-extraction patient prognosis. In some patients after lead extraction, a delayed onset state of shock (at least 30 min of persistent hypotension with necessity of vasopressor >4 h after transvenous lead extraction) was observed. This phenomenon correlates with a poor prognosis, as seen in this graph. (From Younis et al. [26] with permission)

vegetations, to 4–6 weeks duration post-extraction in cases of systemic endocarditis with lead or valvular vegetations [4, 9]. Nevertheless, these patients can usually be reimplanted as early as 72-h post-extraction given there is no evidence of continued systemic infection (even if there was sepsis with positive blood cultures pre-extraction), there is no lead or valvular vegetations, and a blood culture taken at the day of extraction remains negative for at least 72 h [1, 4]. When there is a concern for an ongoing infection post-extraction or in the presence of lead or valve vegetations, delaying CIED reimplantation for at least 14 days of IV antimicrobial therapy post-extraction is required [1, 4, 9]. Meanwhile, one should consider use of wearable defibrillators for patients in need for ICD protection but not dependent on pacing. Alternatively, early surgical intervention (prior to completion of 14-day

antibiotics) for valvular replacement or extensive debridement of vegetations could be considered with epicardial lead implantation [1, 4, 11]. For pacer-dependent patients who have ongoing systemic infection and are considered very high risk for early surgical intervention, the option of minimally invasive epicardial lead implantation per se may be considered. Notably, the introduction of new leadless pacemakers may be advantageous in this setting given their very low risk for infection [20, 27], and their implantation should be considered in patients who remain in need for a pacemaker but can manage with VVI pacing only [28]. Subcutaneous ICD may be advantageous for patients who need ICD protection but are not pacer dependent, given their low risk for device infection and absence of endocardial leads [29].

Importantly, one needs to re-evaluate carefully the need for CIED reimplantation post-extraction based on the original indication for the initial implantation and dynamic changes in the patient's condition since then, acknowledging that many times the original indications may no longer be present. Indeed, multiple registries suggest that up to 30% of cases may not need CIED reimplantation post-extraction [2, 11, 12].

9.4 Organizational Aspects of Lead Extraction: A General Perspective

Given the technical challenges and risks associated with this procedure, we as many other cardiologists highly recommend these procedures to be performed in experienced tertiary centers, operating as "hubs" serving several "spoke" centers which refer their CIED lead extraction candidates to the "hub" center. Such arrangement will enable these expertise centers to maintain a high volume of extractions on a yearly basis, to ensure these challenging procedures are done with a high success and maximal safety. The importance of having a highly experienced extraction centers serving other small centers in their vicinity is under a consensus [1, 4, 22]. Nevertheless, there are diverging opinions as to how "wide" or "global" should this "hub and spoke" perspective be implicated (Fig. 9.6).

Those in favor of a "wide/global" perspective would advocate that the extraction center should be the one to prepare the patient for the extraction procedure. Thus, enabling the operator team to be familiar with the patient and its comorbidities and ensure these are optimally treated prior to the extraction, determine the need for pacing and if the patient is pacer dependent, confirm appropriate antibiotic coverage and have a full plan for post-procedural treatment as well as timing and location of the reimplanted device. Furthermore, this should enable the operators to have a thorough understanding of all lead material to be extracted, which is critical to ensure optimal technical planning of the extraction procedure. Some would even advocate the use of the "hub and spoke" perspective upon initial suspicion of a CIED-related infection, implying the referral of cases with a difficult or uncertain diagnosis of CIED lead infections to the "hub" center. According to this approach the "hub" center should aid in diagnosis of challenging cases, enabling this center to gain experience with the use of advanced PET-CT imaging in diagnosis of

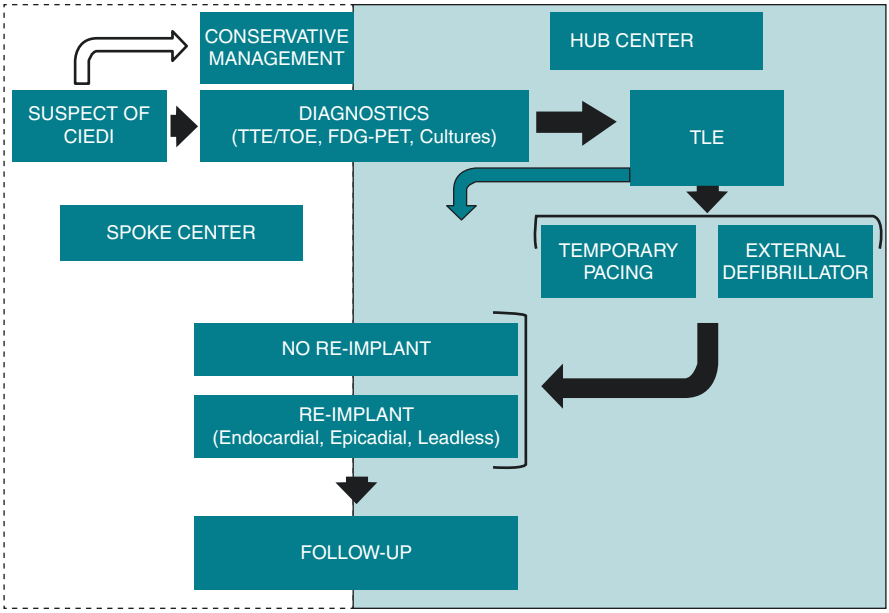

Fig. 9.6 Management of a patient with CIEDI in a "hub and spoke" system. The patient with a suspicious of CIED infection should be referred to a high-volume "hub" center for the completion of the diagnostic workup and for lead extraction. After a monitoring period the patients may undergo reimplantation (if indicated) among the hub center or the spoke center (Reproduced from Boriani et al. [30] with permission). *CIEDI*, cardiac implantable electrical device infection; *TLE*, transvenous lead extraction; *TOE*, transoesophageal echocardiography; *TTE*, transthoracic echocardiography

equivocal cases, for example, patients with subtle clinical manifestations with negative blood cultures and no major TEE finding. To summarize this "wide" or "global" "hub and spoke" approach, patients referred for lead extraction should be admitted to the extracting center soon after the suspicion of CIEDI (even before definite diagnosis in challenging cases). These patients will be hospitalized in the extraction center few days prior to the procedure to enable proper planning and accomplishment of all pre-procedural arrangements. The patients will be referred back to their original centers only once they are stable; all procedural-associated potential complications are reviewed or treated, ideally with a new implanted device and with a precise plan for recommended antibiotic treatment and guided surveillance. Importantly the referring center should provide the "hub" center with all the information on the implanted system and its history as well as on the clinical course of the patient since the initial implantation including surgical procedures, pacemaker dependency, and appropriate ICD therapies over the years.

Alternatively, some systems prefer a more "narrow" perspective, restricted to the extraction procedure itself. According to this approach, all pre-procedural arrangements should be completed by the referring "spoke" centers and critical data (all lead data and their implantation route) supplied to the extracting "hub" center by the

"spoke" centers. Thus, similar to other procedures in which the patient may be transferred to an expertise center just prior (one day) to the procedure and returned to its original hospital the day after, the extraction candidates arrive in the "hub" center a day prior to the procedure and are returned to their original hospitals a day or more after the procedure, once they are stable with or without a taped temporary pacemaker, for those who are pacer dependent (Fig. 9.3). The referring "spoke" centers will continue the antibiotic treatment and perform the reimplantation of new CIED for those who need. This "narrow" approach might at times be due to circumstances of necessity, given the limited "hub" center's bed availability with the need to minimize the stay of all referral procedures. Such an approach was shown to succeed in some Israeli centers.

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Prevention of Device Infection: New Implantable Devices

10

Jean-Claude Deharo and Cristian Martignani

10.1 Introduction: From CIED with Extended Batteries to Leadless Technology

Infections related to cardiac implantable electrical devices (CIEDI) represent a relevant issue both for clinical and economic perspective [1]. The relevance of this complication progressively raised from the beginning of the 2000s as pointed out by the report of Voigt et al. [2]. The authors showed an alarming rising trend in the incidence of CIEDI emphasizing that this phenomenon did not parallel the increase in device implantation during the same period, being much higher in reality. In particular they underlined that in the period 1996–2003, there were no significant changes in the demographic characteristics of patients receiving CIED implantations except that the proportion of patients receiving an implantable cardiac defibrillator (ICD) increased significantly with respect to pacemaker (PM) (from 14% to 27%, $p < 0.001$). In the same period, hospitalizations for CIEDI increased 3.1-fold (2.8-fold for PMs and sixfold for ICDs). These findings coupled with the evidence of an increased incidence of CIEDI associated with replacement of cardiac implantable electrical devices (CIED) vs. first implant procedures (2.06% vs. 0.75%, $p < 0.01$) [3] provided a first possible explanation [4]. In particular, it was highlighted the unbalance between carrier longevity and device longevity for PM vs. ICD recipients leading to a replacement rate of around 80% for ICD carriers vs. 50% for PM carriers [2, 5–7]. These data provided an attractive explanation for the steep slope shown by the incidence of CIEDI hospitalization occurring after 4–5

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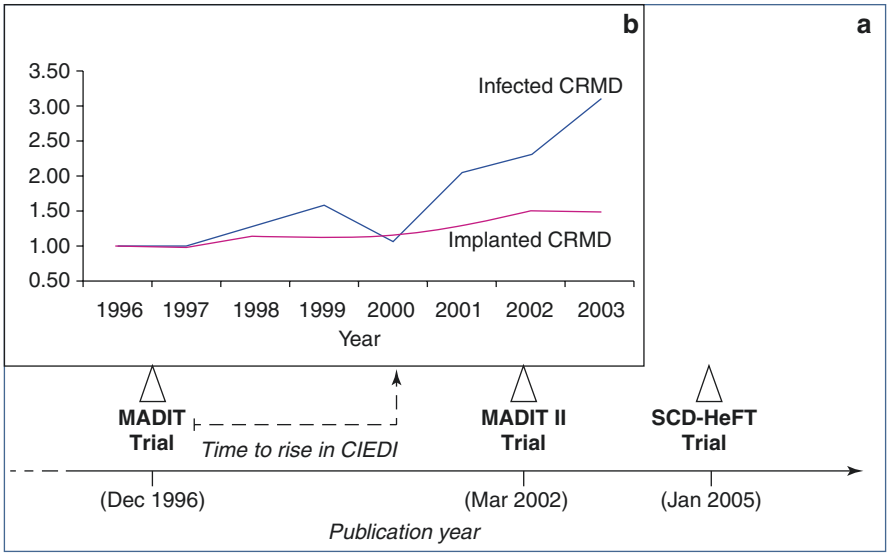

Fig. 10.1 Relationship between publication date of three leading randomized trials on implantable defibrillators for primary prevention of sudden cardiac death (Panel **a** [5–7]) and the disproportionate increase in the number of CIEDI with respect to implantation rate, as reported by Voigt et al. (Panel **b**; reproduced with permission [2]). CMRD = cardiac rhythm management devices

years from publication of the results of the multicenter automatic defibrillator implantation (MADIT) [5]. This period was equivalent to the average longevity of ICD battery at this time leading to the consideration that the rising in ICD replacements caused this fast increase in CIEDI years before completion of the MADIT II trial [6] (see Fig. 10.1). These considerations prompted the development of new CIED with extended longevity, aimed not only at reducing costs related to battery exchange but also to reduce occurrence of CIEDI [4]. However, two additional factors hampered the benefit of extending CIED longevity: comorbidities and lead failures. The first factor derives from the progressive modification of the clinical profile of candidates to CIED implant driven by the broadening of indications to ICD and cardiac resynchronization therapy (CRT) coupled with an increased survival of patients with comorbidities [see Chap. 3 for additional insights]. However, lead failure probably represents the main factor who forwarded the development of the new leadless technologies, especially after the occurrence of two major recalls on ICD leads: the Sprint Fidelis (Medtronic Corp.) and Riata (St. Jude Medical Inc.) [8]. It is interesting to note that both these issues promoted the development and spreading of two great advancements in current CIED technology: remote CIED monitoring (to evidence early signs of lead malfunction before occurrence of clinical events) and leadless technology. It has to be stated that the leadless revolution was not only driven by recalls on CIED leads but also by the presence of several reports regarding a suboptimal performance of CIED leads, especially high-voltage leads [9]. These reports highlighted the presence of a huge gap between the

longevity of CIED leads declared by manufacturers and the real service life in current clinical practice. Noticeably, it has to be stated that a reduced survival of CIED leads can also be attributed to several factors not connected with their production, such as: (a) implanting technique, (b) patients' anatomy, (c) patients' behavior (e.g., work and sports involving repetitive shoulder movement) [10], (d) modifications of the interface between lead and heart (e.g., development of fibrosis and/or ischemia), (e) micro/macro lead dislodgment, and (f) need for CIED system upgrade. However, independently from the case-specific source of suboptimal lead performance, in the last decade the presence of intravascular lead has been pointed out as the Achilles' heel of conventional CIED [11].

10.2 Leadless Pacing

Despite the relatively recent introduction of leadless PM the concept that transvenous leads are the weakest link of conventional PM systems prompted the investigation on possible solutions for leadless cardiac pacing just after development of permanent pacing, more than 40 years ago [11]. This preclinical report demonstrated the feasibility of a totally self-contained intracardiac PM inserted under fluoroscopy through the jugular vein in a dog with an iatrogenic heart block. The cylindrical device was attached to the ventricle by radially directed spiral barbs. Pacing was effectively delivered for >2 months. We had to wait until 1991 years for a second preclinical experience aimed at replicating this pioneering experience in eight dogs [12, 13] with good results and without any complication (Fig. 10.2) [14]. Noteworthy, these devices were made in a university hospital, representing a major achievement for independent research. However, we had to wait for several

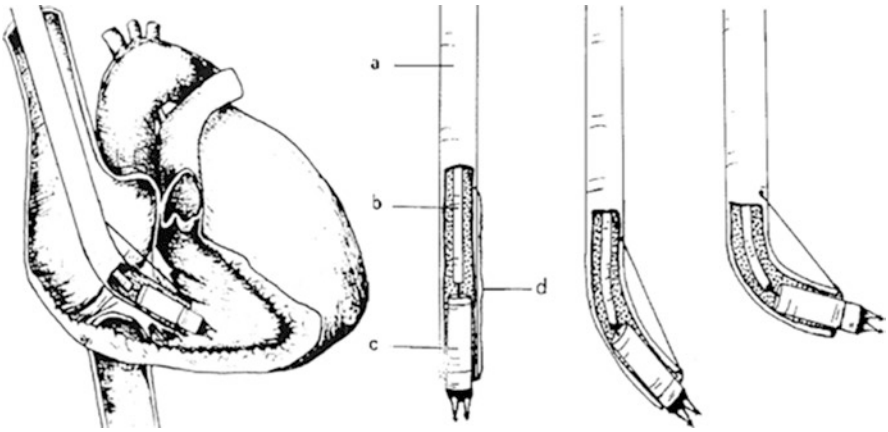

Fig. 10.2 The original representation of the leadless working pacemaker implanted by Vardas et al. in eight dogs (Reproduced from Vardas et al. with permission [13]). a = guiding catheter, b = pushing catheter, c = miniature pacemaker, d = steering arm

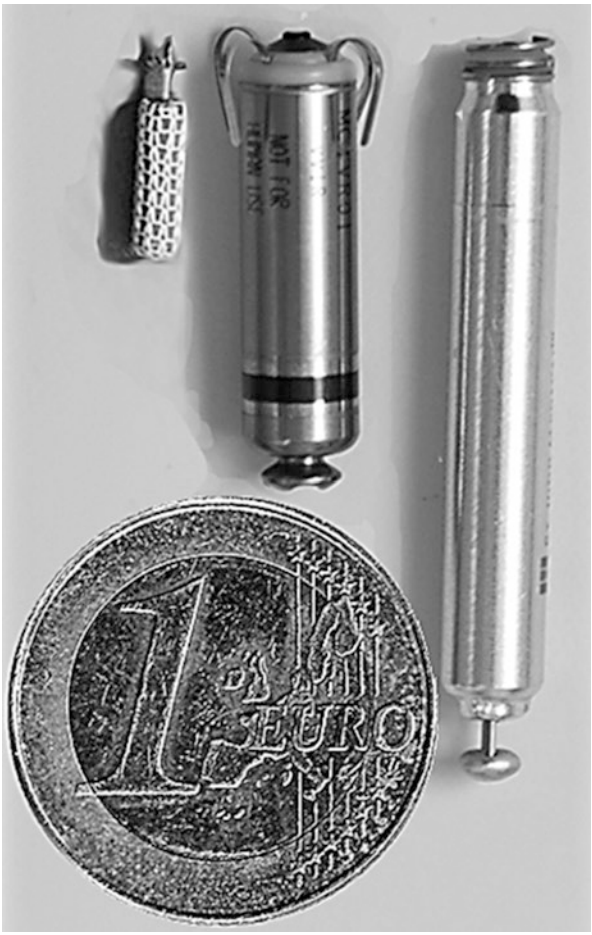

Fig. 10.3 Composite representation of the three commercially available leadless PM (*demo versions*). For the Wise™-CRT (Wireless Stimulation Endocardially for CRT; EBR Systems Inc., CA, USA) pacing system only the intracardiac component is represented

technological advancements to make from this pioneering experience an implantable CIED to be used in clinical practice: catheter-based delivery systems, miniaturized high-density energy sources, low-power electronics, novel packaging capabilities, and novel communication technologies. Three devices are currently available with two very different concepts (Fig. 10.3). Two devices are self-contained leadless intracardiac PM developed for right ventricular pacing, i.e., the Nanostim™ leadless pacemaker (St Jude Medical, St.Paul, MN, USA) and the Micra™ transcatheter pacing system (Medtronic, Minneapolis, MN, USA). Both these PM do not need additional devices for properly working as a PM but only for follow-up (on-site or remote) and programming through radiofrequency transmission (i.e., similar to standard PM) (Table 10.1) [15–19]. A different approach entails the development of multicomponent devices, like the recently introduced Wise™ CRT (Wireless Stimulation Endocardially for CRT; EBR Systems Inc., CA, USA) pacing system, adopting an intracardiac receiver activated through ultrasounds by a subcutaneous pulse generator.

Table 10.1 Principal characteristics of the two commercially available self-contained leadless PM

	Nanostim™	Micra™
Polarity	Bipolar	Bipolar
Pacing modality	VVI (R)	VVI (R)
Sensor	Temperature	Accelerometer
Dimensions (mm)	42.0 × 5.99	25.9 × 6.7
Volume (cc)	1	0.8
Weight (g)	2	2
Sheath size (Fr)	21 OD/18 ID	27 OD/23 ID
Fixation mechanism	Helix (screw in) + tines	Four nitinol tines
Telemetry	Conductive	Radiofrequency
Remote monitoring	Unavailable	Available
MRI compatibility	Yes (1.5 T full body)	Yes (3 T full body)
Battery capacity (mAh)	248	120
Estimated longevity (years)		
ISO 14708 standards[a]	9.8	4.7
Nominal settings[b]	14.7	9.6
Real-life estimates[c]	15.0	12.5

[a]100% pacing, 2.5 V, 0,4 ms, 60 bpm
[b]100% pacing, 1.5 V, 0.24 ms, 60 bpm
[c]Based on 3-month results of clinical trials (LEADLESS II study and Micra™ TPS study) [18, 19]

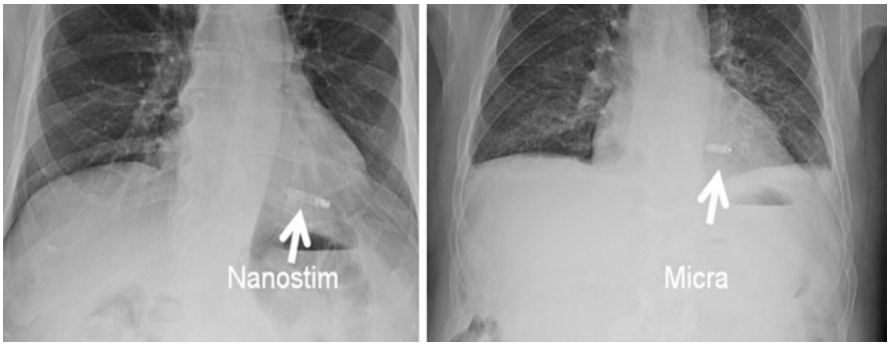

Fig. 10.4 Chest X-ray of two patients implanted with a leadless pacemaker: a Nanostim™ on the left and a Micra™ on the right (Reproduced from Madhavan et al. [20] with permission)

10.3 Self-Contained Leadless Pacing

The Nanostim™ and the Micra™ PM are the two currently commercially available self-contained leadless PM developed for single-chamber pacing of the right ventricle (Figs. 10.3 and 10.4) [20]. These devices are characterized by a single unit fully containing both the pulse generator and sensing/pacing electrodes, thereby eliminating not only the leads but also the need for surgical pocket and within-system connections. The device is delivered to the right ventricle with a dedicated delivery

system through the femoral vein. There are some differences in device size between the Nanostim™ and the Micra™ PM (Table 10.1) but the two main differences are the outer diameter of the delivery sheath (24-F for Micra™ PM vs. 18-F for Nanostim™ PM) and the fixation mechanism. In comparison with standard PM, both devices are significantly smaller, being approximately 1:10 of the volume without considering the length of the intravascular lead. With regard to retention mechanisms, the Nanostim™ PM incorporate an active screw-in helix coupled with three angled nitinol tines perpendicular to the helix as a secondary fixation mechanism. On the contrary, the Micra™ PM includes four self-expanding nitinol tines to attach to the myocardium (Figs. 10.3 and 10.4). Notably, both devices use a tethering mechanism to maintain a connection between the delivery catheter and the device to test positional integrity before final deployment and both devices are reportedly retrievable [17, 21] although data on human being are limited in view of the relatively recent introduction of these devices. In brief, patients are considered eligible if they have indications for single-chamber, right ventricular pacing (VVI [R]) indications. The Nanostim™ PM received the CE mark in 2013, more than 40 years after the first preclinical experience [22, 23]. Between 2013 and 2016, a total of 1423 Nanostim™ PM were implanted worldwide and three clinical trials were initiated. However, reports of (rare) lost telemetry and pacing output due to abrupt battery failure starting >24 months after implant led to a Medical Device Advisory in October 2016 with a global stop to Nanostim™ PM implants [22]. While patients enrolled in the trial continued to be followed according to the protocol, the decision to explant, abandon, or replace was left to clinicians, according to pacemaker dependency and individual patient's clinical history and overall medical condition. Two clinical trials evaluated the safety and efficacy of Nanostim (Table 10.2) [18, 19, 24–26]. After the first LEADLESS pilot study, analyzing 33 patients for 12 weeks for safety purposes, the

