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Cardiovascular implantable electronic device infections: associated risk factors and prevention

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Summary

Infections of cardiovascular implantable electric devices (CIED) are a burden on patients and healthcare systems and should be prevented. The most frequent pathogens are coagulase-negative staphylococci and *Staphylococcus aureus*. The most important risk factors for CIED infections are diabetes mellitus, renal and heart failure, corticosteroid use, oral anticoagulation, fever within 24 hours before the procedure and leucocytosis, implantable cardioverter defibrillator compared with pacemaker, especially in the case of *Staphylococcus aureus* bacteraemia, lack of antibiotic prophylaxis, and postoperative haematoma and other wound complications. Other important risk factors are history of prior procedures and previous CIED infections, number of leads, use of povidone-iodine compared with chlorhexidine-alcohol, and centres and operators with a low volume of implants. To prevent CIED infections, patients undergoing CIED procedures and appropriate devices should be carefully selected, and interventions should be performed by trained operators. Antibiotic prophylaxis should be administered, and skin antisepsis should be done with chlorhexidine-alcohol. Oral anticoagulation should be continued during CIED procedures in high-risk patients for thromboembolism, instead of bridging with heparin. Early reintervention in cases of haematoma or lead dislodgement should be avoided. The implementation of infection prevention programmes reduces infection rates. More randomised controlled studies are needed to evaluate prevention strategies, especially skin preparation and antibiotic prophylaxis with glycopeptides.

Key words: *cardiovascular implantable electronic device; CIED; ICD; pacemaker; infection; prevention; risk factor*

Introduction

Infections of cardiovascular implantable electronic devices (CIEDs) can affect the generator pocket site only, the leads and valves resulting in CIED infective endocarditis, or both. Whereas generator pocket site infections present mostly with inflammatory changes of the skin including pain, swelling and redness, and can cause skin and soft tissue ulceration and drainage, CIED infective endocarditis presents with fever and signs of systemic infection [1]. CIED infective endocarditis represents up to 23% of all CIED infections [2], and involves valves in more than one-third of the cases. The one-year mortality rate is 20% in the case of device removal and 38% in the case of device retention [3]. Moreover, infections of CIEDs cause high healthcare costs [4].

Since CIEDs improve symptoms and survival of patients with heart diseases [5, 6], their use has increased: approximately 178,000 pacemakers (PMs) and 67,000 implantable cardioverter defibrillators (ICDs) were implanted in 2004 in the USA, a 25% increase for PMs and 145% for ICDs since 1997, and the number of implanted devices rose further to 235,567 new implanted PMs and 133,262 new ICDs in 2009 [7, 8]. Simultaneously, the rate of CIED-associated infections rose from 1.53% in 2004 to 2.41% in 2008, probably due to an increase of patients with multiple comorbidities [9]. The most frequently isolated pathogens causing CIED infections are coagulase-negative staphylococci (CNS) and *Staphylococcus aureus*. Besides these, a variety of other microorganisms have been documented in CIED infections, including *Pseudomonas aeruginosa*, *Enterococcus* species, *Propionibacterium acnes* and, more rarely, yeasts and moulds [10–16].

Diagnosis of a CIED pocket infection is a clinical one. Diagnosis of CIED infective endocarditis is based on clinical parameters, blood cultures, and echocardiographic findings [17]. A major limitation of the use of the finding of a "vegetation" on a lead as an echocardiographic criterion to support a diagnosis of CIED infection is that, depending on the type of echocardiography, the incidence of finding "clots", or "masses" on leads in patients without evidence of infection ranges from 1.4% to 30% [18–22]. In an autopsy series, 48% of leads had "thrombi" [23]. Atrial fibrillation may be a risk factor associated with lead clot formation [22]. Investigations continue to define better the subgroup of patients with no evidence of pocket site infection and bloodstream infection who do or do not have CIED infection.