Table 10.2 Summary of the infections reported in various leadless RV PM studies and registries

Author	Year	Type of study	Centers included	Device	Patients	Follow-up duration	Infectious issues
Martínez-Sande et al. [25]	2018	Prospective registry	Multicenter	Micra™	137	123 ± 48 days	None reported
El-Chami et al. [24]	2018	Prospective registry	Multicenter	Micra™	1817	6.8 ± 6.9 months	Three infections (one sepsis, one groin, one abdominal wall)
Reynolds et al. [19]	2015	Prospective study	Multicenter	Micra™	725	6 months	None reported
Sperzel Europace [26]	2018	Prospective study	Multicenter	Nanostim™	470	6 months	None reported
Reddy et al. [18]	2015	Prospective study	Multicenter	Nanostim™	300	6 months	None reported

large multicenter LEADLESS II IDE trial, evaluated PM performance and safety at 6 months. Inclusion criteria of both trials were as follows: (a) permanent atrial fibrillation with atrioventricular block and/or slow ventricular response, (b) normal sinus rhythm with second- or third-degree atrioventricular block, (c) sinus bradycardia with infrequent pauses, or (d) unexplained syncope with electrophysiological findings justifying a single-chamber PM. On the opposite the exclusion criteria were (a) complete pacemaker dependency, (b) significant pulmonary hypertension, (c) presence of a mechanical tricuspid valve prosthesis, (d) pacemaker/defibrillator leads, and (e) presence of an inferior vena cava filter. Later, the enrollment criteria of the LEADLESS Observational Study Europe were broader, being limited to indication for single-chamber pacing, a life expectancy of at least 1 year, and were believed to be suitable candidates based on overall health and well-being. Despite a general good performance with a successful implantation rate > 90% the subsequent evidence of a learning curve of about ten procedures coupled with the occurrence of two lethal cardiac perforations led to suggest operator training while limiting indications to those of the LEADLESS studies [22]. About 3000 Micra™ PM have been implanted until now, and the principal data derive from the Micra™ IDE study and the global Micra™ registry. The Micra™ PM received both CE mark and Food and Drug Administration (FDA) (2015 and 2016, respectively). The Micra™ IDE study assessed device efficacy and safety [19] among 725 patients, suitable candidates for VVI pacing and with a class I or II guideline-based indication for pacing [27, 28]. The study also excluded patients with recent acute coronary syndrome, presence of neurostimulator or any other chronically implanted device which uses electrical current, left ventricular assist device, morbidly obese, femoral venous anatomy unable to accommodate the 23F introducer, life expectancy <12 months, and pregnant or breastfeeding women [23]. The Micra™ PM was successfully implanted in 99% of the patients, with 3.4% experiencing device-related major complications, including: cardiac perforation (1.5%), vascular complications (0.7%), and venous thromboembolism (0.3%). Notably no systemic infection was observed (Table 10.2). This was confirmed at 12-month follow-up reporting four additional major complications: three heart failure events and one pacemaker syndrome [23]. The recently published results of the MICRA™ post-approval registry on 1817 patients substantially confirmed the results of the IDE study with an effective implantation in >99% of the patients, with a low complication rate (2.7% at 12 months, 95%CI 2.0%–3.7%). Indirect comparisons with historical cohorts of standard single-chamber PM seem to support a reduced incidence of major complications with self-contained leadless PM, evidencing a reduction in risk of pneumothorax, subclavian vein thrombosis/occlusion, lead-related complications, and pocket hematoma, but increased risk of femoral vein complications [21, 23, 26]. These findings claim for a randomized comparison of these technologies. In the meantime other considerations should be made when considering these devices which are costs, especially for older patients and device longevity for younger candidates. However, there are several candidates who can potentially obtain a great advantage by this technology and above all patients at increased risk of pacemaker-related infection or after lead extraction for CIEDI (Fig. 10.5).

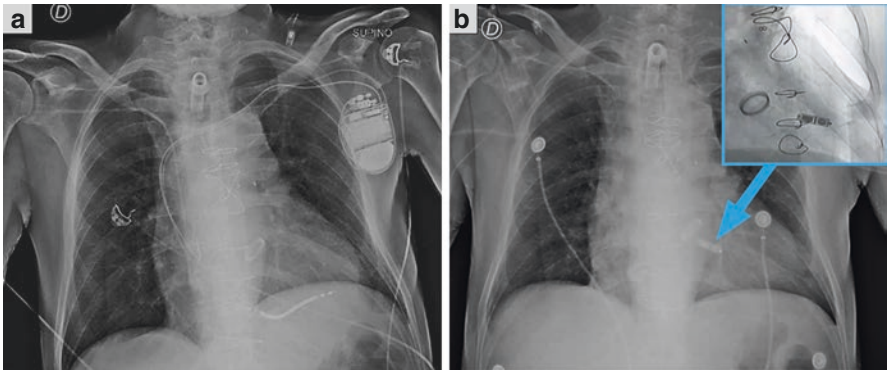

Fig. 10.5 Chest X-ray of a patient implanted with a Micra™ leadless PM (Panel **b**; in blue a particular of the intra-procedure X-ray) after lead extraction for CIEDI (X-ray showing the previous implanted dual-chamber defibrillator is shown in panel **a**)

10.4 Multicomponent Leadless Pacing

The only multicomponent leadless PM available is the WiSE-CRT™ System (EBR Systems, Sunnyvale, California). This device was not developed to substitute standard PM, but to overcome some issues associated with cardiac resynchronization therapy (CRT). CRT is an effective treatment for patients with wide QRS and heart failure to reduce hospitalization and mortality. However, there is still a large proportion of candidates (30–40%) who will not respond to this treatment for several reasons or who present anatomical constraints preventing an effective epicardial stimulation via the coronary sinus: absence of appropriate venous site, occlusion of the upper extremity venous system, phrenic nerve stimulation, or high pacing threshold [29–31]. For this reason it has been previously tested the possibility of transeptal implantation of an endocardial left ventricular pacing lead with interesting results as confirmed by a prospective multicenter study [32] (Fig. 10.6). However, while transeptal LV endocardial stimulation may provide a more physiological ventricular activation (compared with epicardial left ventricular pacing), this approach is limited by the need for lifelong systemic anticoagulation and theoretical concern for mechanical effects on the mitral valve. These considerations provided the basis for the development of the WiSE-CRT™ system. This device consists of four components (Fig. 10.7): (a) a 12-F steerable delivery catheter system with an atraumatic inflatable polyester balloon at the catheter tip, (b) an 8F retractable delivery catheter with a pre-mounted receiver electrode capable of converting ultrasounds to electrical energy through piezoelectric crystals (implanted in the endocardium of the left ventricle via a transaortic retrograde approach), (c) a pulse generator (containing an ultrasound energy pulse transmitter and a battery) implanted in a subcutaneous pocket, and (d) the programmer. This system was investigated in the WiSE-CRT study and the more recent SELECT-LV study [33, 34]. The WiSE-CRT study was a multicenter, prospective feasibility study aimed at

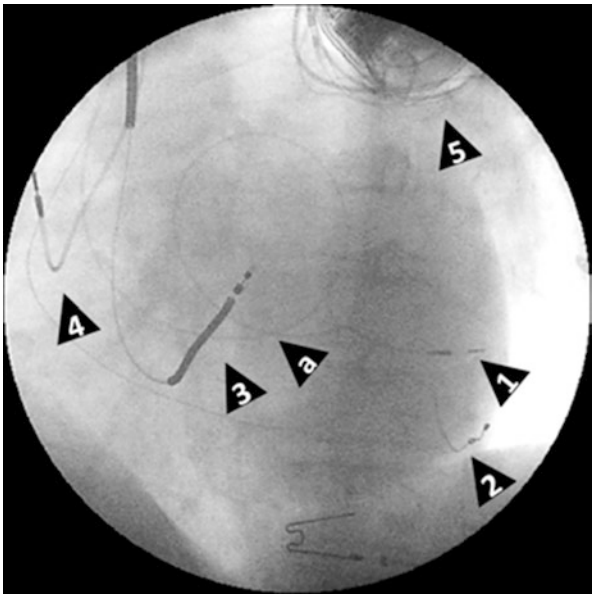

Fig. 10.6 Intra-operatory X-ray of a nonresponder to resynchronization therapy implanted with a left ventricular endocardial lead (Cortesy of Dr. Mauro Biffi, Institute of Cardiology University Hospital of Bologna Italy). 1 = left endocardial lead making a loop (a) after crossing the interatrial septum, 2 = coronary sinus lead (originally used for resynchronization), 3 = defibrillator lead, 4 = atrial lead, 5 = CRT-D device

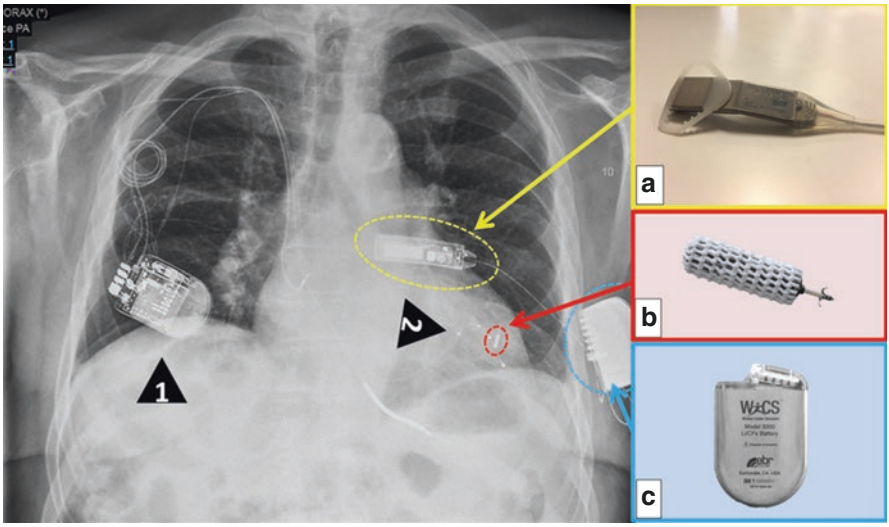

Fig. 10.7 Chest X-ray of a patient with a previous CRT-D system (1 = CRT-D device, 2 = multipolar coronary sinus lead) later upgraded with implantation of an EBR system for absence of response and limited venous access. **a** = ultrasound transmitter implanted submuscular, **b** = receiver electrode, **c** = WiSE-CRT™ can and battery

enrolling 100 patients with conventional PM/ICD who met standard criteria for CRT implantation, along with failed LV lead patients/nonresponders. Despite promising results in terms of efficacy, it was terminated early due to three cases of

Table 10.3 Summary of the infections reported in various WiSE-CRT system studies and registries

Author	Year	Type of study	Centers included	Patients	Follow-up duration	Infectious issues
Auricchio et al. [33]	2014	Prospective study	Multicenter	17	6 months	None reported
Reddy et al. [34]	2017	Prospective study	Multicenter	35	6 months	Two suspected infections, one proven infection with consequent system removal

pericardial effusions associated with implantation of the left ventricular device, resulting in one death [17, 21, 23]. The delivery system was redesigned and reassessed in the SELECT-LV study that enrolled 35 patients with an indication for CRT and a failed conventional CRT implantation. The authors reported no perforation/pericardial effusion with the new delivery system but there were three serious procedure-related or device-related events: a ventricular fibrillation during implantation of the LV electrode (resulting in patient death), embolization of the left ventricular transducer to the left tibial artery, and development of a femoral artery fistula that required surgical intervention. Notably, the authors reported an improvement in NYHA class in 85% and 66% showed an absolute increase in left ventricular ejection fraction ≥5%. On these basis, a new multicenter randomized trial has started the SOLVE-CRT (Stimulation Of the Left Ventricular Endocardium for Cardiac Resynchronization Therapy in Non-Responders and Previously Untreatable Patients) study (Clinical-Trials.gov NCT02922036) [21, 23]. Patients who are non-responders to conventional CRT or failed to have a successful coronary sinus left ventricular lead will receive a WiSE-CRT system and then be randomized to system on or off (sham comparator). The endpoints include assessment of left ventricular end systolic volume, heart failure events, functional class, quality of life measures, and death at 6 months. Moreover, safety outcomes related to the device and the implantation procedure will also be assessed. Finally, coupled with these studies it has been recently started the WiCS Post Market Surveillance Registry (Clinical-Trials.gov NCT02610673) that enrolled until August 2018 68 patients with a 97% effective pacing of the left ventricle [35]. Table 10.3 [33, 34] reports the principal studies on WiSE-CRT system with the reported incidence of CIEDI.

10.5 Leadless Pacemaker and CIED-Related Infections

Looking in more detail self-contained leadless PM are expected to reduce CIED infections because this system does not create physical connections between the endocardium and the subcutaneous pocket. It is also hypothesized that the small size, the potential for encapsulation, and the absence of cutaneous incision may all lead to a reduced infection rate. In self-contained PM the lack of a generator pocket and the

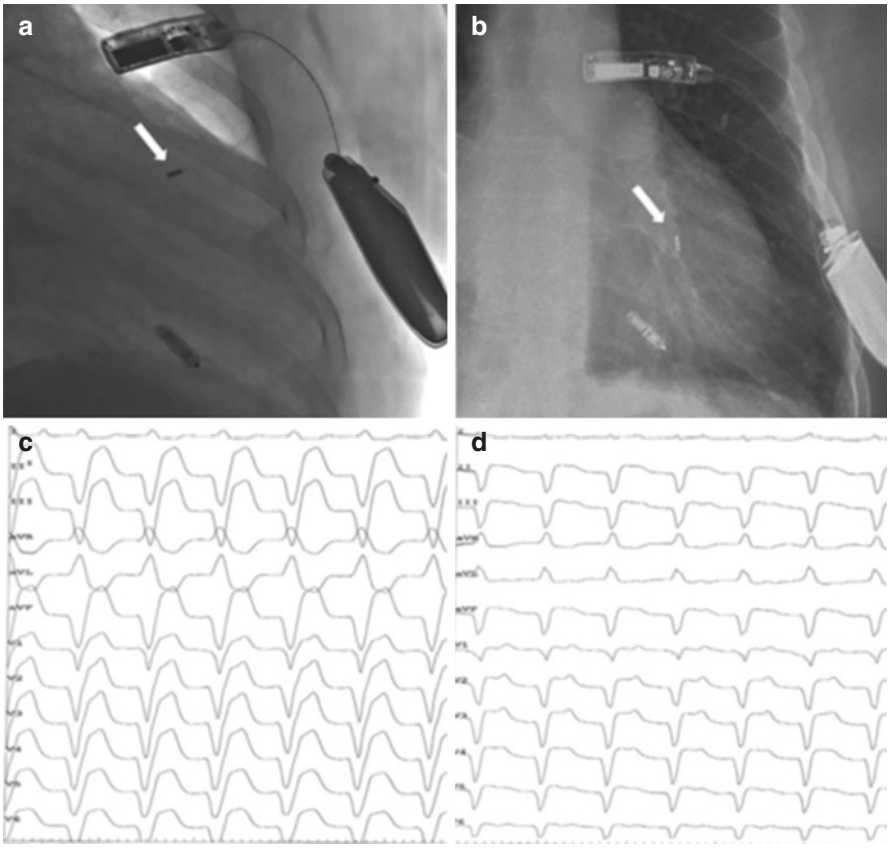

Fig. 10.8 (**a**, **b**) First reported case of reimplantation of a leadless CRT system after lead extraction for CIEDI showing the two intracardiac devices (a Micra™ PM in the bottom of both X-ray and the WiSE-CRT receiver indicated by the arrow). In the bottom it is represented patient's rhythm under right ventricular (**c**) and biventricular (**d**) pacing (Reproduced with permission from Galand et al. [36])

absence of long-term venous hardware also have obvious potential advantages in terms of infectious risk. This is different for the only currently available multicomponent system. The current WiSE-CRT™ system both requires a device pocket (for the pulse generator) and a second intracardiac device for synchronizing the pacing stimulus, which is usually performed by a transvenous PM/ICD. However, it could be speculated to have both a self-contained PM and a WiSE-CRT™ system in a patient with atrial fibrillation and (spontaneous or induced) AV block. A similar approach has been recently reported by a French group who implanted an 81-year-old man with a WiSE-CRT™ system coupled with a Micra™ PM after lead extraction for pocket CIEDI (Fig. 10.8) [36]. To date, limited data are still available on the true infection risk of leadless pacemakers but the majority of leadless pacing datasets did not report relevant infectious complications (Tables 10.2 and 10.3) [18, 19, 37].

Of note, in "real life" many of the patients implanted with a leadless pacemaker carry a high risk of infection. In the Micra Transcatheter Pacing System Post-Approval Registry [37], 20.9% of 795 patients were allocated to a leadless cardiac system owing to at least one condition contraindicating a transvenous approach including a history of or risk for infection in 9% of the patients and dialysis in 5%. Bilaterally infected patients were also shown to be candidates for leadless pacing [38]. Kypta et al. reported the implantation of a leadless pacemaker in six patients with severe device infection who were pacemaker dependent [39]. Three patients had pocket infection only, whereas the other three had both pocket and lead infection. Lead extraction was performed in all patients and four were bridged with a temporary pacemaker before leadless implantation (2 h to 2 days after extraction), whereas two patients had the leadless pacemaker implanted during the same procedure just before lead extraction. All patients stayed free of infection during 12 weeks of follow-up and positron emission tomography imaging indicated no signs of an infection around the leadless pacemaker. In contrast with this reassuring data, Koay et al. reported the world's first case of infected leadless pacemaker which eventually led to its percutaneous extraction 1 month after implantation [40]. While the patient developed fever, chills, and rigors 1 month after implantation, methicillin-resistant *Staphylococcus aureus* was isolated in two separate blood cultures and transesophageal echocardiography demonstrated a vegetation on the device. After unsuccessful antibiotic therapy the device was removed percutaneously and an infected vegetation was identified on the device. The reimplantation strategy was not reported. In summary, device infection in leadless PM has been extremely rarely reported. This is all the more encouraging as, to date, a significant proportion of patients at high risk for infection have received a leadless pacemaker. Longer-term data are still needed to confirm that device encapsulation has a protecting effect against late infection.

10.6 The Subcutaneous ICD

Since the introduction, ICD technology proved to be cost-effective in reducing sudden death and overall mortality both in primary and secondary prevention [41]. However, as previously reported, the incidence of device-related complications challenged the benefits provided by widespread adoption of ICD therapy in a long-term perspective with some authors advocating for a "non-replacement approach" in patients without ICD intervention from implant to the physiologic exhaustion of ICD battery [42]. In particular, a meta-analysis found an overall ICD complication rate of 9.1% in randomized controlled studies being about three times greater to figures reported in ICD registries suggesting un underreporting from real-world studies [43]. Notably, these findings are quite complete for acute complications (e.g., pneumothorax, pericardial effusion, lead dislodgment, and hematoma) but it can be hardly extended to CIEDI since a relevant amount of these complications can manifest late and in a greater proportion after upgrade/replacement procedures [4, 29]. Moreover, among these issues the lead-related complications represent the vast majority especially in light of the recalls affecting several ICD leads and the underperformance of ICD leads in real-life

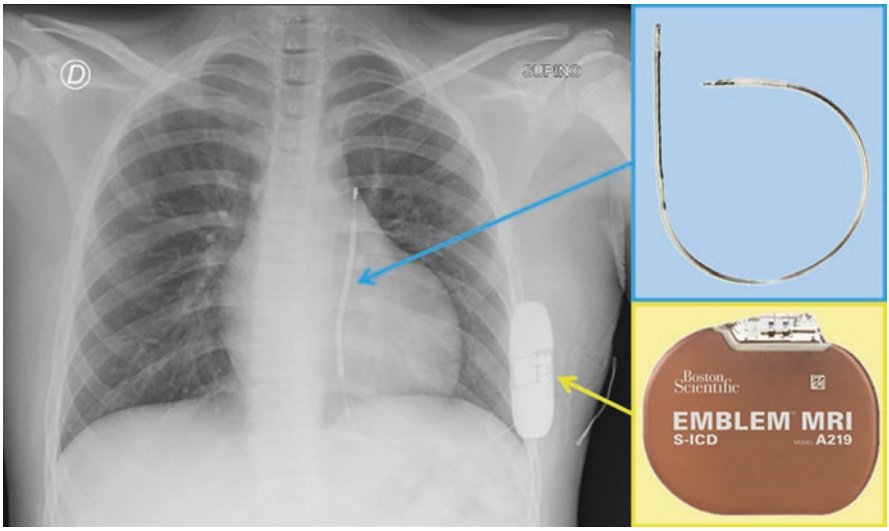

Fig. 10.9 A patient implanted with a subcutaneous cardioverter-defibrillator. On the right are represented the implanted lead (top) and device positioned submuscular (bottom)

service beyond the field actions [9, 44, 45]. All these considerations prompted the development of a completely subcutaneous ICD (SC-ICD) was developed as an alternative to the transvenous-ICD (TV-ICD) system. The SC-ICD system provides high-energy defibrillation shock (80 J) for the treatment of ventricular tachyarrhythmias through a pulse generator and a subcutaneous electrode. The generator is placed subcutaneously in a left lateral position and connected to a subcutaneous tripolar parasternal electrode (Fig. 10.9). The SC-ICD has not capability for bradycardia or anti-tachycardia pacing (ATP), but can deliver up to 30 s of post-shock transthoracic pacing. The device has two programmable zones of tachycardia detection: a conditional VT zone and a VF zone. In the conditional zone, complex morphology-based algorithms discriminate VT/VF from supraventricular tachycardia (SVT), while in the VF zone heart rate is the only criterion to determine whether the DC shock will be delivered or not (Fig. 10.10). In 2010 the initial feasibility study was published reporting both the initial evaluation of optimal configuration of generator and defibrillator coil and outcomes on a total of 61 patients [46]. After this publication three other multicenter studies have been reported showing interesting results both in terms of efficacy and safety [47–49] with conversion rates >97% in both spontaneous and induced VT/VF with complications well below the figures previously shown by the meta-analysis by Ezzat et al. [43]. Outcomes in particular patient populations have been studied, supporting the safety/efficacy of SC-ICD also in challenging situations: (1) patients with concurrent pacing either transvenous [43], leadless [50], or epicardial [51]; (2) end-stage renal disease [52] and dialysis [53], who are at very high risk for CIEDI [4, 54]; (3) hypertrophic cardiomyopathy [55, 56]; (4) arrhythmogenic right ventricular cardiomyopathy [57]; and (4) congenital heart disease [58, 59].

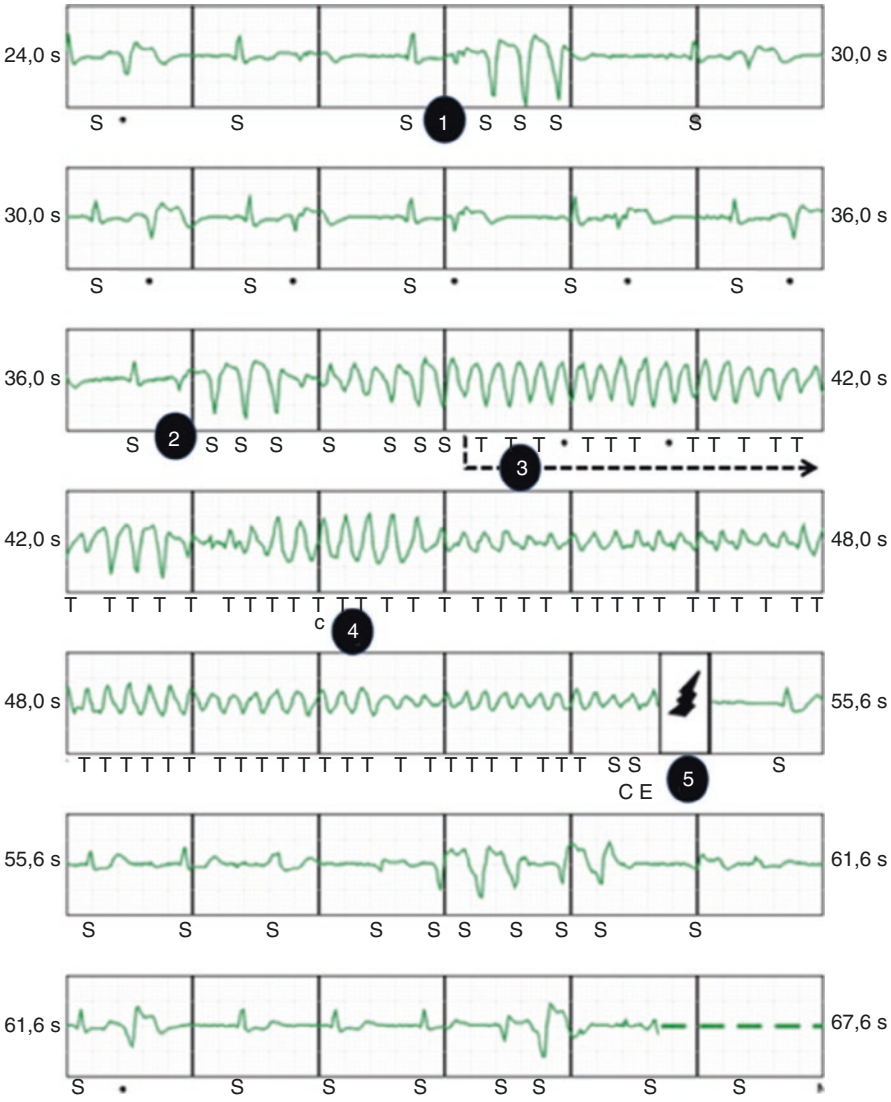

Fig. 10.10 Example of effective conversion of a ventricular fibrillation to sinus rhythm by a subcutaneous defibrillator. Polymorphic non-sustained ventricular tachycardia in a patient with prolonged QTc (1). R-on-T phenomenon (2) degenerating in polymorphic ventricular tachycardia and ventricular fibrillation which is recognized by the device (3) and after few seconds it charges the capacitor (4) and finally delivers the shock (5)

Focusing on infective complications, Table 10.4 [47, 60–64] summarizes the data on CIEDI reported in various SC-ICD studies and registries. The rate of infections resulting in explanation or revision of this new device was not lower than that reported in TV ICD registries. However, it should be emphasized that none of the documented device infections were systemic.

Table 10.4 Summary of the infections reported in various S-ICD studies and registries

Author	Year	Type of study	Centers included	Patients	Follow-up duration	Infectious issues
Köbe J et al. [63]	2013	Matched case-control study	Multicenter	69 S-ICD 69 SC-TV-ICD	217 ± 138 days	1 (S-ICD) 1 (SC-ICD) Infections requiring hardware removal
Burke MC et al. [47]	2015	Registries	Multicenter	882 SC-ICD	651 ± 345 days	1.7% infections 1.2% erosions 0.3% incision/superficial infection
Honarbakhsh S et al. [62]	2016	Propensity matched case-control study	Single center	69 SC-ICD vs. 69 TV-ICD	31 ± 19 months (S-ICD) 32 ± 21 months (TV-ICD)	1 SC-ICD vs. 4 TV-ICD ($p = 0.37$) All required hardware removal
Brower TF et al. [60]	2016	Retrospective propensity matched case-control study	Two Dutch centers	140 SC-ICD vs. 140 TV-ICD	5 years	Injections: 5 (SC-ICD) 4 (TV-ICD) ($p = 0.36$) Erosions: 3 (SC-ICD) 2 (TV-ICD)
Friedman DJ et al. [61]	2016	Propensity matched cohort study	US national database	1920 S-ICD 1920 SC-ICD 1920 D-ICD	2012–2015	1 (S-ICD) 0 (SC-ICD) 2 (D-ICD)
Mithani AA et al. [64]	2018	Retrospective matched cohort study	Single center	91 S-ICD 91 SC-TV-ICD	6 months	3.3% S-ICD 1.1% TV-ICD Infections requiring explant

S-ICD, single-chamber ICD; *SC-ICD*, subcutaneous ICD; *TV-ICD*, transvenous ICD; *D-ICD*, dual-chamber ICD

In a recent meta-analysis comparing efficacy and safety outcomes between SC-ICD and TV-ICD, Basu-Ray et al. did not demonstrate a significant difference in infections between the SC-ICD and TV-ICD groups (OR, 0.75; 95% CI, 0.30 to 1.89) [65]. The total infection rate among SC-ICD recipients was 0.35% in this meta-analysis. This is much lower than the infection rate of 3.9% (95% CI, 2.2% to 5.7%) among SC-ICD recipients reported in the first large international cohort of real-world data from SC-ICD population [49]. Patients in this registry had been implanted since 2009 and followed-up over 60 months post-implant. The higher rates of infection in the registry may be related to procedural inexperience of and unfamiliarity with the surgical approach of left lateral thoracotomy and placement of the lead. The long observation time in the registry may have also partly contributed to the higher infection rate. Another plausible explanation may be that SC-ICD infections were primarily related to device implantation, which is not expected to be different from TV-ICD. However, the evolving technique of SC-ICD implant brings the potential for greater reduction in procedure-related complications, including CIEDI [66–68]. Regardless, the consequences of SC-ICD infection appear to be less severe, as no intravascular infection has been noted with SC-ICD infection. Once available, long-term data will be of high importance, particularly the infection rate after generator changes which is expected to be higher than the initial implant. It will be also helpful to collect not only cases which needed complete hardware removal but also the ones which have been successfully treated conservatively. At this regard there are some interesting reports on the use of SC-ICD for reimplantation after device extraction for CIEDI. These reports evidenced a good performance of SC-ICD also in this particular setting [69, 70].

10.7 Future Perspectives

Despite the high interest in the development of leadless PM, after several years from their introduction leadless PM remains a minority option. According to a survey promoted by the European Heart Rhythm Association in 2018 [71] standard PM represent >90% of implanted PM. Among the different reasons underling this phenomenon, more are related to economic considerations and above all there are device costs and reimbursement barriers. Despite these considerations it has been estimated that the global leadless PM market will reach from 47 million US dollars in 2017 to about 270 million US dollars by 2026 with a compound annual growth rate of 21.9% from 2018 to 2026 [72]. The second main obstacle to a broader adoption of leadless PM represents the single-chamber nature of these devices which are not well suited for the majority of patients requiring to preserve atrioventricular (and interventricular when possible) synchrony. To obtain a multichamber leadless system (Fig. 10.11) [73] these devices must communicate wirelessly with each other. However, a typical scenario entails a quick inter-device communication (to permit response from the receiving device, e.g., the ventricular PM after atrial pacing) at low energy consumption (due to the highly restricted battery volumes). Therefore, the communication must be very energy efficient

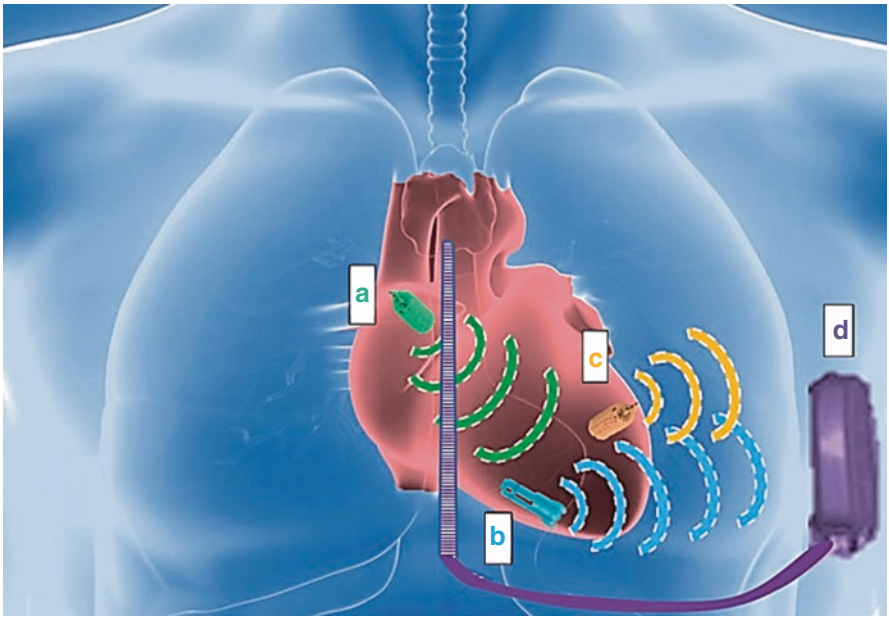

Fig. 10.11 A theoretical entirely leadless CRT-D system including (**a**) atrial pacing device (**b** right ventricle pacing device), (**c**) left ventricle pacing device, (**d**) extravascular defibrillator (Reproduced with permission from Boriani et al. [73])

and should not significantly reduce the lifetime of a PM. This cannot be met with wireless data communications based on radiofrequency telemetry and inductive coupling. For this reason galvanic coupled intra-body communication has been tested with in a proof-of-concept experiment involving three animal models [74] with promising, albeit pioneering, results also in the field of CRT devices [75]. There is a challenging equilibrium between device endothelialization/integration and the possibility of device retrieval/extraction which entails several potential risks: infection, embolization, thromboembolism, "overcrowding," and device-device interaction. Long-term data in younger patients are needed to clarify these questions. A possible answer can derive from different approaches of powering CIED to address many of the current limitations of current devices. The use of piezoelectric systems that harness the kinetic energy of cardiac motion into electrical energy is one of the possibilities [76]. On the contrary the possibility to implant a small magnet inside the atrial chamber could enable atrioventricular synchronization even without an additional powered device (Fig. 10.12) [77]. Another attractive option is the development of biologic pacemakers by insertion of "pacing" genes into patient's own myocytes to provide automaticity or through stem cell therapies [78, 79] as shown in a proof-of-concept study in a porcine model [80]. In the field of the treatment of cardiac tachyarrhythmias two additional devices are under development with a completely different approach: the implantable string subcutaneous defibrillator (Newpace Ltd., Israel) developed to

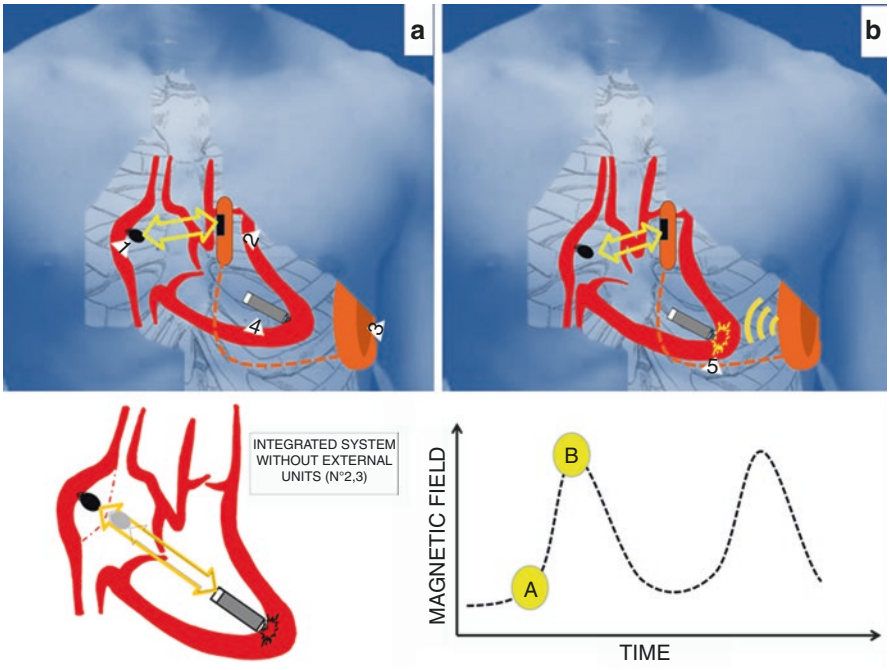

Fig. 10.12 Leadless monitoring of heart activity. A magnet (1) is placed in the right atrium and, through an external subcutaneous Hall effect sensor (HES) (2), its movements are revealed during the cardiac cycle. Starting from the atrial diastole (**a**), the distance between the magnet and the HES decreases, with a consequent increase of the magnetic field that reaches a maximum when the distance is minimal (atrial systole **b**). Once the atrial activity is revealed, the external device (4) can drive a ventricular leadless PM (3). To reduce the number of external subcutaneous devices, an HES can be probably inserted directly in the leadless ventricular PM. (Courtesy of Ivan Corazza BS, Department of Experimental, Diagnostic and Specialty Medicine. University of Bologna. Italy) Based on the paper by Corazza et al. [77]

eliminate the need for an active can by integrating the ICD components and functionality into a single flexible string shape device that is inserted subcutaneously [81] and the development of a novel lead designed specifically for pacing/sensing/defibrillation after being inserted into the substernal space. The ASD2 study was a prospective multicenter, worldwide, nonrandomized, acute, proof-of-concept clinical study showing highly promising results both in terms of PM and ICD function. However, further experimentations are needed to support these new approaches. Finally, it has been recently introduced the Empower system which includes a rate-responsive, single-chamber leadless PM pacemaker and an SC-ICD [82]. Firstly developed to provide anti-tachycardia pacing to SC-ICD carriers, this solution introduces the concept of "modular" CIED systems (like to what is proposed in Fig. 10.11). The availability of different devices which can interact combining their function can potentially create a CIED system able to overcome the evolution of patient needs without removing/abandoning previous hardware.

10.8 Conclusion

Newly developed technologies and devices represent attractive options to reduce the incidence of the extremely concerning issue of CIED infections, especially by eliminating CIED leads. The leadless PM seems associated with fewer infections but longer-term follow-up data are needed, while it is highly advocated the development of multichamber leadless devices. The infection rate observed with the subcutaneous ICD seems to be in the range of the transvenous ICD infection rate but, importantly, the infections are not systemic and at least in some of them can be treated without device removal. Several novelties are under development and in the forthcoming years we will probably see a completely different scenario in CIED-based medicine.

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Prevention of Device Infection: Procedural Aspects, Drugs, and Preventive Tools

11

Igor Diemberger, Giuseppe Boriani, and Jean-Claude Deharo

11.1 Introduction

Although the recently reported results of the PADIT study [1] indisputably bring a positive message by showing that the infection rate within the first year after cardiac implantable electronic device (CIED) implantation in advanced care systems was "only" 1% in high-risk patients, infection associated with the use of CIED (CIEDI) remains a serious complication leading to significant morbidity and mortality. These infections can be the result of initial pocket infection, usually due to surgical site contamination (more frequently) or secondary to hematogenous seeding of the leads or pocket during an episode of bacteremia due to remote septic foci or associated with either intravascular catheters or invasive procedures. As previously discussed in Chaps. 3 and 4, the principal agents involved in the development of CIEDI are gram-positive Staphylococci, and the main factors promoting the infective process can be classified into (a) patient-related, (b) device-related, (c) procedure-related, and (d) related to operators' experience. In this chapter, we will focus on the various aspects of periprocedural modifiable risk factors: anticoagulation, antisepsis, antibiotic prophylaxis, and wound care. We will discuss both available evidence

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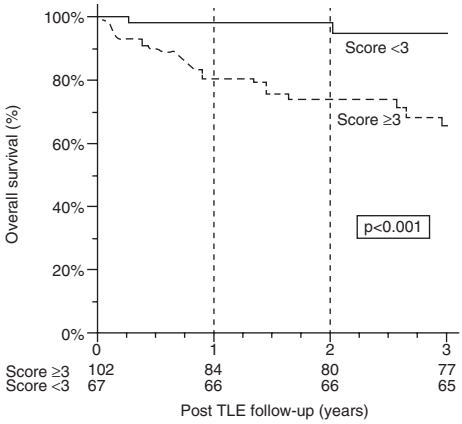


Items included in the Shariff score (recorded as present at last CIED procedure before development of CIEDI)
Diabetes mellitus
Heart failure
Oral anticoagulation
Chronic steroid use
Renal function impairment
Prior CIEDI
More than two leads
Any epicardial lead
Temporary PM at implantation
CIED generator replacement/System upgrade

Fig. 11.1 Long-term survival from death for any cause after complete system extraction according to the Shariff score at last CIED procedure. The Kaplan-Meier curves derive from a multicenter study on 169 patients after effective lead extraction for CIEDI (Reproduced with permission from Diemberger et al.) [3]. Patients were considered at high vs. low risk according to having <3 vs. ≥3 points at the 10-points Shariff score [4] as reported in the table on the right. *CIED* cardiac implantable electrical device, *CIEDI* CIED-related infection, *PM* pacemaker

supporting standard approaches and recently introduced devices to improve CIED procedures. On the contrary, prevention of CIEDI through adoption of new CIED technologies, patient-tailored choice of the device, implanting procedure, and long-term follow-up are discussed in Chaps. 10 and 12.

11.1.1 Comorbidities

Greenspon et al. clearly showed an imbalance between increasing incidence of CIEDI and the trend in new CIED implants, underlying that the rising in the burden of comorbidities could serve as the more plausible explanation [2]. Notably, many of them not only predict the risk of CIEDI but also the long-term survival after successful lead extraction [3, 4] (Fig. 11.1). While we cannot avoid many of these factors (beyond excluding patients from the implant when risks clearly outweigh the benefits), we should carefully focus on those we can manage (Table 11.1). Several reports evidenced that presence of fever <24 h before CIED procedures is associated with an increased risk of CIEDI (OR 4.27; 95%CI 1.13–16.12) [5]. For this reason, the procedure should be postponed (whenever possible) in patients with fever (until >24 h apyrexia). In case of ongoing infections without fever, the best approach is less defined, and the role of systemic markers of infection, e.g., CRP or white cell count, has not been studied. However a similar conservative approach is rational, at least until resolution of systemic involvement [6]. Two additional risk factors deserving additional investigation are glycemic control and prevention of contrast-induced nephropathy. Diabetes mellitus has been identified as a predictor

Table 11.1 Suggested interventions to reduce the risk of CIEDI: patient characteristics

Recommendations ¼
Defer CIED procedure in case of fever or ongoing infection, until resolution/apyrexia >24 h
Careful glycemic control throughout the entire perioperative phase
Limit the use of temporary PM to high-risk symptomatic bradycardia (e.g., third-degree AV block)
Limit the risk of acute kidney injury (e.g., limit use of contrast medium and nephrotoxic drugs)
Tailored management of anticoagulation/antiplatelet therapy, throughout the peri-operatory period, according to patient-/procedure-specific bleeding risk and indication for this treatment (see Sect. 11.1.2)

Based on De Maria et al., Sandoe et al., Padfield et al., Gleva et al. [6, 13, 46, 72]
AV atrioventricular, *CIED* cardiac implantable electrical device, *PM* pacemaker

of CIEDI (OR 2.08, 95%CI 1.62–2.67; see Chap. 3), while it cannot be avoided, it has been reported that glucose levels >11.1 mmol/L in the immediate postoperative period are associated with increasing surgical site infection (SSI), and a strict glycemic control in the perioperative period significantly reduced major infectious morbidity and its associated socioeconomic costs [7]. These data suggest to extend the approach to a closer glycemic control also in the CIED setting, according to what is suggested in different surgical settings [6, 8, 9]. Renal failure is not only a leading risk factor for development of CIEDI but also for long-term survival after CIEDI treatment [3, 10]. Considering that up to 15% of the patients are undergoing complex CIED procedures [11], the adoption of measures should be carefully considered to avoid acute kidney injuries by properly managing periprocedural drugs and by adopting all measures for the prevention of contrast-induced nephropathy especially for candidates to cardiac resynchronization therapy. The last point to be discussed is the use of a temporary pacemaker which was reported to be associated with a more than doubled risk of CIEDI (see Chap. 3). Despite being recognized by several authors that it should be limited to very selected patients [12, 13] with severe symptomatic bradycardia (usually third-degree atrioventricular block with low escape rhythm or patients), it is not covered by many guidelines on about use of CIEDI or management/prevention of endocarditis [14–17]. Close monitoring of the patient coupled with timely implantation of permanent CIED and use of isoprenaline or adrenaline should always be considered [12, 13].

11.1.2 Management of Anticoagulation and Antiplatelet Drugs

Pocket bleeding after CIED is a relevant complication since it causes patients discomfort and pain while prolonging/requiring hospital admission in many cases, and also it can lead to pocket revision (Fig. 11.2), thereby increasing the costs of CIED therapy [18]. More relevant, pocket hematoma has been associated with an increased risk of CIEDI of 8.46 (95%CI 4.01–17.86; *see* Chap. 3 *for additional information*). The principal risk factor for pocket hematoma is anticoagulation therapy (and dual

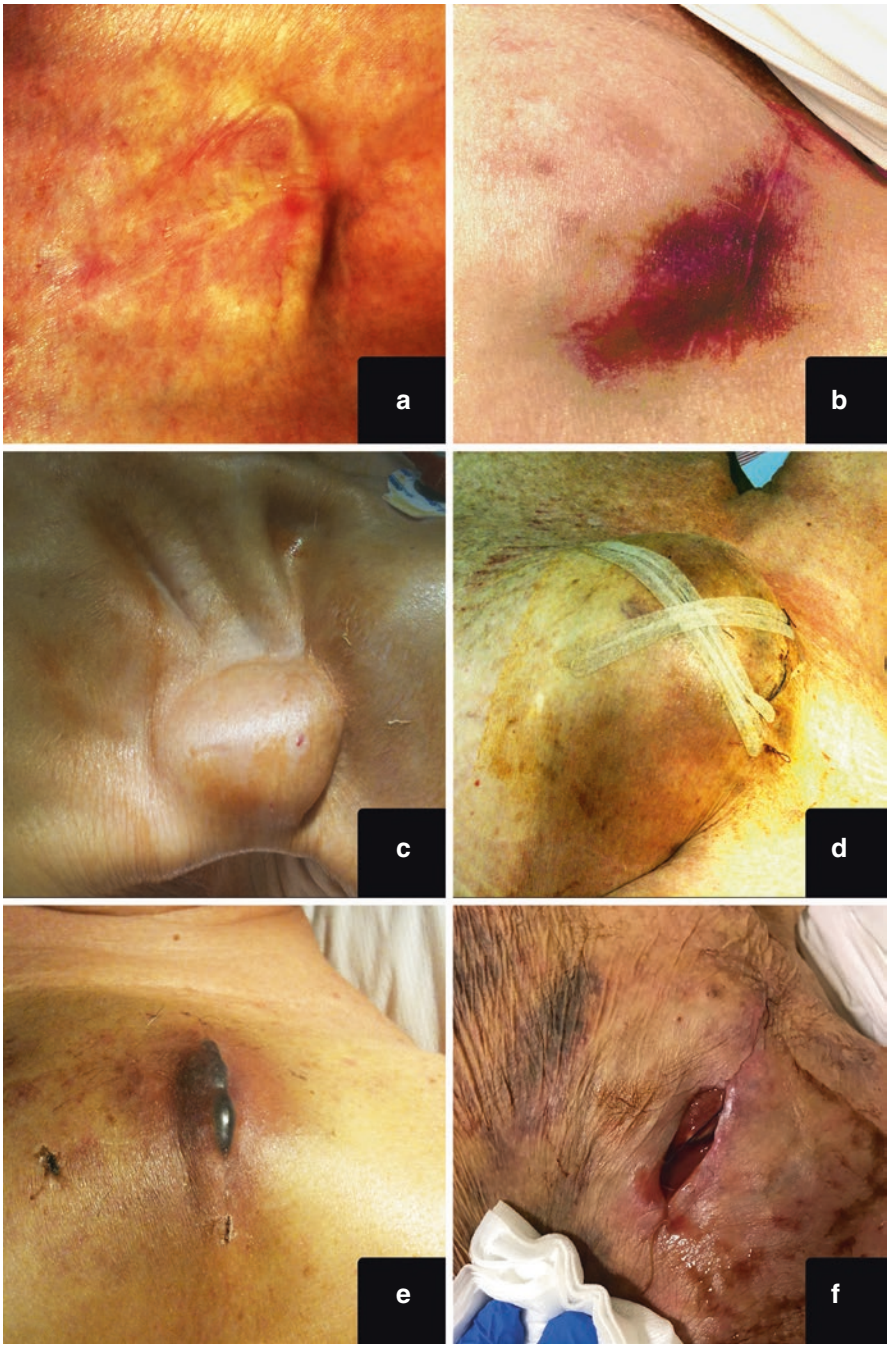


Fig. 11.2 Different patterns of CIED pocket hematoma. The clinical relevance of the patterns progressively increases from **a** to **f**. In particular pattern **a**, **b** can be management with ambulatory surveillance. Pattern **c**, **d** deserves interruption of anticoagulation. Moreover, hospital admission should be seriously considered to avoid progressive dehiscence of the suture line (**e**) leading, if not urgently revised in the EP lab, to complete opening of the wound (**f**). At this point, it has to be considered complete CIED extraction

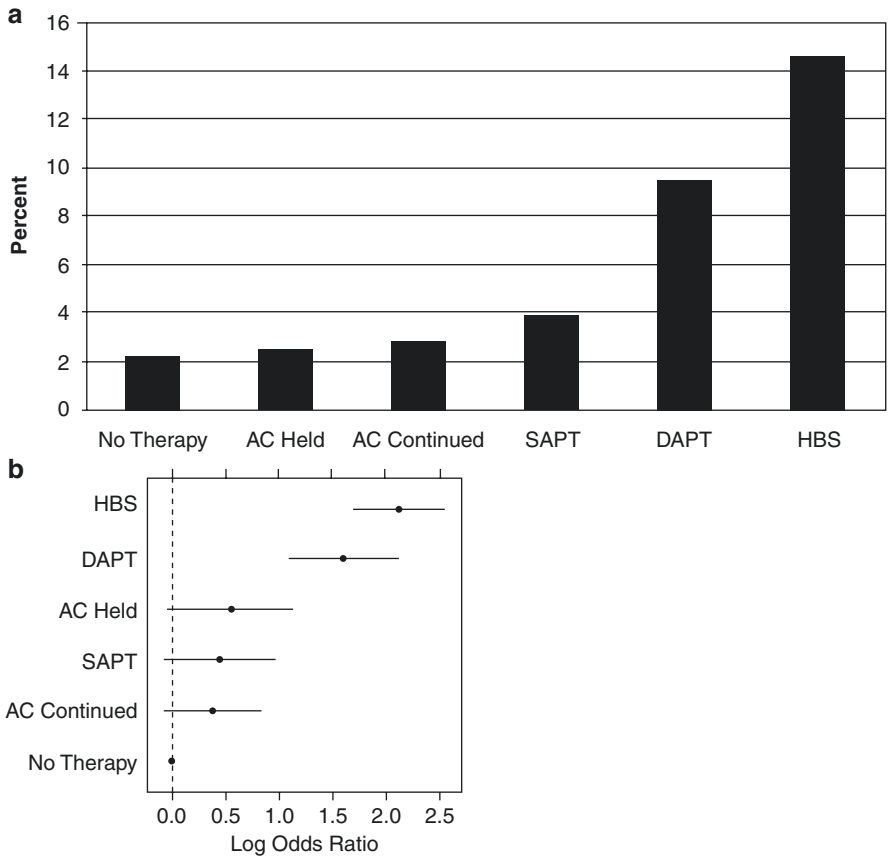


Fig. 11.3 Association between different anticoagulant/antiplatelet regimens and risk of bleeding complications both in terms of incidence (**a**) and odds ratio (**b**). *AC* anticoagulant, *DAPT* double antiplatelet therapy, *HBS* heparin bridging, *SAPT* single antiplatelet therapy (Figures adapted from Bernard et al. [19] with permission)

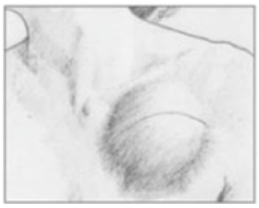
antiplatelet, as more recently reported) [19], which has also been recognized as an independent risk factor for CIEDI. However, the association between CIEDI and pocket hematoma is not consistently reported among the studies [20], and various explanations could be advocated for this: study design, inhomogeneous definition/reporting of pocket hematoma [21], additional comorbidities, study settings (type of CIED and procedure involved), but more importantly the management of pocket hematoma [22].

According to a comprehensive meta-analysis, the prevalence of pocket hematoma in current literature can be estimated around 4.6% ranging between 2.2% in untreated patients and 14.6% in patients undergoing heparin bridging [19] in accordance with the type of anticoagulant/antiplatelet therapy (Fig. 11.3). Notably, dual antiplatelet therapy provided a bleeding risk significantly higher than any oral anticoagulation approach without bridging. It is interesting to note that these figures are significantly higher than those reported by the meta-analysis of acute complications after ICD implant in randomized studies and registries (being, respectively, 1.2%

Grade 0: No swelling/bruising. Normal appearance.
Treatment: None

Grade 1: Ecchymosis or mild effusion in the pocket. No pain or swelling to device pocket.
Treatment: Observation

Grade 2: Moderate effusion in the pocket leading to swelling and causing functional impairment or to device pocket.
Treatment: Analgesia/pressure dressing/interruption of anticoagulant



Grade 3: Large effusion in the pocket leading to swelling and functional impairment or pain to device pocket.
Treatment: Analgesia/evacuation /interruption of anticoagulant/prolonged hospitalisation

Fig. 11.4 The Bristol Heart Institute scale to grade severity of pocket hematoma [28]

and 0.86%) [23] and in a very large retrospective claim-based analysis [24] showing a range between 0.58 and 2.81%. These figures clearly underline the importance of providing a clear definition of pocket hematoma. According to De Sensi et al. [21] inside the literature, the definition of hematoma was recorded as an outcome ranged from any ecchymosis occurring in the surrounding area of the CIED pocket to any palpable mass requiring a dedicated intervention (reoperation, hospitalization, interruption of anticoagulation, blood transfusion) [25–27]. The authors recognized the importance of recording any phenomenon regarding the pocket, for the potential relationship with subsequent CIEDI, but stratifying it in a standardized manner, later modified by the Bristol Heart Institute scale [28] (Fig. 11.4).

The evidence of the heavy impact of hematoma on patients' outcome led to organization of many randomized studies aimed at verifying the impact of different strategies for managing oral anticoagulation (Table 11.2) [25, 26, 29–32]. In summary they confirmed data from previous observational studies [33] evidencing that

Table 11.2 Randomized trials on perioperative management of oral anticoagulation

Author, year	Patients *N* (characteristics)	Study arm	Control	TE		Bleeding		Infections
				Study Arm	Control	Study Arm	Control	
Michaud, 2000 [29]	49 (37% McV, 2% pulmonary TE, 61% AF)	AVK stop 3d before + UFH		0%	0%	17% PH	23% PH	Michaud, 2000
		UFH start 24 h after	UFH start 6 h after					
Tolosana, 2009 [31]	101, high TE risk (53% McV, AF at high risk, AF + prior TIA/stroke)	AVK uninterrupted (INR 2 ± 0.3)	AVK stop 4d before, restarted <24 h after UFH (60 U/kg) at INR < 2 (stop 6 h before, restart 24 h after, suspend at INR > 2)	0%	0%	8.0% PH	7.8% PH	2% in study arm
Airaksinen, 2013 [26]	213, AF (94%) or TE, no McV	AVK uninterrupted	AVK stop 2d before	0.0%	1%	6% MB	6% MB	1% only control arm
Birnie, 2013 [25]	681 (any indications for AVK and annual TE risk >5%; 30% McV)	AVK uninterrupted (INR ≤ 3.5 if McV, else ≤3.0)	AVK stop 5d before start <24 h after. Bridge with LMWH (start 3d – stop 24 h before) or UFH (stop 4 h before). Heparin restarted 24 h after	0.6%	0.0%	3.5% CSH	16.0% CSH	0.6% (study arm) 1.8% (control arm)
Birnie, 2018 [30]	662 (DOAC** for AF and CHA2DS2-VASc score ≥ 2)	DOAC uninterrupted	Apixaban, rivaroxaban stop 2d before Dabigatran stop according to GFR. All DOAC resumed >24 h after	0	0.3%	2.1% CSH	2.1% CSH	N.R.
Douketis, 2015 [32]	1884* (100% AF, no McV)	AVK stop 5d before start <24 h after		0.4%	0.3%	MB 1.3%	MB 3.2%	N.R.
		Placebo	LMWH 100 IU/kg tpd					

* 18.8% underwent minor cardiothoracic interventions, mainly CIED procedures ** apixaban, rivaroxaban, or dabigatran

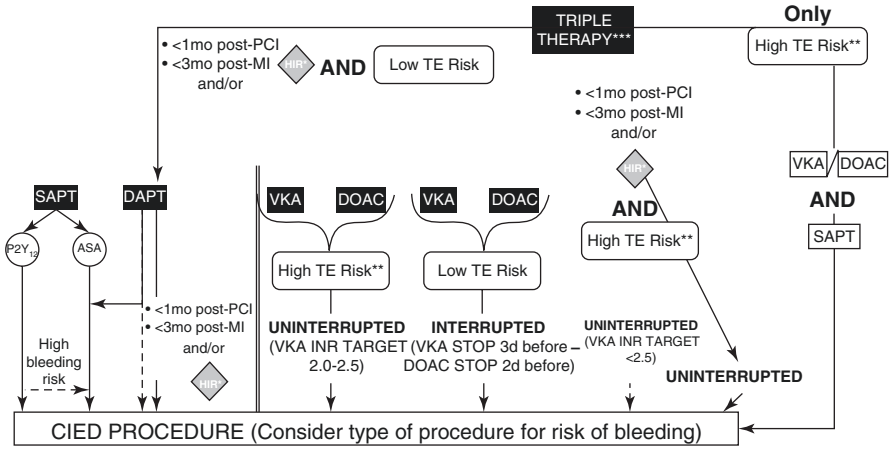
AF atrial fibrillation, *AVK* vitamin K antagonists, *CSH* clinically significant pocket hematoma, *d* days, *DOAC* direct oral anticoagulant, *h* hours, *LMWH* light molecular weight heparin, *MB* major bleeding, *McV* mechanic valve, *N.R.* not reported, *PH* pocket hematoma, *tpd* twice per day, *TE* thromboembolism, *TIA* transient ischemic attack, *UFH* unfractionated heparin

interruption with oral anticoagulation and heparin bridging are associated with an increased risk of bleeding (mainly pocket hematoma), while perioperative continuation of warfarin reduces the occurrence of clinically significant CIED pocket hematoma and the duration of hospital stay, without any increase in thromboembolic events. Another finding that should be underlined is the very high ratio between bleeding and thromboembolic events explaining the results. The only limitation is the absence of a randomized study comparing warfarin interruption without bridging and uninterrupted warfarin. However, after the introduction of novel oral anticoagulants, the attention is shifting to these agents that are becoming the standard for anticoagulation for most of CIED patients. Beyond the reports on observational data [34, 35] and sub-analysis of authorization trials [36], the recently published BRUISE CONTROL-2 [30] trial evidenced that when considering direct oral anticoagulants, a strategy based on continuation (maximum interval between doses 12 h) and the choice of a brief interruption (median 72 h) are both associated with very low complications (Table 11.2).

The final consideration regards antiplatelet therapy. Single antiplatelet therapy is associated with an increased incidence of pocket hematoma [19], with inconsistent reports on higher effect provided by clopidogrel when interrupted for <5 days like to what occurs for other surgeries [37]. However, there is a considerable amount of data supporting a relevant increase in occurrence of pocket hematoma when CIED procedure is performed under dual antiplatelet therapy, estimated as a threefold increase [19, 37, 38].

According to the results of all these studies, it cannot be suggested a generalized approach to manage anticoagulation/antiplatelet therapy in patients candidates to CIED procedures. In general the use of heparin should be strongly discouraged, while the choice of interrupting or continuing oral anticoagulation should be balanced on patient thromboembolic risk, complexity of planned procedure, and risk of deferring the procedure. In particular, an uninterrupted approach should be considered in patients with a CHA2DS2-VASc score ≥ 4, previous stroke, recent ablation/cardioversion of atrial fibrillation, old mechanic valve prosthesis, and/or urgent procedure [39]. Conversely, other patients should be managed with appropriate interruption of oral anticoagulant. A recent report evidenced that a similar integrated approach has the potential to significantly decrease the incidence of pocket hematoma (from 6.5 to 1.6%) without paying in terms of an increase in ischemic events [40]. Notably, the authors adopted a lower INR value in the patients with uninterrupted anticoagulant therapy, a decision supported by the real values recorded in the BRUISE CONTROL trial [25]. Figure 11.5 provides a possible approach to manage anticoagulant/antiplatelet therapy considering the previously discussed literature.

The last consideration on the prevention of bleeding complications to reduce CIEDI is on operative technique. Each characteristic of CIED procedure can affect the bleeding risk, well beyond the underlying anticoagulant/antiplatelet treatment: (a) type of procedure; (b) vascular access (cephalic vs. subclavian); (c) creation of CIED pocket (site, tools, approach); and (d) preventive measures. While the points from (a) to (c) will be covered later (*see the subsequent sections of this chapter and* Chaps. 10 and 12), the last point needs a specific discussion. Several approaches



High-risk features of stent-driven recurrent ischemic events according to ESC guidelines 2017
• Prior stent thrombosis on adequate antiplatelet therapy
• Stenting of the last remaining patent coronary artery
• Diffuse multivessel disease especially in diabetic patients
• Chronic kidney disease (i.e. creatinine clearance <60 mL/min)
• At least three stents implanted
• At least three lesions treated
• Bifurcation with two stents implanted
• Total stent length >60 mm
• Treatment of a chronic total occlusion

High Thromboembolic Risk according to EHRA position paper 2015 on VKA management before CIED

Atrial fibrillation/flutter
- Patients with non-valvular AF and a CHA_2DS_2-VASc score of ≥3
- Patients with AF planned to cardioversion or defibrillation testing at device implantation
- Patients with AF rheumatic valvular heart disease

Prosthetic heart valves:
- Prosthetic mitral valve
- Caged ball or tilting disc aortic valve
- Bileaflet aortic valve prosthesis and AF and CHA_2DS_2-VASc score of ≥2

Other:
- Recent VTE (within 3 months)
- Severe thrombophilia

Fig. 11.5 Proposed management of antiplatelet for CIED procedures according to current literature [39, 46, 121]. **HIS* high ischemic risk, see table in the left corner [121]; ** high thromboembolic risk, see table in the right corner [39]; *** preferably discussion between operator and interventional cardiologist. *Note that submuscular CIED procedures and lead extraction are not covered by this scheme. DAPT* dual antiplatelet therapy, *DOAC* direct oral anticoagulants, *HIS* high ischemic risk, *MI* myocardial infarction, *SAPT* single antiplatelet therapy, *TE* thromboembolic, *VKA* vit. K antagonists

have been suggested to reduce the incidence of pocket hematoma independently from the management of anticoagulation/antiplatelet therapy. Beton et al. [41] reported the results of a single-center case-control retrospective study on 135 patients under warfarin (>50%) or dual antiplatelet therapy (>25%) comparing use of topical tranexamic acid and showing an impressive reduction in hematomas (overall and clinically relevant) and reoperations. As recognized by the authors, this report can be only hypothesis generating, but in view of the low impact (in procedural time and costs), it should be considered for additional exploration. Another approach, routinely adopted in ophthalmologic and stomatologic procedures, is the topical infusion of epinephrine to promote vasoconstriction. Ilov et al. [42] reported the results of a randomized study on 133 patients to receive either epinephrine or saline solution, which were added to a local anesthetic administered during pacemaker implantation. Notably, only a half of the patients were under anticoagulant/antiplatelet therapy before CIED procedure. The study showed that use of local

epinephrine was associated with an increased incidence of pocket hematoma (9% vs. 2%; OR = 5.95; CI: 2.1–7.3, $p = 0.003$). The provided explanation was that temporary vasoconstriction induced by epinephrine may lead to a false impression of adequate hemostasis with later bleeding at the end of the effect. A different approach adopted in three other reports is to put procoagulant agents inside CIED pocket. Ohlow et al. published a negative case-control study [43] on the use of D-Stat Flowable Hemostat™ (Vascular Solutions, Inc., USA). This device containins a mixture of thrombin and collagen approved by FDA indicated for use in the local management and control of bleeding in percutaneous and surgical procedures for patients at increased bleeding risk. Among the 163 enrolled patients, 50% were under anticoagulation, and 38% received dual antiplatelet therapy; the study arm presented more hematomas (14.6% vs. 3.7%; $p = 0.03$) but more importantly a trend for higher pocket infections (6.1% vs. 1.2%; $p = 0.21$) not associated with reoperations. In a second study, Tscholl et al. [44] evaluated the use of PerClot™ (CryoLife, Inc. Kennesaw, GA, USA) a CE-marked system to deliver a mixture of absorbable polysaccharide particles derived from purified plant starch with the properties to cause local dehydration accelerating clotting cascade through concentration of platelets, red blood cells, and procoagulant proteins. However, the study was stopped early, after enrollment of one third of the patients ($n = 51$) due to significant incidence of fever and raised inflammatory markers in the PerClot™ group even without clinical signs of infection or later device explantation. Finally, another option under evaluation [45] is the also the use of oxidized regenerated cellulose, a plant-based topical hemostatic agent, which couples procoagulant action with (in vitro) bactericidal properties (Surgicel® Fibrillar™ Hemostat; Ethicon Inc., USA). However, the only available report provides just feasibility data in a limited population.

11.1.3 Skin Preparation

Several measures are routinely undertaken by many operators in current practice with the aim to reduce bacterial skin colonization (Table 11.3). However, we have limited and contrasting data supporting them. Removal of adhesive left by monitoring electrodes is rational, but it should be carried out gently, with the use of alcoholic solutions avoiding excessive rubbing to prevent skin erythema [6]. Preoperative shaving derives from the common belief that hair removal could reduce the incidence of wound infection, and in many institutions, it is performed the night before. However, microscopic injuries secondary to this procedure can theoretically increase the risk of infection. There is evidence that the use of razors is associated with an increase in SSI, leading to the practical suggestion to use clippers (with a single-use head) on the day of the procedure [8, 9, 46]. Another possibility could be use of depilatory cream the day before the operation, but it has no supportive evidence [6]. Chlorhexidine shower proved to diminish skin bacterial count (particularly, *Staphylococcus* spp.), but no robust data confirm a reduction in postoperative infections [8, 9]. More recently, the guidelines for the prevention of SSI issued by

Table 11.3 Suggested interventions to reduce the risk of CIEDI: Skin preparation

Recommendations 2/4
Chlorhexidine bath/showers before elective procedures: Especially axillae and surgical site
Preoperative shaving: Use clippers immediately before. Avoid razors and shaving brushes
Remove central venous catheters if not strictly required
Gently remove residues of monitoring electrodes: Avoid excessive rubbing
Position ipsilateral peripheral venous access in case of venography. Prefer contralateral site after CIED procedure (to limit the risk of phlebitis)
Surgical site skin disinfection: Prefer chlorhexidine alcohol solutions (but also iodine). Prefer single-use units. Avoid pooling and leave to dry
Use of adhesive sheets at discretion of the operator. Prefer iodophor-impregnated adhesive incision drape. Position only after the antiseptic has completely dried. Do not remove or reposition during the procedure

Based on De Maria et al., Sandoe et al., Padfield et al., Gleva et al. [6, 13, 46, 72]
CIED cardiac implantable electrical device

the US Centers for Disease Control and Prevention in 2017 [47] provide a strong recommendation to advise patients to shower/bathe (full body) with soap at least the night before the operative day. However, this recommendation is supported as an "accepted practice," since there is uncertainty regarding the optimal timing, the total number of soap/antiseptic agent applications, and the type of agent (as clearly reported by the supplementary material). Notably, the same guidelines did not mention the practice of removing hair before surgery. More data support the disinfection of the surgical site to reduce bacterial colonization (without irritating the skin). The results of a recent study on 1326 patients showed no difference between aqueous and alcoholic povidone-iodine solutions regarding CIEDI prevention [48]; in general it is suggested to adopt alcohol-based (for higher skin penetration) antiseptic agent for intraoperative skin preparation (unless contraindicated) [46, 47]. Notably, single-use units should be preferred to avoid contamination during repeated opening of large bottles, while the skin preparation should be left on for a minimum contact time of 30 s and should not be allowed to pool (to avoid the fire risk from diathermy) [46, 49]. Iodine and chlorhexidine both in 70% alcohol are the two most effective skin antiseptics [6, 50]. The comparison between these agents presents conflicting results in available literature. In the EHRA survey, the centers are split with 57.8% using povidone-iodine solution [51]. Povidone-iodine was also the preferred antiseptic agent in the participating centers at higher infection rates in the large REPLACE registry suggesting a higher protective action provided by chlorhexidine [52]. This was supported by a randomized multicenter trial in candidates to different types of surgery (CIED procedures were not included) showing a significant reduction in SSI with chlorhexidine (9.5% vs. 16.1%, $p = 0.004$) [53]. However, in a very recent retrospective cohort including 2792 patients undergoing 2840 CIED procedures, no difference in infection rates was found between povidone-iodine and chlorhexidine groups [54]. This inhomogeneity is also present in current guidelines [46, 47] showing a preference for chlorhexidine only for the Joint British guidelines on CIEDI management and prevention [46] mainly based on the extension of the EPIC3 guidelines recommendation for central line [55]. On the

contrary, the US guidelines on SSI prevention prefer a more conservative approach, not reporting a preference for any of the two agents [47] but acknowledging the divergent data. Remarkably, a recent report showed an interesting strategy based on a staged bundled antiseptic skin preparation including (a) application of 75% alcohol over the anterior chest and covering with sterile gauzes after taking a shower on the night before the procedure, (b) povidone-iodine at the incision site 10 min before operation, and (c) standard antiseptic preparation [56]. 270 patients prepared according to this protocol were compared with 395 patients who received the standard skin antiseptic preparation in the same institution in the 2 years before. The authors reported a drastic decrease in CIEDI (0.7 vs. 4.3%, P = 0.007) confirmed by multivariate analysis. Albeit interesting the limitations in study design do not permit to solve the concerns on the best approach for antisepsis before CIED procedures. A final remark involves the adoption of warmed antiseptic solutions to improve patient comfort. This approach was found to be at least non-inferior to use of a standard antiseptic regimen in a recent randomized comparison [57]. Finally, also the use of adhesive sheets to preserve sterility of the surgical site has no definite proof of reducing SSI. Anyway if adopted, it is recommended to choose an iodophor-impregnated adhesive incision drape [6, 46, 47]. When used, it should be carefully considered that partial or complete removal before suturing can contaminate the wound [58], and different antiseptics can influence the adherence of the incisional drape [59].

11.2 Procedural Aspects

Table 11.4 reports suggested behavior according to best clinical practice in surgery interventions, to minimize the risk of infections [6, 46]. Beyond these recommendations, mainly based on consensus and established clinical practice, there are some data supported by scientific evidence. Kozon et al. recently reported an interesting study [60] on 60 candidates to CIED procedure. Both first operator and assistant imprinted their outer gloves on agar plates before manipulating the device while a wound swab was performed. Samples were cultured, and the presence of bacteria. Contamination occurred in 80% of replacements and 67% of primary implantations. Coagulase-negative *Staphylococcus* occurred in 52%, and *Propionibacterium* spp. occurred in 84% of positive cases. According to these data, the authors suggest changing outer gloves before handling the device. However, we deserve additional confirmatory data to suggest a similar, albeit rational, approach since contamination of the other area involved in the procedure could dramatically reduce the impact of a similar preventive measure. Notably, the additional evidence that contamination of the operators' glove significantly increased every 15 min of procedure time stress the need to simplify procedures as much as possible.

Another relevant issue relates the surgical technique and tools adopted, especially during upgrade and replacement procedures. Nichols et al. provided an interesting analysis on a US claim database on >40,000 patients undergoing a CIED replacement procedure. Incidence of lead damage was 0.46% for PM, 1.27% for

Table 11.4 Suggested interventions to reduce the risk of CIEDI: Procedural aspects

Recommendations ¾
Operating room appropriately ventilated (at least 15 but ideally 25 air changes/h) settled to preserve sterility while favoring access to the patient and post-operatory cleaning Consider hybrid rooms for complex/high-risk procedures (e.g., lead extraction)
Cover any equipment brought into the operating field to reduce the risk of contamination
Cover radiographic and lighting equipment with sterile bags
Devices and surgical equipment should be left uncovered for the minimum possible time
Limit personnel traffic to the minimum. All personnel wearing appropriate attire (head cap, facemask, dedicated shoes, and clothes) without any jewelry
Full surgical scrubbing of forearms and hands according to the 2009 WHO guidelines
Full aseptic body gowning and gloving for all the operators. Consider double gloving and change of the upper glove before manipulation of the CIED
Patient should wear only the operatory room attire and a hat without any jewelry
Prefer a large fenestrated drape to cover the patient, including the head
Tailor the size and location of the pocket to hardware and patients' characteristics. Avoid complete capsulectomy (if not required)
Secure the device with suture, and place the leads comfortably to avoid sharp bends and excessive pressure
Bleeding control: Use of electrosurgical scalpel can help, but cutting settings should be carefully set to avoid lead damages. Use of topical application of procoagulants has no clear demonstration in reducing hematoma/CIEDI. Consider pressure dressing (new devices under evaluation)
The wound should be closed with multiple layer sutures. Consider to use a monofilament (absorbable) suture for the last, subcuticular, layer. Glue-like agents are not suggested, while new "noninvasive" devices for wound closure, albeit promising, deserve additional evidence

Based on De Maria et al., Sandoe et al., Padfield et al., Gleva et al. [6, 13, 46, 72]
CIED cardiac implantable electrical device
Note that device selection and post-procedural follow-up are discussed in Chaps. 10 and 12

ICD, and 1.94% for CRT ($p < 0.001$). After adjustment patients with ICD and CRT-D presented a risk of lead damage that was, respectively, double and > 2.5 times that of patients with PM [61]. Lead damage occurred at a median of 107 days following the CIED replacement procedure, while age had a protective effect with a halved incidence for patients >65 years old. These issues were associated with an average cost of $25,797. Previous studies showed an incidence of lead failure ranging between 0.6 to 1.2% for PM replacement and 2.2 to 5.1% for ICD replacements [62–64]. These figures are not negligible since repairmen procedures are at increased risk of CIED infections [65]. At this regard, the technique and the tools adopted for the procedure can be as important as the operators' experience. Lim et al. analyzed effects of standard cautery blade transvenous lead insulation materials considering different outputs, pulse duration, orientation of the blade, and composition of the outermost insulations of the lead [66]. They evidenced a significant insulation damage, especially in polyurethane leads or when the blade was used with a perpendicular direction with outputs >20 W. To overcome these issues, two devices have been recently studied: PlasmaBlade™ (Medtronic, Minneapolis, MN, USA) and PhotonBlade™ (Invuity, San Francisco, CA, USA); until now no report regarding

other devices (e.g., laser or ultrasonic scalpels) has been reported in CIED procedures. In a retrospective study comparing 508 patients undergoing CIED replacement with standard approach (including use of scalpel, scissors, and electrocautery) with 254 patients in which the operators used the PlasmaBlade™ device, Kypta et al. [67] showed a dramatic reduction of lead damages occurred (5.3% vs. 0.4%; $p < 0.001$), and the procedure time was significantly longer with standard approach (47.9 ± 24.9 and 34.1 ± 18.1 min; $p < 0.001$). These results turned into an average return of €81 for each patient. However, the retrospective design coupled with the very high incidence of lead failure in the control group limits transferability in other settings. On the contrary, Wasserlauf et al. proposed a direct comparison of PlasmaBlade™ and PhotonBlade™ on an animal model (each lead positioned into grooves 1–2 cm deep made in a chicken breast. Later it was positioned on a grounding pad for monopolar cautery) [68]. Applied force and duration of contact were also controlled. The authors tested different operative settings (COAG vs. CUT; 20 W, 35 W, 40 W; blade orientation) and lead external insulation. Lead damage was scored on an ordinal scale of 0–4. They found a lower incidence of lead damages with PhotonBlade™ (75% vs. 40% at higher power; 39% vs. 13% at CUT 20 W settings). Moreover, they underlined the compatibility of the PhotonBlade™ with any standard electrosurgical generator. Despite the limitations of the design of these findings, requiring verification in clinical studies, they underline the importance of tailoring the different settings of these new cutting devices when used for CIED procedures. Another interesting suggestion is provided by an observational retrospective report on the single-center adoption of the PlasmaBlade™ for standard CIED procedures [69]. Their aim was to evidence possible benefits of this device in reducing pocket complications in view of good data in other settings (e.g., ear, nose, and throat procedures and) where it showed good precision with lower local damages (thermal injury, inflammatory response, and scar formation) in comparison to conventional electrocautery. Despite these premises, they found an overall perioperative complication rate of 3.9%, mainly driven by pocket hematoma (3.2%) without any lead failure (among 282 patients) within 6 months. The authors suggest as the most plausible explanation a sub-optimal management of anticoagulation that was not in line with the results of the BRUISE CONTROL study [25]. However, the retrospective design of the study does not permit to rule out the real mechanism.

In different settings, Servello et al. [70] proposed the use of PlasmaBlade™ to perform complete "capsulectomy" during elective replacement of generators used for deep brain stimulation. The reason to perform elective "capsulectomy" rises from the evidence of a higher prevalence of device infections after replacement procedures (vs. first implant), similar to what occurs in CIED settings [65, 71]. Among the possible explanations, it has been suggested the theory of a lower penetration of antibiotics used for prophylaxis due to a "barrier-effect" provided by fibrotic tissue surrounding the generator. After a CIED procedure, the pocket tissue undergoes all the process of wound repair: (a) inflammation, (b) reepithelialization, (c) keratinocyte proliferation, (d) matrix metalloproteinase deposition, (e) angiogenesis, and (f) contraction and closure [72]. Coupled with this process, there is the

physiologic response to a foreign body leading to formation of this fibrotic avascular capsule that Kleemann et al. [73] showed to be associated with a high prevalence of bacterial colonization (about one third in this report). Moreover the authors evidenced that after a median follow-up time of 203 days after CIED revision, CIEDI occurred in 7.5% of patients with culture-positive vs. 2.4% in culture-negative patients not reaching significance in view of the small size of the involved population (122 patients). However, they underline that culture-positive patients later developing overt device infection presented the same type of agent. Albeit highly intriguing this study presents several limitations: samples were taken after CIED removal (increasing the risk of contamination both of samples and pocket), and two among three CIEDI in culture-positive patients were lead endocarditis, while all underwent only CIED replacement (without lead revision). This concept was challenged in the MAKE IT CLEAN trial [74] where 258 patients were randomized to pocket revision (i.e., complete capsule excision including floor, roof, and surrounding the leads) and a more conservative/standard approach. Patients in the first group experienced significantly more hematoma (6.1% vs. 0.8%, P = 0.03) (despite not being bridged with heparin) but without any difference in terms of CIEDI (1.5% vs. 4.7%; $p = 0.13$). Notably, despite being a "negative" trial, the presence of conflicting results between hematoma (which is a recognized risk factor for CIEDI) and CIEDI can be interpreted as a partial confirmation of the role of CIED capsule in promoting later development of infection. However, a similar approach cannot be suggested in current practice. Interestingly there are data suggesting both a relationship between disposition of the leads inside CIED pocket and amount of fibrotic tissue on one side [75] and presence of fibrous tissue in CIED pocket and adhesions during lead extraction [76]. These elements will require additional studies in the near future to identify modifiable factors or predictors of later development of fibrosis.

Another field of research is the approach of wound closure. Standard approach to closure of CIED pocket is performed by multiple layers of sutures, with a tendency to favor intradermal suturing for the superior layer. However, several devices have been developed to improve wound closure: (a) tissue adhesive (2-octylcyanoacrylate) [77]; (b) barbed sutures [78]; and a (c) new adhesive device, the Zip™ Surgical Skin Closure (ZipLine Medical, Inc., Campbell, CA, USA). This device, approved for low-tension noninfected surgical wounds, is a sterile single-use system with two self-adhesive hydrocolloid pressure-sensitive strips linked with individually adjustable self-locking fasteners [79, 80]. All of them have been previously studied in different surgical settings, usually without involvement of implantable devices, with good results in terms of reduction of closure time, esthetic results, and wound healing. However, in the specific CIED settings, the only available benefits reported with respect to standard suture are a reduction of closure time for the Zip™ Surgical Skin Closure [80] (Fig. 11.6) showing a reduction of 5 min in closure time (14.9 ± 6.8 vs. 20.1 ± 11.09 min, $p = 0.0003$). The same authors claimed for a reduction in overall procedure time coupled with a tendency for less CIEDI. However, the nonrandomized design coupled with a greater prevalence of ICD in the control arm which was also followed for a longer time represents a significant limitation. It has

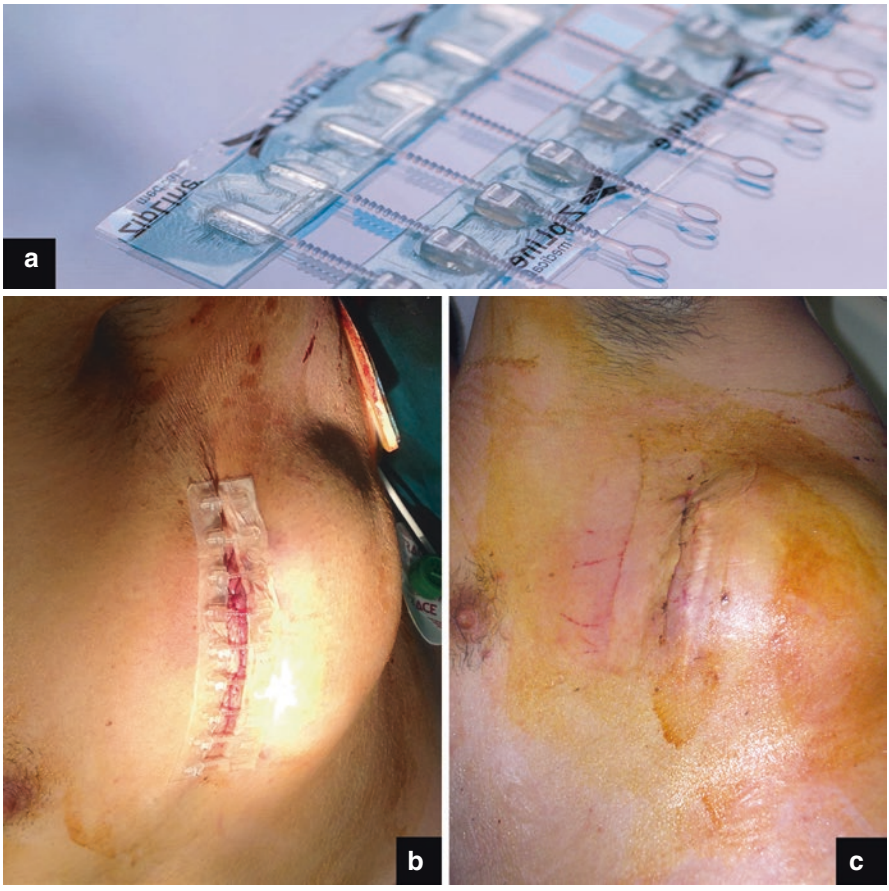


Fig. 11.6 Example of the ZIP™ device for noninvasive wound closure. The two self-adhesive hydrocolloid pressure-sensitive strips are linked with individually adjustable self-locking fasteners (**a**) and should be positioned along the suture after completion of subcutaneous or other deep, tension-reducing sutures (**b**). The final result is good also in difficult sites like after implant of subcutaneous defibrillator (**c**) (Panel **b, c** are courtesy of Elia De Maria Cardiology Unit, Ramazzini Hospital, 41012 Carpi (Modena), Italy)

to be recognized that standard sutures/staples hold incisions together at single points (in which the material passes through the incision) creating an area of increased wound tension where the lesion created by the suture material can promote spreading of bacteria. For this reason, a monofilament continuous absorbable intradermal suture probably provided the best healing process among the "standard approaches" which could be exceeded, albeit theoretically, by the "noninvasive" Zip™ Surgical Skin Closure device. However, future studies are needed to confirm this hypothesis.

The use of elasticated pressure dressings has been studied with positive results in patients undergoing breast surgery/lymph node clearance [81]. In the CIED setting,

it has been proposed a postsurgical elastic vest to prevent pocket hematoma, in view of the associated risk of CIEDI. The device, manufactured by L & M Innovations (Leawood, KS, USA), is a disposable synthetic expandable vest available in different sizes with two adjustable straps (shoulder and chest) to appropriately fit the body habitus of the patient and with a specially designed pocket containing a support wedge for additional pressure. This device was evaluated in a feasibility case-control study involving 40 anticoagulated patients, assuming also antiplatelet treatment in >85%, candidates to CIED procedures. Turagam et al. [82] evidenced a significant reduction of pocket hematoma, showing a significant reduction at 7 days of pocket hematoma in the vest group (0 vs. 30%, $p = 0.02$), despite a significantly higher INR in the vest group (2.7 ± 0.4 vs. 2.2 ± 0.3 = <0.001). These highly promising results deserve additional confirmations in larger randomized studies including various types of CIED procedures and anticoagulation/antiplatelet regimens.

11.3 Antibiotic Prophylaxis

11.3.1 Evidence Supporting Antibiotic Prophylaxis

Intravenous antibiotics targeted against Staphylococci, which are involved in more than 70% of CIED infections, should be used in all the candidates to CIED procedures [6]. This approach is supported by a large amount of data, but the first randomized experience supporting the use of antibiotic prophylaxis for CIED procedures dates to 1994 when Mounsey et al. [83] showed a significant reduction of CIEDI with the administration of flucloxacillin (clindamycin if patient was allergic): the rate was 0% vs. 4% in the control arm ($p = 0.003$). Notably, several interesting features characterize this study: the antibiotics were continued for 48 h, and reoperation was described as a risk factor for CIEDI as far as prolonged procedures or reduced operators volume. However, the most robust evidence derives from the landmark double trial by de Oliveira et al. [84] randomizing patients to receive 1 g i.v. cefazolin or placebo immediately before CIED procedure. The study was stopped early before enrolling the planned 1000 patients in view of the dramatic reduction in CIEDI (0.63% vs. 3.28%, $p = 0.016$). These findings have been later confirmed by other randomized studies and two meta-analyses showing that antibiotic prophylaxis grants a reduction of CIEDI in a range between one third and one eighth [5, 85–88]. In 2010, the American Heart Association published a scientific statement "Update on Cardiovascular Implantable Electronic Device Infections and Their Management" and recommended that a parenteral-administered antibiotic be given 1 h before the procedure [17]. However, several aspects were less investigated: (a) type of antibiotic; (b) timing of administration; (c) the need for postoperative antibiotics; and (d) the use of local pocket antibiotics (Table 11.5) [6, 13, 46, 72, 89].

Table 11.5 Suggested interventions to reduce the risk of CIEDI: Antibiotics

Recommendations 4/4
Systemic antibiotic prophylaxis should be used prior to CIED implantation
The time from administration of i.v. antibiotics to skin incision should consider pharmacokinetics of the antibiotic and the specific characteristics of the incision site (e.g., presence of old fibrous capsule) Usually at least 30–60 min (more in case of slow infusions: vancomycin)
The choice of prophylactic agent should be based most likely on local pathogens in CIED infection Cefazolin and glycopeptides are generally preferred
No evidence supports the use of repeated administration of antibiotics after skin closure albeit in some settings have been advocated (mainly for the risk of inducing antibiotic resistance)
No evidence supports the use of local antibiotics/antiseptics
The use of the antibacterial envelope (TYRX™; Medtronic, Minneapolis, MN) is now supported by a recent randomized controlled trial to prevent pocket CIEDI. Identification of subjects at increased benefit is required

Based on De Maria et al., Sandoe et al., Padfield et al, Gleva et al., Tarakji et al. [6, 13, 46, 72, 89]
CIED cardiac implantable electrical device

11.3.2 Antibiotic Agents and Routes of Administration

Among the different agents, cefazolin is the first choice in view of the data in CIED procedures, cardiac surgery, and for the wide spectrum of activity on gram-positive agents. Notably, it has been shown to be not inferior to glycopeptides even in the case of high prevalence of methicillin resistance with a high tolerability and low costs [84, 90–95]. Obviously, the final choice critically depends on site-specific prevalence of bacteria species and antibiotic resistance. For example, in a study of over 50,000 isolates from 495 hospitals in 26 European countries, methicillin-resistant *Staphylococcus aureus* prevalence varied from 1% to over 40% [13]. In case of an institution with known high prevalence of antibiotic resistance or in case of coexistence of other risk factors (i.e., prolonged hospitalization, recurrent admissions, chronic bed rest, living in a retirement home, or recent antibiotic treatment), glycopeptides, in particular vancomycin and teicoplanin, are probably the best choice [6, 46, 96]. Teicoplanin use is simpler since it can be administered in a single bolus which lasts also for long procedures. However, teicoplanin resistance is more frequent, and dose-response is more affected by patient-specific characteristics [46, 97, 98]. Adding gentamicin to glycopeptides can be useful to increase the antibacterial spectrum, but the benefits are unproven, and it may be advisable to avoid gentamicin in patients with impaired renal function, particularly those where a deterioration in renal function may precipitate the need for long-term renal replacement therapy [46]. However, an increase in nephrotoxicity was not seen with a 2 mg/kg single-dose prophylaxis regimen in cardiac surgical patients [99].

In a meta-analysis, preoperative prophylaxis was found to be superior to postoperative antibiotics (RR = 0.14 (0.03–0.60); $p = 0.008$); however no trial formally addressed this question [86]. To achieve the appropriate concentration of antibiotic in the tissues during CIED procedures, timing of administration is crucial [17, 100,

101]. When cefazolin is adopted, it should be administered 30 min before the procedure, considering the half-life of 1.6 h and a peak concentration in 30–60 min, with a repeated dose in case of procedures taking >3 h. When considering the use of vancomycin, having a half-life of 6–12 h with a peak tissue concentration around 60 min, it should administered 1–2 h prior to surgery and requires a slower rate of infusion (1 g/h) to prevent systemic vasodilatation and erythema. As previously stated, teicoplanin can be administered in a single 5 min i.v. bolus eliminating the longer infusion of vancomycin.

The necessary duration of the treatment is also poorly established. Although prolonged courses of antibiotics may be theoretically useful in selected circumstances, available data does not support this behavior [86, 102]. In particular, Dwivedi et al. found no difference in the rate of CIEDI following 1 week of postoperative antibiotics compared to 2 days [87]. In the prospective REPLACE study which included a pre-specified infection analysis, a higher infection rate was seen in patients treated with postoperative antibiotics. However, in this registry, the use of any or no postoperative antibiotics was left to the individual investigator, thus limiting any specific conclusions [52]. More recently, Krahn et al. [103] published the results of the PADIT Trial. The study prospectively evaluated the practice of postoperative antibiotic administration to reduce CIED infection. This investigative strategy involved an investigative center-based cluster-crossover design to evaluate the role of incremental antibiotics before, during, and after the CIED procedure. Each implanting center was randomized to pre-incision cefazolin (or vancomycin in penicillin-allergic patients) alone or with intraoperative bacitracin 50,000 U in normal saline wound irrigation and a 2-day postoperative course of oral cephalexin or clindamycin in penicillin-allergic patients. Patients eligible for inclusion are those who present for generator replacement, revision or upgrade procedures, or cardiac resynchronization procedures [72]. 19,603 patients were enrolled among 28 centers, 12,842 were defined at high risk. Infection occurred in 99 patients (1.03%) under conventional treatment and in 78 (0.78%) receiving incremental treatment (OR 0.77; 95%CI: 0.56–1.05; $p = 0.10$). In high-risk patients, hospitalization for infection occurred in 77 patients (1.23%) receiving conventional antibiotics and in 66 (1.01%) receiving incremental antibiotics (OR: 0.82; 95%CI: 0.59–1.15; $p = 0.26$). Subgroup analysis did not identify any characteristics with significant benefit from incremental therapy.

The last point is the optimal route of antibiotic administration. Darouiche et al. examined two studies comparing systemic vs. intraoperative local antibiotics and found no significant difference (OR 0.45; 95%CI 0.10–2.03) [86]. However, it should be noted that they were both clearly underpowered also for being metanalyzed since they reported 7 CIEDI events among 177 patients overall. The meta-analysis also found no evidence that concomitant local antimicrobials offered any benefit and concluded that local instillation of antimicrobials did not reduce infection rates. Moreover, also pocket irrigation with povidone-iodine showed no additional benefit in reducing CIEDI in a small study [104]. Irrigation of the pocket with saline probably reduces the bacterial concentration, though there is no evidence to indicate that it reduces CIEDI.

11.3.3 The Antibacterial Envelope

The concept of using antibiotic coating to decrease SSI was tested more than 20 years ago, showing good results both for central venous catheters [105, 106] and ventricular drain catheters [107]. However, in the same years, it was launched a different approach to fight bacterial colonization, through introduction of a different coating. St. Jude Medical (SJM, St. Paul, MN, USA) addressed this problem by introducing a modified prosthesis, the "Silzone" valve, with the sewing ring made of a dense layer of a silver-based alloy bound to the surface of the polyester fibrils by ion beam-assisted vapor deposition [108, 109]. Notably, this was based on the known capacity of silver to behave as a broad-spectrum antimicrobial agent. However, after launching a randomized controlled trial to test the superiority in reducing early endocarditis, the product was withdrawn voluntarily on the basis of a higher incidence of paravalvular dehiscence (4.4% vs. 1.0%) probably driven by inhibition of fibroblastic reparative action [110]. At the end of the 1990s, also the antibacterial envelope, currently known as TYRX™ Absorbable Antibacterial Envelope, was born using the same antibiotics: minocycline and rifampin. The first name was AIGIS (from the Greek word meaning shield), and the polymer technology was invented in the laboratories of Prof. Joachim Kohn at Rutgers University. Later it was tested on four different bacterial strains in a rabbit model with good results [111]. In 2010 the Food and Drug Administration (FDA) approved the use of the $AGIS_{RX}$ to reduce infection after CIED implant. Before closure of the pocket, the generator is inserted into an antibacterial polypropylene mesh sleeve that releases within approximately 7 days minocycline and rifampicin in the generator pocket (Fig. 11.7). Both minocycline and rifampin have broad-spectrum antibacterial coverage, and biofilm penetration and local concentrations of the drugs are very high (with negligible systemic concentrations). The first-generation envelope was nonabsorbable; the last one uses a fully bioabsorbable polymer that dissolves within 9 weeks, now called TYRX™ (Medtronic, Minneapolis, MN). Observational studies showed favorable outcomes in reducing the rate of CIED infections in high-risk patients (Table 11.6) except the one of Hassoun et al. [112] which was conducted in a rather small population and showed higher infection rates in patients who received the envelope. Reasons for this result could include the presence of severe comorbidities and a higher incidence of revision surgery in the TYRX™ group. The authors also suggest that the envelope may have acted as a nidus for infection. A meta-analysis was performed on controlled studies of the antibiotic envelope. Five studies were included, corresponding to 1798 patients implanted with an antibiotic envelope and 2692 without [113]. The envelope was associated with a 69% relative risk reduction in CIED infection (0.31 [0.17, 0.58] 95% CI, $p = 0.0002$). Propensity-matched data from three studies were analyzed to ensure accurate comparison. In the risk-matched cohort, infections were significantly lower in the envelope group (3 vs. 26, $p < 0.0003$).

In their study, Shariff et al. [4] have considered economic implications related to the use of TYRX™. Out of 1476 patients undergoing CIED procedures, 365 received the TYRX™ envelope. Nineteen patients in the no-TYRX™ group

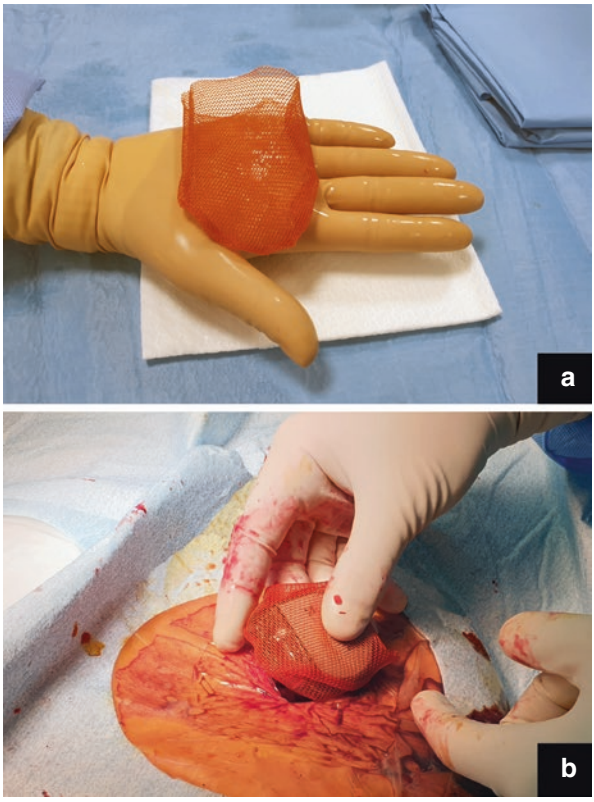


Fig. 11.7 The TYRX antibacterial envelope is prepared before insertion of the CIED (**a**) in a diabetic patient undergoing a replacement of an epicardial pacemaker (**b**)

experienced CIED infection versus 0 in the TYRX™ group ($p = 0.006$). The mean duration of hospitalization stay related to infection was 13 ± 11 days. The average cost of treating CIED infections was calculated $54,926 ± $11,374 per patient, mostly attributable to inpatient care. Applying the infection rate observed in the no-TYRX™ group, it was estimated that 6.2 additional patients would have experienced infection if the device had not been used in the TYRX™ group. The estimated cost of treating those infections was similar to the cost of using TYRX™ in every patient. Patient subsets in which greater cost-efficiency was observed included those with high preoperative infection risk score and those who had undergone early reintervention. It was calculated that, even at an infection rate of 1.59% (instead of the observed 1.71%), the cost of infection care would be approximately balanced by the cost of using TYRX™ in every patient. In the study of Kay et al. [114], the cost-effectiveness of TYRX™ vs. standard of care was assessed from the UK National Health Service perspective. Probabilities of infection were derived from the literature, and resource use included mainly drugs, hospitalization, device extraction, and replacement. Over a 12-month time horizon, TYRX™ was less costly and more effective than standard of care when utilized in patients with an ICD or CRT-D. The results of the randomized WRAP-IT clinical trial (Table 11.1) confirmed the

Table 11.6 Principal trials involving the TYRX™ envelope

Author	Year	Type of study	Patients	Follow-up duration	Conclusions
Bloom HL et al. COMMAND study [122]	2011	Retrospective multicenter cohort study (10 US centers)	624 consecutive patients receiving the envelope	1.9 ± 2.4 months	3 (0.48%) major infections
Kolek MJ et al. VANDERBILT study [123]	2013	Retrospective single-center matched cohort study	260 pts with envelope *versus* 639 matched patients	> 90 days	0.4% infection rate in the envelope group 3% infection rate in the control group
Mittal S et al. VALLEY HEALTH study [124]	2014	Retrospective single-center dual cohort study	Pre-envelope era: 1651 patients Envelope era: 275 of 1240 patients	6 months	Pre-envelope: 1.5% infection rate Envelope era: 0.6% infection rate Highly effective in high-risk patients
Kolek MJ et al. VANDERBILT and WAKE FOREST study [125]	2015	Retrospective single-center cohort study	Patients with ≥2 risk factors for infection absorbable envelope: 135 patients Nonabsorbable envelope: 353 patients No envelope: 636 patients	> 300 days	Absorbable envelope: 0% infection Nonabsorbable envelope: 0.3% infection No envelope: 3.1% infection
Shariff N et al. UPMC study [4]	2015	Retrospective single-center cohort study	Envelope: 365 patients No envelope: 1111 patients	6 months	Envelope: 0 infection No envelope: 1.7% infection Cost of the envelope similar to the cost of avoided infections

Henrikson CA et al. CITADEL and CENTURION studies [120]	2017	Prospective observational single-center study	1129 patients with ICD replacement or CRT implantation Controls: published and matched cohorts	12 months	ICD patients: Envelope: 0.2% infection Benchmark rate: 2.2% infection CRT patients: Envelope: 0.4% infection Benchmark rate: 2.2% infection
Hassoun A et al. [112]	2017	Retrospective single-center cohort study	92 envelope versus 92 no envelope		Envelope: 5.4% infection rate No envelope: 1.2% infection rate
The World-wide Randomized Antibiotic Envelope Infection Prevention Trial WRAP-IT Study [89, 126]	*2019*	*Randomized, prospective, multicenter, international, single-blinded study*	*6983 CIED generator replacement, upgrade, or revision, or a de novo CRT-D implant, randomized (1:1)*	*12 months*	*Envelope: 0.7% infection rate* *No envelope: 1.2% infection rate*
Perioperative antibiotic therapy to prevent cardiac implantable electronic device infection ENVELOPE study (NCT02809131)	*Ongoing*	*Randomized, prospective, single-blinded, non-inferiority study*	*1492 CIED recipients with ≥ 2 risk factors for infection*	*6 months*	*Not reported* *The primary endpoint is major CIED infection*

CRT cardiac resynchronization therapy

efficacy of the antibacterial envelope. 6983 patients were randomly assigned in a 1:1 ratio to receive or not the envelope at the end of the CIED procedure. The use of TYRX was associated with a 40% reduction of major CIEDI at 1 year (0.7% vs. 1.2%; HR 0.60; 95%CI 0.36–0.98; $p = 0.04$). The same result was confirmed at the end of the entire follow-up of 20.7 ± 8.5 months (HR 0.63; 95%CI 0.40–0.98). [126] The published subgroup analysis did not show any specific group with significantly higher benefit from use of TYRX, albeit this analysis is clearly limited by the small number of events that was far below what it was expected in the development of the study design. In fact, the sample size was calculated assuming a 2% 12-month infection rate, about the double of what the actually authors found. Notably, there was an evident discrepancy between the expected and found incidence of CIEDI in high-power vs. low-power devices (respectively, 2.4%/1.3% vs. 0.6%/0.8%) leaving much room for future analysis [89]. At this regard, we are still waiting for the results of the ENVELOPE study to better clarify these aspects. The study will evaluate whether the TYRX™ envelope alone offers protection against CIED infections without the use of intraoperative antibacterial solution and postoperative oral antibiotics in patients at high risk for infection. This randomized non-inferiority study will enroll nearly 1500 patients at one site in the USA. In summary, the use of a minocycline/rifampin envelope in patients requiring a CIED proved to be effective in reducing CIEDI, but further research is still needed to define the most appropriate patient groups that would benefit more from this approach.

11.4 Integrated CIEDI Infection Protocols

Several interventions showed a dramatic reduction in the incidence of CIEDI; as discussed in the previous sections and chapters (see Chaps. 1, 3, 10), some have been already introduced in current guidelines (e.g., antibiotic prophylaxis and avoidance of temporary pacemaker); some others not (e.g., use of antibiotic envelope). Regarding CIEDI, like to many other diseases, several recommendations present in current guidelines/consensus documents are based on common practice and opinion from the experts [14, 46, 47, 115] since it would be almost impossible to demonstrate any single intervention both from a feasible and ethical point of view (e.g., preparation of the operatory field). Moreover, it is extremely difficult to analyze any single intervention alone with complete control of all other variables in such a complex setting with relatively few events. For these reasons, it is extremely interesting looking at the effects of wide protocols including multiple interventions. Ahsan et al. reported the results of a retrospective analysis of the impact of a specifically designed infection-control protocol (including antibiotic prophylaxis determined by risk stratification, improved glycemic control, specific skin preparation, and closure techniques, as well as different diathermy settings) on the incidence of CIEDI in a tertiary referral center [116]. They found a 54% reduction in the incidence of CDI (from 1.3 to 0.6%; $p = <0.03$) associated with a relevant cost saving (about 70,000 GBP per annum) driven by the reduction in the costs associated with management of new cases of CIEDI, while the cost per patient varied between 85 GBP and 115 GBP according to infection risk and drug intolerance. The same

protocol was adopted in completely different settings, on five low-volume centers in China [117], showing a dramatic reduction in CIEDI from about 4 to 1% in these centers justifying the authors suggestion for the adoption of an integrated protocol in all low-volume centers. More recently Manolis reported the results of his personal preventive strategy to CIEDI evidencing the occurrence of only two infections among 762 patients [118]. Despite the limitations of the design (single operator, teaching hospital, long-time window), this report provides really interesting results with a rather different protocol from the previous one. The preventive strategy evaluated in the PADIT trial was narrower compared to the two previously reported, being more focused on antibiotic treatment [119]. However, looking deeply in the design, at least four different aspects were covered: (a) risk stratification (only high-risk patients are considered); (b) pre-procedure antibiotic; (c) use of pocket wash; and (d) post-procedure continuation of antibiotic. This was a well-conducted randomized controlled trial which however failed to demonstrate a significant benefit of the incremental antibiotics strategy [103], but the principal reason seems to be the very low incidence of CIEDI (1.03% in the control group vs. 0.78%; $p = 0.10$) which made the study underpowered. Notably, these results are different from the before-and-after design of previous reports in this topic (e.g., CITADEL/CENTURION studies or the report from Ahsan et al.) [116, 120] but similar to the results of the WRAP-IT trial [89]. The more plausible reason is the presence of a bias introduced by the investigational setting, maybe due to operator/site selection or modification of operator's behavior in response to participation to the study. Additional sub-analysis of these two landmark trials integrated with future studies will probably help us identify the factors we have to focus on in order to drastically reduce CIEDI (Fig. 11.8).

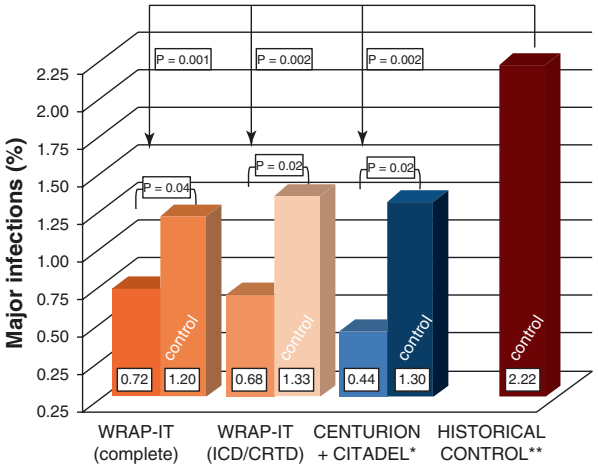


Fig. 11.8 Comparison of infection rates among the three main trials on the TYRX antibacterial envelope (WRAP-IT, CENTURION, and CITADEL trials) (data from [120, 126]). From left to right, the bars represent incidence of 12 months CIEDI with matched control in the whole WRAP-IT cohort, in the same cohort after exclusion of pacemaker patients (CRT + ICD), and in the combined CENTURION/CITADEL cohorts (CRT + ICD). * Site-matched controls (see [120]), ** published controls (see [120])

11.5 Conclusions

Newly developed technologies and strategies represent attractive options to reduce the incidence of the highly concerning issue of CIEDI, in particular, avoidance of promoting factors (e.g., temporary pacemaker, pre-operatory fever), tailored management of anticoagulation, appropriate antibiotic prophylaxis, accurate intra-procedure aseptic approach, and careful post-procedural follow-up. All these factors probably concur to the final result, and we should not focus on a single ingredient but in the whole receipt that should be tailored to each costumer. However, rooms of improvement are clearly present to optimize our preventive strategies and obtain the best results for our patients.

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Prevention of Infection: Indications, Device Programming, Patient Follow-Up

12

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12.1 Indications

CIED indication is a crucial step in a patient's medical history, as it sets the premises for future events and for their critical appraisal. It is well-known from literature that the first CIED surgery carries the lowest possible complication risk, whereas any type of CIED reintervention is burdened by a much higher complication rate [1]. Thus, assessment of the CIED indication is the cornerstone of this process, as it intrinsically carries on the need of replacement at the end of power supply. Careful review of the patient's medical history and forward-thinking of the most likely clinical evolution are mandatory to undertake a patient-centered decision about CIED therapy. While indication is often straightforward at the first implantation owing to specific situations such as severely symptomatic bradycardia or resuscitated VT/VF, device selection remains an important step: planning the appropriate device is key to minimize the risk of long-term complications. On the contrary, CIED replacement can become highly debatable in patients who no longer fulfill the indication or who have poor survival expectancy owing to severe comorbidities [2]. In these latter scenarios, discussing the no-replacement option with the patients is recommended, and information is often well accepted. A sizable proportion of patients (up to 15%) would indeed consider non-replacement of an ICD outside an end-of-life scenario, when engaged into the decision-making process [3].

CIED replacement optionality: Avoidance of repeated CIED surgery is indeed the first step to prevent complications; thus it should be considered in patients no longer meeting CIED indication at the time of device end-of-service (Table 12.1). This is frequently observed in SND patients without indication to ventricular

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Table 12.1 Situations where CIED replacement should be avoided or discussed with the patient

Indication at first implant	Clinical scenario at ERI	Specific considerations	Recommendation
Sinus node disease	Permanent AF	No indication to ventricular stimulation	No replacement
Unexplained syncope, possibly neurally mediated	Asymptomatic, age < 70, no paced activity at DDI = 30 bpm	No rhythm abnormality by EP test run by the device	Discuss with the patient, discourage replacement
AVB	AVB with stable intrinsic rhythm above 40 bpm	Elderly patients bed restricted, frail with comorbidities	Discuss replacement with patient and caregivers Follow until device EOS
Primary prevention of sudden death	No heart failure, clinically stable, no detected VT/VF	Age ≥ 80, EF > 40%	Discuss with the patient replacement optional
Primary prevention of sudden death	NYHA≥3, EF < 30%, significant comorbidities frail patients No treated VT/VF	Impossibility to correct the clinical scenario → competing causes of mortality prevalent	Discuss with the patient: discourage replacement Follow until device EOS
Primary prevention of sudden death	End stage organ disease, metastatic neoplastic disease	Discuss with the patient his/her end-of-life wishes	Follow until device EOS No replacement
CRT for heart failure	Super responder with EF >50%	No other comorbidities, no ICD therapy delivered	Downgrade to CRTP possible; DF-4 connector an issue
CRT for heart failure	Non responder in end stage heart failure Frequent flyers, sometimes on inotropes	No other therapy for heart failure available. Discuss patient end-of-life wishes	Follow until EOS consider CRTP for pacemaker dependent. DF-4 connector an issue
CRT for heart failure	Non responder with worsened cardiac function, NYHA 3	Indication IIB or III at implantation, no indication to pacing	Turn OFF CRT Evaluate until EOS Evaluate for other treatments

stimulation found to be in permanent atrial fibrillation (AF) by pacemaker recordings; while not being an issue in the minority implanted with an AAIR pacemaker, it becomes a relevant one in those treated by dual-chamber pacemakers because of the risk of VOO pacing during battery exhaustion. Recently, the improvement of pacemaker technology has made the end-of-life phase easier by programmability of the ODO or OOO mode, as to avoid the danger of asynchronous ventricular pacing. ICD patients can be considered for non-replacement in the absence of treated arrhythmias and improved ventricular function by other medical interventions, whereas those still meeting indication criteria represent a high-risk subgroup. In fact, a >5% ICD intervention/year at follow-up (FU) has been observed in unselected patients having replaced a first device without any intervention [4]. CRTD

recipients who no longer met ICD indication at the time of device replacement had a 7% occurrence of ICD interventions over a median 14 months FU, making the point that patients' aging and disease evolution/comorbidities matter for the onset of ventricular arrhythmias; hence functionality downgrading also requires careful patient evaluation beyond improvement of left ventricular (LV) ejection fraction (EF) [5].

CIED selection at implant: It has been reported in literature that CIED-related complications are associated with device complexity (number of implanted leads) and size (bulkier ICD/CRTDs) [6–8] and with operator experience [9], but more importantly device upgrades with new lead/s addition carry the greater risk [1, 7, 8, 10–12]. While considering a risk minimization strategy by the avoidance of redundancy in a "Less is More" approach at device selection, a long-sighted perspective should always go with decision-making. Indeed, a patient-centered management aiming to minimize the number of pocket entries and of lead additions is the key to prevent CIED complications [1, 7, 8, 13–15]. It stems out of these considerations that forward-thinking of the most likely patient evolution in the next few years may lead to a strategy other than "Less is More": to meet the future patient's clinical need, a more sophisticated device may be indicated, thus sparing a costly and risky upgrade procedure at mid-term FU. This is typically observed in the pacemaker selection process, where dual-chamber pacemakers are implanted to prevent the unwanted effect of VVI pacing, namely, loss of atrioventricular synchrony. The rate of single-chamber implants varies across countries and across centers within the same country. Though dual-chamber pacemakers were associated with increased complications risks compared to single chamber in the past, the actual rate is <5% in contemporary registries [16–18]. On the contrary, the choice of a single-chamber ventricular pacemaker is burdened by a crossover rate at FU as high as 36% owing to pacemaker syndrome/heart failure symptoms/AF onset, which poses hazard to the patients and huge economic pressure on health systems owing to hospitalizations, repeated CIED surgery, and related complications, of which infectious are the most expensive [1, 19, 20]. It seems from real-life registries that the use of dual-chamber systems is prevalent (88%) in high volume and teaching hospitals, where lead-related complications are also lower [1, 17, 18]. Despite CIED therapy being on the clinical ground for 60 years, formal training programs to ensure the best lead and CIED performance at FU are missing at many universities/teaching centers, contrary to other interventions such as lead extraction, percutaneous valve implants, endovascular procedures, owing to a "perceived" simplicity.

Thus, the trade-off between avoidance of hardware redundancy and avoidance of repeated surgery for system upgrade is the pivotal decision for each patient. In the view of minimizing repeated CIED surgery for reasons other than physiologic battery depletion [15], a comprehensive medical evaluation with definition of the therapeutic goals for the future needs to be achieved before undertaking CIED selection. Several points that are difficult to be captured in medical literature may shift physician preference to a simpler or a more complex device, to a leadless or to a non-transvenous one: how much of the decision-making is based on perception rather than on objective data is not available. For instance, in the OPTI-MIND, registry

acceptance of AF as the ultimate rhythm at FU was probably the main reason to implant VVI pacemakers in 17% of SND patients, a choice not supported by guidelines [21]. A dual-chamber pacemaker with state-of-the-art algorithms would indeed be indicated when sinus rhythm maintenance was the therapeutic target. Among non-class 1 CRT candidates (those with no or at best debatable CRT indication), those with advanced first-degree AV block (that is a marker of more advanced cardiac disease) maintain the same heart failure and survival benefit of class 1 CRT recipients, thus should receive a CRTD despite absence of left bundle branch block [22]. Individual's physical and clinical factors may be associated with the perception of increased complication risk, such as body habit, frailty, history of atrial arrhythmias, and comorbidities, hence may influence the decision toward the simpler (minimize the risk) or the most sophisticated technology (face the risk only once), depending on the therapeutic goal. In summary, the same markers of vulnerability may lead to opposite behaviors in device selection when the therapeutic purpose has been clearly defined; the absence of purpose definition is associated with upgrades and complications at FU. The selection process of the CIED is a complex framework where different factors entangle to each other: recommendations as per the actual guidelines, individual patients' characteristics that dictate the ultimate therapeutic goal, and personal experience of the implanting physician with his/her attitude to reach the therapeutic goal and minimize future complications.

Defining the therapeutic target is the priority in this process; planning of device selection and procedure strategy according to the patient individual characteristics is key to minimize both repeated interventions in the future and procedural complications/hardware redundancy ("Less is More" approach). The therapeutic targets can be considered as follows:

Sudden death prevention: A subcutaneous ICD enables freedom from endovascular hardware, early reimplantation after lead extraction at low infection risk [23], and low complication risk in thin patients when placed intermuscularly under the latissimus dorsi. Addition of pacemakers or CRTP at a later stage has been achieved without unwanted effects [24, 25]. In the setting of a thin habit patient requiring ATP or cardiac pacing, a subpectoral transvenous device is preferred when skin erosion is threatened. Current developments are leading toward communicating devices where the S-ICD plays the role of computing, rhythm detection, and analysis, while leadless units work the bradycardia pacing/ATP needs. The shorter longevity compared to contemporary transvenous ICDs, compelling more frequent replacements, is the major downside of S-ICD: future development to increase S-ICD longevity (such as a lower output capacitor at 60 J) will probably fill this gap [26].

Prevention of heart failure and treatment of systolic LV dysfunction: Maintenance of AV and inter-intraventricular synchrony are the pathophysiologic standpoints for this goal. While implant is most commonly achieved with an atrial lead and one or two (CRT) ventricular leads, a lead- and vascular-sparing approach can be adopted [27]. In fact, single-lead VDD may suit AV block patients with difficult vascular access, or with abandoned, non-functional leads, showing good results at long-term FU [28]. Though it requires careful placement of the atrial dipole to maintain P wave detection at long term, the outcome is comparable to a dedicated atrial lead,

when atrial pacing is not needed. A similar approach has been adopted in CRT recipients [29] that typically do not have atrial stimulation indication [30]. A randomized trial with DX technology that can amplify the atrial signal up to fourfold at no trade-off with background noise is currently testing this strategy versus 3 leads CRT [31]. In AV block patients with mild LV dysfunction, biventricular stimulation and His bundle pacing (HBP) seem superior to conventional RV pacing [32–34], though HBP can reduce the number of implanted leads in presence of intact His-Purkinje conduction. The risk of repeated surgery is, however, >4% with an infection rate of 1.3%, that compares to the most complex ICD/CRTD procedures [35, 36]. In terms of hardware minimization, newer development of the leadless pacemaker can ensure AV synchrony by tracking the mechanical atrial activity as detected by the accelerometer: though the efficiency is suboptimal at this preliminary stage, especially for heart rates above 90 bpm, it can probably suit the majority of elderly AV block patients with limited physical activity and preserved LV function, thus sparing the risk associated with CIED surgery (hematoma, pneumothorax) and to endovascular leads [37]. Clinical application is awaited in the next future, with a possible role for >75 years old recipients and reasonably preserved LV function. The setting of ventricular stimulation is the clear dichotomy between the most physiologic treatments (HBP) at the cost of most complex procedure against the fastest procedure with lesser physiologic outcome (non-physiologic ventricular depolarization with incomplete AV synchrony), the choice being driven by a comprehensive patients' evaluation.

CRT delivery in systolic dysfunction patients requires a stable LV capture in the targeted site at low current drain to increase device longevity: it is hence mandatory to ensure lead stability, freedom from phrenic stimulation below 5 V (upper range of LV pulse delivery), and feasibility of LV capture at least at two sites. Lead technology appears as the key to successful CRT delivery at long term. While the use of quadripolar LV leads has greatly decreased the technical challenges of CRT and is associated with superior outcome compared to old unipolar and bipolar leads in observational cohorts [38], novel active fixation LV leads have further increased CRT implementation by enabling the targeting of short and thin veins, or very unstable placements in long and large veins [39]. Beyond superior performance, this technologic platform was conceived with a view to easy extractability, the side helix being soft enough to be elongated by a <1 kg traction force at long-term FU [40, 41], thus representing a first-choice lead to ensure CRT delivery. LV lead selection and stable placement are the most important steps in CRT implementation, since LV dislodgement may preclude reimplantation owing to thrombosis of the target coronary vein [42]. Phrenic nerve stimulation is nowadays easily managed by quadripolar leads; however a short-spaced dipole provides superior efficacy [43]. In the setting of frail or poor vein access CRT candidates with normal AV conduction and absence of LV scar [44], LV-only stimulation can warrant clinical success [45] with minimal hardware (Fig. 12.1), when phrenic stimulation can be managed. The availability of active fixation bipolar and quadripolar leads makes theoretically possible to envision a single-lead CRT for selected patients with normal AV conduction to minimize intravascular hardware and risk of thoracic veins obstruction [29, 39]. The

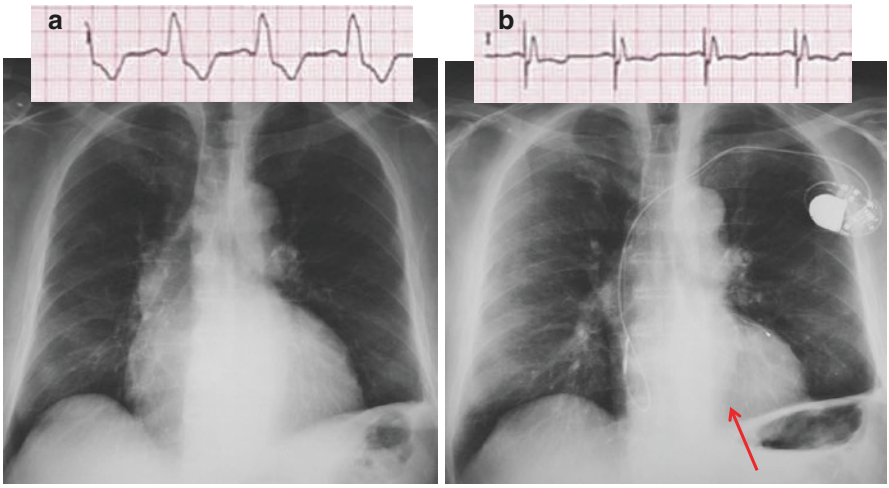

Fig. 12.1 Hardware minimization in a CRT recipient: (**a**) before implantation (LBBB, EF = 29%, ESV = 128 mL); (**b**) after implantation of dual-chamber pacemaker with RA and LV leads (LV-only pacing with fusion on His-Purkinje conduction, EF = 55%, ESV = 60 mL). Red arrow: absence of the RV lead

correction of LBBB by HBP has prompted a "lean" approach (single His lead) at CRT implementation; however, several unsolved issues need to be addressed: stability of His-Purkinje conduction by long-term, ventricular sensing and defibrillation still requiring a defibrillation lead when CRTD is indicated, stability of His pacing threshold, and need for an LV lead upgrade in case of failure to correct LBBB at long term.

Prevention of atrial fibrillation and stroke: Physiologic pacing is the cornerstone of AF prevention in patients with indication to stimulation because of bradycardia; sinus node disease especially benefits from atrial-based stimulation. Stability of right atrial leads can be improved by atrial fixation in enlarged atria or operated on patients that should be preferred to minimize displacement. AF prevention is accomplished by physiologic pacing aiming at improvement of the LV function. Alternative atrial stimulation sites have never proved superior to right appendage pacing [46], though the coupling between interatrial and atrioventricular conduction, that may play an important role, was never considered in the past [47]. Patients with brady-tachy syndrome can probably benefit from automatic termination of atrial tachycardias to decrease permanent AF onset [48], so this capability should be considered at the time of device selection in patients with brady-tachy syndrome. Stroke prevention strategies stand on detection of subclinical atrial fibrillation by CIEDs. AF detection by dedicated algorithms with intracardiac electrogram recording (EGM) and quantification of episode duration is nowadays fundamental for a stroke prevention strategy: when coupled to remote patient monitoring with automatic alerts, it

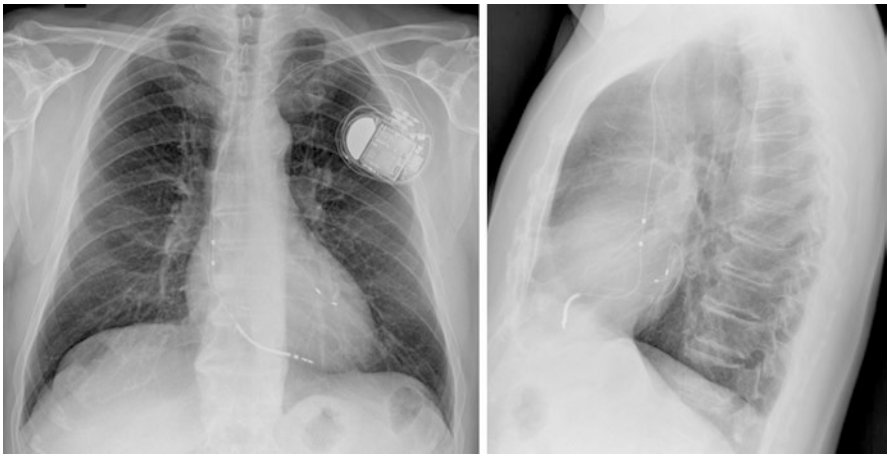

Fig. 12.2 Super-responder patient after implantation of a two leads CRTD (CRTD-DX by Biotronik): note the atrial dipole built on the RV lead [29]

helps patients' management by enabling a timely decision-making. The need to minimize intravascular hardware makes single-lead devices with dedicated AF diagnostics or with a floating atrial dipole (VDD) the preferred choice in the absence of indications to atrial stimulation [49, 50]. The former approach determines AF presence by the Lorenz plot of RR interval changes along time, so does not require the atrial EGM; the latter is based on the atrial signal detected by a VDD single lead that is processed by fourfold amplification and filtering as to maintain a very high signal-to-noise ratio (DX technology). The DX technology is currently undergoing a randomized trial to detect subclinical AF in single-chamber ICD candidates [51]: in the single study of CRTD recipients with DX technology (Fig. 12.2), it proved as reliable as customary CRTDs with dedicated atrial leads [29]. Detection of atrial rhythm is also a cornerstone of arrhythmia diagnosis in ICD/CRTDs to minimize the risk of inappropriate therapy delivery; although dual-chamber diagnostic was never able to prove a consistent benefit over single-chamber ICDs in the past, the value of the atrial channel information is gaining more importance in recent studies with refined detection settings both for slow and fast ventricular tachycardias [51, 52]. Atrial channel increases the confidence with diagnosis a posteriori [53]; thus the availability of the atrial signal with a single lead becomes particularly attractive.

Enabling optimal CIED performance in challenging situations: This is a very important goal in specific patients' subgroups, where lead stability and performance at long term are mandatory. They share the picture of the difficult RV placement such as congenital heart disease with univentricular heart or single ventricle double-inlet, large ventriculotomy or patches; small amplitude RV signals (arrhythmogenic cardiomyopathy, RBBB); clinically relevant tricuspid regurgitation with or without pulmonary hypertension; prosthetic tricuspid valve; and abandoned lead/s across the tricuspid valve. Where the coronary sinus is accessible, LV leads can take the place of the RV in all the abovementioned clinical scenarios [54]; defibrillation can

be achieved by a co-implanted S-ICD or by transvenous shocking coils placed in the azygos vein, in right atrium or in the coronary sinus [55]. Active fixation LV leads have the same stability and performance of RV leads and help to overcome most of the abovementioned challenges, especially in the setting of tricuspid regurgitation or of a single ventricle [54]. Epicardial lead implant should be considered in patients having a pacemaker/CRT indication at the time of cardiac surgery, or at high risk of AV block during cardiac surgery [56]: modern suture epicardic leads have similar performance to transvenous ones [57]. When any of these situations needs to be addressed in an ICD/CRTD candidate, the choice of DF-1 and IS-1 connections is mandatory to enable lead/s interchangeability. When single-chamber pacing is needed, leadless pacemakers can be considered in these challenging scenarios, among which failure to deliver effective CRT is an emerging one, owing to different reasons: anatomic difficulty to reach a suitable coronary vein for targeted LV stimulation, failure to elicit LV capture, and lack of clinical improvement. LV endocardial pacing has proven to increase CRT outcome thanks to enhanced possibilities of a targeted LV placement and faster LV activation [58]. Leadless LV stimulation may overcome several hurdles at endocardial pacing implementation, among which anticoagulation requirement at long term is of the outmost importance [58, 59].

Minimizing lead issues and skin complications: The majority of CIED infections stem out of repeated surgery due to lead issues and skin/wound complications; hence extra care is needed to ensure long-term lead functionality [60, 61]. Suboptimal lead placement is the main reason for loss of lead functionality at long term; lead implantation technique should become a major step in CIED training. A cephalic vein and/or axillary vein access for lead placement is associated with the lowest possible risk of subclavian crush syndrome or insulation defects, owing to avoidance of lead/s engagement with the first rib-clavicular space structures (Fig. 12.3). Coiling of the lead/s in an appropriately sized pocket without sharp angles and pressure on the CIED can are other precautions to minimize lead damage (Fig. 12.4).

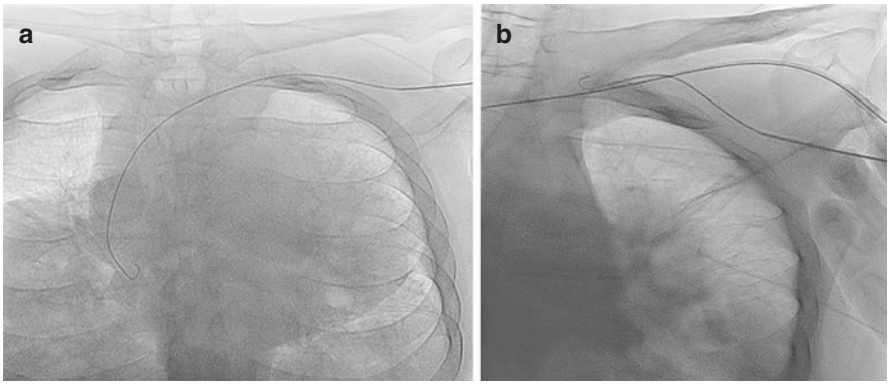

Fig. 12.3 Vascular access to maximize lead integrity at long term. (**a**) Axillary vein puncture above the second rib, AP view 35°caudal. (**b**) Cephalic vein access + axillary vein puncture above the second rib, AP view 35°caudal

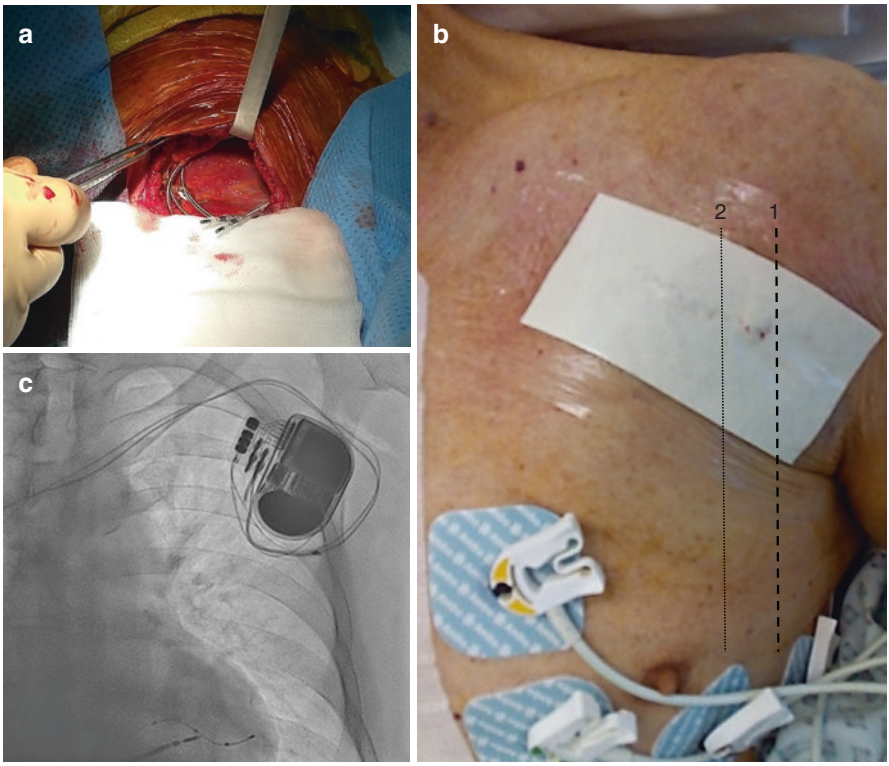

Fig. 12.4 Prevention of mechanical issues at the CIED pocket. (**a**) Appropriate pocket sizing to accommodate coiling of the pacing leads. (**b**) CRTD location (lateral border = line 2) medial to the anterior axillary line (1) to prevent inside out pressure and skin erosion. (**c**) CRTD placement to prevent long-term mechanical issues. Note: axillary access of the leads, can location below the leads line and medial to the anterior axillary line, outer lead coiling spaced enough to prevent contact with the CRTD can, inner lead coiling below the device

CIED pocket should be sized as to avoid inside-out pressure and be located at a medial prepectoral location, at least 2 cm medially to the anterior axillary line and inferiorly to the pectoralis-deltoid line to minimize the risk of skin erosion at the most vulnerable skin sites (Fig. 12.4b, c). Suturing the CIED at the pectoralis muscle is one important step to prevent device migration and skin erosion at follow-up, an event particularly threatened in thin habit and elderly patients.

12.2 Device Programming

CIED programming is the main intervention to decrease infection by extending device longevity: exposure to the risk of repeated surgery is the true reason for increased complication rate of ICD/CRTDs compared to pacemakers, device longevity meeting more closely pacemaker recipients' life expectancy than ICD/CRTD

recipients [62]. CIED longevity has greatly increased in the past decade despite enabling a much superior data computing and support to patient clinical management, owing to more efficient data processing and improved power source, especially in ICD/CRTDs. Projected pacemaker longevity ranges nowadays from 11 to 16 years, whereas ICD/CRTD from 8 to 13 years. CIED programming aims to improve patients' quality of life while extending as much as possible battery longevity. This latter task can be generically achieved by low-consumption processors and by saving the energy wasted in paced activity by the use of algorithms for the automatic management of pacing output (that minimize the safety margin at no compromise with patients' safety) or for the avoidance of unnecessary pacing (rate hysteresis, AV interval hysteresis, single AAIR/dual-chamber mode commutation, single LV pacing in CRT). Algorithms with unproven efficacy like atrial overdrive pacing, rate smoothing, and ventricular stimulation triggered in response to sensed intrinsic activity or for rate regularization during AF lead to increased energy drain and should be turned off.

Capability of automatic verification of capture and output management was the first breakthrough innovation 25 years ago [63] and leads to increased patients' safety and pacemaker longevity [64, 65], the benefit being greater at higher pacing thresholds [17]. These algorithms are available in all cardiac chambers nowadays but are active by shipment in only two manufacturers, thus require to be turned on and to be tuned to achieve their best performance. It is noteworthy that each manufacturer has its own peculiar specificities in terms of beat-to-beat capture verification, maximum capture threshold that can be managed by automated capture verification, and possibility to work at different pulse widths or with differently manufactured leads (low vs high polarization) (Table 12.2). Beyond increasing patients' safety and CIED cost-effectiveness, automatic pacing output management is mandatory also in the perspective of remote patient monitoring to trigger appropriate interventions in the event of relevant changes. One important step for the future of physiologic cardiac stimulation will be the development of a dedicated pacing technology (delivery sheaths, pacing leads, and pacemaker circuitry) for His bundle pacing (blanking and refractory settings, timing to detect the evoked response, V-V offset). Indeed, the time window to detect the evoked response of current pacemakers/CRT devices (20–80 ms) may not be sufficient to warrant verification of capture in the event of prolongation of the H-V interval, as for the case of antiarrhythmic drugs or other medications with Na channel block properties (Fig. 12.5a, b).

Beyond pacing output management, remote patient monitoring is key to ensure adequate system functioning and lead performance, prompting timely intervention in the event of lead issues or of pacing threshold increase that can be addressed by pacing vector reprogramming, for instance, from bipolar to unipolar or from a proximal to a distal cathode in CRT (lead dislodgement toward the coronary sinus). Remote patient monitoring also increases the confidence with the CIED reliability in the ERI-EOL period that is highly dependent on device release and physician experience, resulting in a non-negligible variability in time to device replacement [66]. Observation of patients at high risk of adverse events following repeated CIED

Table 12.2 Algorithms for automatic management of cardiac stimulation: key aspects according to manufacturers

	Dedicated Lead needed	Beat-to-beat capture verification with backup pulse	Maximum adapted pacing threshold	Energy drained at 4 V at 0.4 ms threshold, 500 Ω impedance	Algorithm applicability
RV chamber					
Abbott	Yes, low polarization	Yes No in ICD/CRT	3.875 V at 1.5 ms	20 μJ	96% of patients
Biotronik	No	Yes No in ICD/CRT	4.8 V at 0.4 ms	16 μJ	97% of patients
Boston scientific	No	Yes No in ICD/CRT	3 V at 0.4 ms 3 V at 0.4 ms	50 μJ 30 μJ	94% of patients
Medtronic	No	No	2.5 V at 0.4 ms	50 μJ	94% of patients
Microport	No	No	2 V at 0.4 ms	50 μJ	Not available
RA chamber					
Abbott	Yes, low polarization	No	3.875 V at 1.5 ms	20 μJ	70% of patients
Biotronik	No	No	4.8 V at 1.5 ms	16 μJ	93% of patients
Boston scientific	Bipolar atrial lead	No	3 V at 0.4 ms	30 μJ	84% of patients
Medtronic	No	No	2.5 V at 0.4 ms	50 μJ	90% of patients
Microport	No	No	3 V at 0.4 ms	50 μJ	Not available
LV chamber					
Abbott	Yes, low polarization	No	3.875 V at 1.5 ms	20 μJ	94% of patients
Biotronik	No	No	4.8 V at 0.4 ms	16 μJ	Not available
Boston Scientific		No	7 V at 2 ms	16 μJ	97% of patients
Medtronic	No	No	5.5 V at 1.5 ms	16 μJ	95% of patients
Microport	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable

surgery from ERI into the EOL phase may be safely undertaken, owing to remote monitoring, until a more favorable clinical profile is achieved to undergo device replacement/upgrade; replacement can alternatively be avoided in the situations where the risk/benefit ratio recommends against continued CIED therapy, or patients' expected survival declines owing to the global clinical profile.

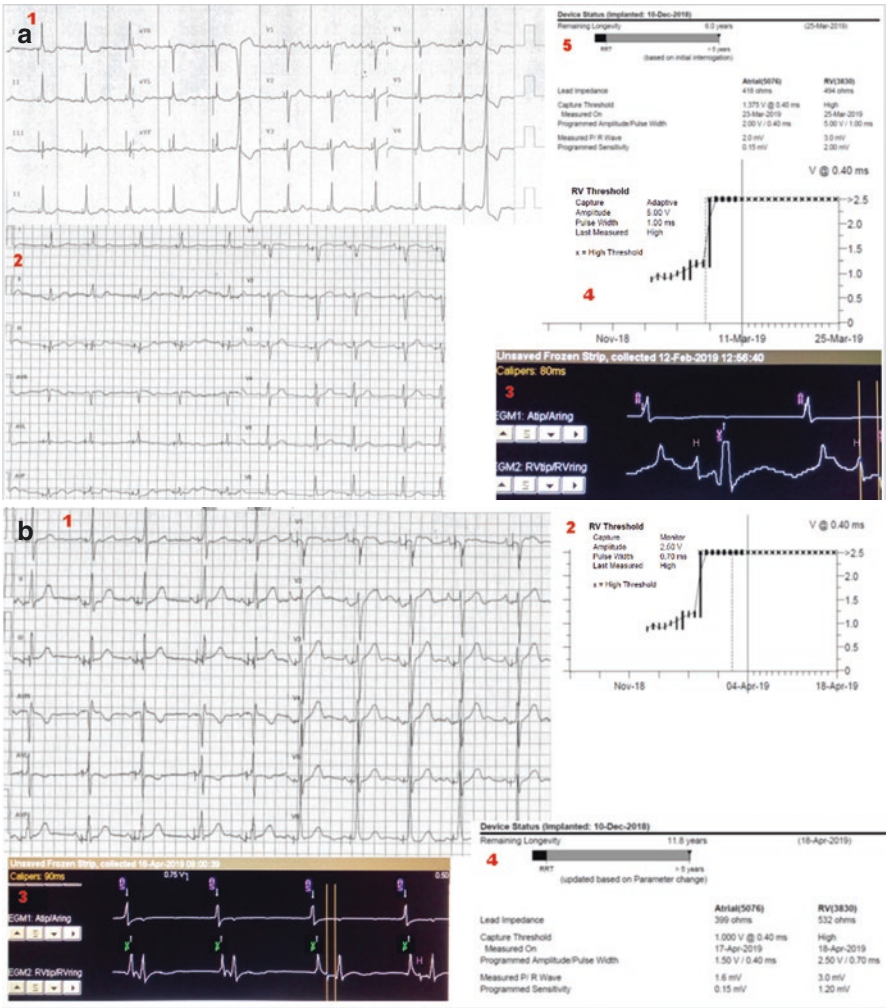

Fig. 12.5 (**a**, **b**) Need for dedicated pacing setting in His bundle pacing. (**a1**) > Recurrent atrial fibrillation in a His bundle-paced patient with intermittent AVB 2nd: note the stimulus-QRS < 60 ms (equal to an H-V conduction time). (**a2**) > 2 days later, after flecainide loading and resumption of sinus rhythm: note the stimulus-QRS = 80 ms. (**a3**) > Snapshot of intracardiac recording during spontaneous rhythm on the same day: note the A-H-V sequence on the RV channel (lead placed at His pacing site) with an H-V interval of 80 ms, equal to stimulus-QRS in **a2**. (**a4**) > 40 days later, threshold trend: capture management was unable to measure a pacing threshold owing to the prolonged H-V conduction due to flecainide effect that prevented to detect a suitable evoked response (ER) in the ER detection window. High threshold declared and reversion to high-output setting. (**a5**) > Device follow-up on flecainide chronic treatment: reversion of capture management to a high threshold output (5 V at 1 ms) with sudden decrease of projected longevity to 6 years, despite a stable His pacing threshold around 1.5 at 0.4 ms. (**b1**) > Follow-up after 2 months flecainide treatment; sinus rhythm with stimulus-QRS >80 ms. (**b2**) > Threshold trend showing persistent impossibility to measure RV threshold. (**b3**) > His capture occurs at 1 V at 0.7 ms, please note the prolongation of AV interval on the third and fourth beat upon loss of capture at 0.75 V. (**b4**) > Owing to a fixed-output setting (2.5 V at 0.7 ms) in the previous month, pacemaker projected longevity increased to 11.8 years

12.3 Patient Follow-Up

The persistence of effective CIED therapy is the goal during FU until end-of-service. CIED features adapt to the changing clinical scenario automatically or via reprogramming. Unanticipated CIED surgery may sometimes occur and is usually due to loss of CIED functionality or necessity to upgrade at a superior one. While upgrading can be mitigated by forward-thinking at the time of CIED selection, loss of functionality usually appears unpredictably. Loss of cardiac stimulation or sensing issues (both undersensing and oversensing) is the most common causes of CIED-repeated surgery, which in turn is the leading cause of CIED infection. Upgrading to a superior function is the second cause of repeated CIED surgery, followed by device advisories affecting either leads or CIED, that might pose an unpredictable hazard to patients' health owing to an anticipated risk of sudden loss of CIED functionality. Though all these situations arise as loss of the appropriate CIED functionality, a clear distinction shall be made between those not compromising the therapeutic goal (for instance, loss of atrial capture in CRT) and those leading to loss of therapy (for instance, LV lead displacement or loss of atrial sensing in CRT). While a conservative approach is possible in the former scenario, repeated intervention is mandatory in the latter, with significant difference in term of infection risk. Surgery-sparing solutions to fix lead issues are indeed welcome to avoid CIED pocket entry. Awareness of this unmet clinical need has recently arisen and has promoted the development of leadless technologies as preventative of lead malfunction (*if it isn't there it can't break.* Henry Ford) rather than enhanced electronic programmability to fix pacing/sensing issues without surgical lead revision (*The pessimist complains about the wind, the optimist expects it to change, the realist adjusts the sails.* William Arthur Ward). Though lead issues are the most common cause of CIED malfunction, the underlying cause is rarely a lead fracture apart in recalled leads; more frequently it is a change in the lead-tissue interface or an insulation defect [67]. Several adjustments have been used to restore CIED functionality without a new lead addition that has both procedural (pneumothorax, bleeding) and long-term (tricuspid regurgitation, vein occlusion, infection) complications.

The most common issues to be addressed during follow-up stem from atrial or RV channel performance, being the LV channel until now not used for sensing or rhythm classification.

Atrial channel issues: While loss of consistent atrial sensing dictates repeated surgery to be fixed, loss of atrial stimulation in patients with normal sinus function and adequate atrial sensing is not an issue: tracking of the P waves in AV block or CRT patients is the therapeutic target in this setting. A new lead addition is unnecessary in this scenario and should be avoided. A sizeable number of VDD lead recipients have atrial stimulation capability at long term [29]: extensive atrial pacing programmability (any electrode programmable as cathode in any possible configuration with the can) should be considered in future developments, to enable atrial stimulation in case it were needed at follow-up without unnecessary repeated surgery. This could also be envisioned in HBP recipients (single lead VDD HBP) to minimize intravascular hardware.

RV channel issues: Pacing and sensing issues are the most threatened complications at follow-up, since transvenous CIED rely on the RV channel for rhythm detection and classification and for life-supporting cardiac stimulation. The occurrence of the Sprint Fidelis integrity issue prompted programmability of ventricular pacing and sensing as tip-to-coil in ICD/CRTDs to prevent both pacing failure and oversensing leading to inappropriate therapy delivery in the event of proximal ring conductor failure, thus confirming that sensing programmability is indeed feasible when clinically needed [68, 69]. In the event of RV lead malfunction, an already existing ventricular lead—either RV or LV—can be used for rhythm detection and classification sparing a new lead addition that increases the infection risk [54]. However, this dictates that all ventricular connections are IS-1 to allow lead interchangeability, thus may not become possible with the widespread adoption of DF-4 and IS-4 connections [70]. Moreover, the harbinger of CIED infection—repeated pocket entry—is dictated anyway when LV to RV lead switching is done, making a strong call for all manufacturers to make available electronic programmability of the sensing channel [54]. Rhythm detection and classification should become possible by the use of any dipole among the existing ventricular electrodes in the implanted system—LV electrodes included—to avoid repeated surgery [14, 15]. Indeed, the possibility to select the sensing vector is the key of the S-ICD success to manage sensing and arrhythmia detection despite the challenges posed by a large dipole mimicking a surface ECG; changing the EGM source from tip-to-ring to tip-to-coil has also proved effective to address sensing issues in transvenous ICDs [68, 69].

LV channel: The left ventricular lead is mostly burdened by its stimulation performance, being responsible of CRT efficacy. In the event of loss of RV capture or very high RV threshold, LV-only stimulation is an adequate solution to maintain CRT efficacy and maximize device longevity without repeated surgery [45, 71]. The ongoing ADAPTIVE-CRT trial is testing its superiority compared to conventional CRT [72]. LV-based sensing and pacing are the optimal solution in patients with previous failure of RV lead/s, to minimize the risk of tricuspid regurgitation and of repeated RV lead failure in the setting of a new lead addition at follow-up [54]. It is also an optimal first choice to master a difficult RV placement. LV stimulation can be achieved by a leadless technology in the setting of subclavian stenosis/obstruction, failure to achieve an acceptable LV lead placement or pacing threshold, nonresponse to a working CRT in place, and high-risk upgrades to CRT. All these situations portend a high infective risk; thus implementation of CRT by an approach not requiring pocket entry and new lead addition has a high safety and efficacy profile (Fig. 12.6).

An important aspect of infection prevention along follow-up is screening for the potential situations at risk of CIED malfunctioning and/or infection. On one end, the medical community should be aware of the potential for CIED infection during the course of concurrent illnesses or in the occurrence of surgical/interventional procedures that might promote bacterial seeding of the endovascular component of the implanted system; on the other end, patient empowerment can help to minimize the risk of infection or damage to the implanted system. The former is specifically addressed in the setting of acute illnesses, in intensive care units, or whenever i.v.

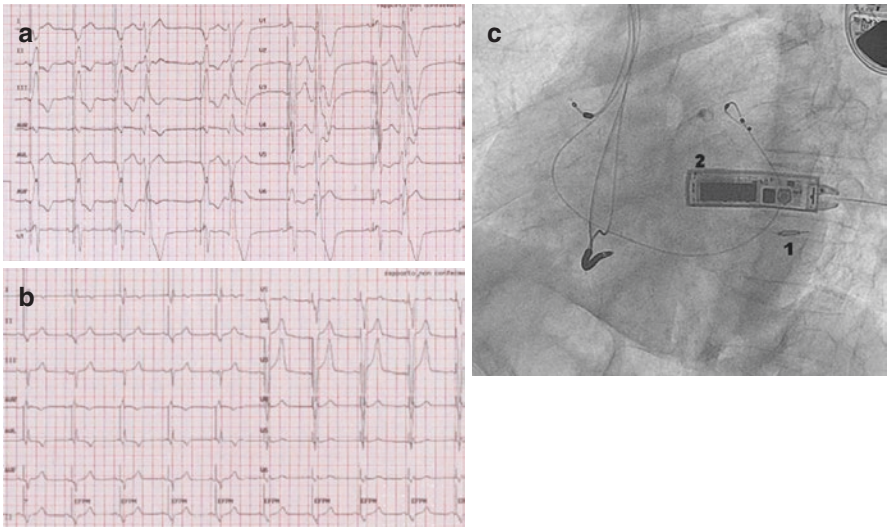

Fig. 12.6 Leadless endocardial CRT. (**a**) ECG in a CRT non responder. (**b**) Same patient, endocardial leadless pacing >> note the marked QRS narrowing compared to **a**. (**c**) Endoventricular leadless system >> 1 = endoventricular receiver, 2 = intercostal ultrasound transmitter

lines are placed in a CIED recipient: the risk of biofilm formation on indwelling catheters and subsequent seeding of the leads is well-known, especially in dialysis or in oncologic patients. Cautious use of long-standing i.v. lines, careful access site management, and perioperative antibiotic prophylaxis to avoid biofilm formation and bacterial resistance are key to prevent CIED infection in the hospital setting. Closed-pocket CIED infections have the worst prognosis, being mostly endovascular, thus should be aggressively targeted at the "prevention" level [73]. It is also extremely important to avoid misinterpretation of benign findings as lead masses in patients without clinical suspicion of CIED infection, to prevent unnecessary and potentially harmful diagnostic workup, antibiotic treatment, and lead extraction: Golzio and coworkers have recently reported on a long-term follow-up (5 years) of such patients without any clinical infection arising [74]. This knowledge makes the search of lead masses a mandatory aspect of echocardiography in CIED recipients, to rule out or confirm a possible infection in those patients already known to be asymptomatic carriers of lead masses [74].

Patient empowerment aims at education to prevent physical/leisure activity that might pose a lead integrity issue, or a mechanical/electrical damage to the CIED. Periodic inspection of the skin overlaying the implanted device is also helpful to detect early signs portending skin erosion or pocket infection, such as reddening or swelling, to engage timely in corrective actions. Patient empowerment leads to the understanding of the therapeutic target and of its evolution along follow-up in the context of the patients' specific medical condition, so that the most difficult steps in the clinical history of CIED recipients can be shared once they come up. The most difficult decisions in a CIED recipient history should be discussed first at

Table 12.3 Main steps to minimize CIED infection

Minimize pocket entries	Replacement optionality	End-of-life decision
		Lack of indication
		Changed clinical conditions
	Maximize battery longevity	Avoid unnecessary stimulation
		Avoid unnecessary algorithms
		Automatic output adjustment
		Shock reduction: long detection and discriminators in ICDs
	Lead issues prevention	Avoid lead dislodgement
		Use preexisting functional leads
		IS-1 connectors to enable leads switching
		Electronic programmability
Minimize procedure complexity and intravascular hardware	AF as "destination rhythm"	Single-chamber unit
	Sporadic pacing foreseen	
	Limited life expectancy	
	Atrial stimulation unnecessary	Single-lead VDD
		AF detection by Lorenz plot
	Access issues, previous extraction	Subcutaneous ICD
	CRT implant failure/CRT non-response	Leadless systems
	Tricuspid valve issues and pulmonary hypertension	Leadless systems
		Coronary sinus leads implant
		Epicardial leads at the time of surgery

the time of CIED indication with the patient and his/her family and later reassessed at each follow-up, to consider possible perspective changes and to redefine the patient's priorities. This particularly applies to replacement optionality, end-of-life decision-making, and downgrading opportunity, where the patients' and caregivers' expectations shall reflect a well-balanced appraisal. The psychological burden of these decisions should be lifted up during the years of continued CIED therapy by discussion with the medical team, rather than being a hasty task at ERI.

12.4 Conclusion

The prevention of CIED infection is a multifaceted process (Table 12.3) that starts at the time of indications and later unwinds along the many pathways of device/s implantation, programming, and patients' follow-up in a comprehensive medical perspective to the best-tailored individualized approach.

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