For the identification of the causative organism, cultures of the generator pocket site, of the leads and from blood are needed. Although the sensitivity of a tissue culture is high-

er than that of a swab culture from the pocket site, up to 30% of patients with clinical signs of CIED infections have a negative culture result [24]. However, sensitivity can be improved to up to 94% by sonication of the device [15, 16]. CIEDs can become infected during procedures of implantation or replacement, or become haematogenously infected in the case of a bacteraemia due to another infection. Staphylococci are able to build biofilms on surfaces of foreign bodies such as CIEDs. Once formed, the biofilm mechanically traps bacteria, which – in a dormant phase – are resistant to killing by antibiotics acting via inhibition of cell wall biosynthesis, such as beta-lactam antibiotics [25]. Therefore, patients with infection of a CIED treated with antibiotic therapy alone have a high relapse rate and an increased risk of dying compared with patients in whom the CIED was removed. Thus, the CIED, including leads, should be removed in the event of CIED infection, and appropriate antibiotic therapy should be administered for up to 6 weeks in the case of CIED infective endocarditis [17]. Usually, the hardware can be completely removed percutaneously, but with significant retained hardware after attempts to remove it percutaneously, open thoracic surgery can be necessary [10, 17]. Although major complications of transvenous lead extractions are rare, heart perforation and procedural death can occur [26].

Risk factors for CIED infections

Risk factors can be related to patients, to devices, to procedural characteristics, and to microorganisms. Table 1 gives an overview of the results of studies identifying risk factors for CIED infection. The most important risk factors are diabetes mellitus, renal and heart failure, corticosteroid use, oral anticoagulation, fever within 24 hours before the procedure and leucocytosis, ICD compared with PM, lack of antibiotic prophylaxis, and postoperative haematoma and other wound complications. Other risk factors are younger age, male sex, haemodialysis, chronic lung disease, cerebrovascular disease, presence of a prosthetic heart valve, history of previous CIED procedures and CIED infections, immunomodulatory therapy, generator change or upgrade compared with a first implantation, dual- or triple-chamber compared with a single chamber device, cardiac resynchronisation therapy (CRT) including defibrillation function compared with CRT with pacemaker function only, epicardial leads and number of leads, use of povidone-iodine instead of chlorhexidine-alcohol as topical antiseptic, temporary pacing wire, postoperative lead dislodgement, early reintervention because of adverse events, duration of hospitalisation, and centres and operators with a low volume of implants [27–44]. Patients who have an ICD or pacemaker implanted at centres with a low procedural volume are more likely to have an adverse event such as haematoma or lead dislodgement than patients who undergo these procedures at high-volume centres [45, 46]. A case-control study including 30 patients compared PM- with ICD-patients suffering from *Staphylococcus aureus* bacteraemia (SAB) from a primary source unrelated to the CIED: patients with an ICD were more likely to develop an infection of their CIED than patients with a PM (81.8% vs 18.2%) [47]. Another study analysing 62 patients with SAB in the presence of a CIED found that 22 (35.5%) patients had a CIED infection. A total of 60% of patients with an ICD had a CIED infection, compared with 24% of patients with a PM [48]. In contrast to bacteraemia with Gram-positive bacteria, CIED infection with Gram-negative bacteraemia is rare: of 49 CIED-patients with a Gram-negative bacteraemia, only 2 (4%) had a definite generator pocket site infection [49]. The higher risk of ICD and Gram-positive bacteraemia for infection was also shown in a population-based study, in which the ICD infection rate was 8.9 (95% confidence interval [CI] 4.2–18.6) per 1,000 device years compared with 1.0 (95% CI 0.5–2.2) per 1,000 device years in patients with a PM. CIED infection occurred in 12 of 22 (55%) *Staphylococcus aureus* bacteraemias compared with 3 of 25 Gram-negative bacteraemias ($p = 0.004$) [50]. Finally, devices wrapped with an expanded polytetrafluoroethylene sheet for prevention of local allergic reactions were more likely to become infected: from 11 devices, 3 became infected during a mean follow-up of 46 months [51].

Prevention of CIED infections

Table 2 gives an overview of prevention strategies. First, patients for implantation or replacement of CIED should be carefully selected according to the indications for implantation of a CIED, and the implantation of unnecessary hardware should be avoided [52, 53]. In patients with signs of systemic infection such as fever or leucocytosis, implantation of a CIED should be postponed, because fever within 24 hours before implantation and leucocytosis is a risk factor for CIED infection [32, 33]. Since central venous catheters are a risk factor for Gram-positive and Gram-negative bacteraemia [54], they should be removed before CIED implantation whenever possible. If a patient has limited subcutaneous tissue and is at increased risk for erosion, a retropectoral pocket should be considered [17]. Procedures should be done in an adequately ventilated operating theatre. To remove hair, only electronic clippers should be used [39].

Second, preoperative antibiotic prophylaxis has been proven effective for the prevention of CIED infections in several studies. From a Danish register of patients with a PM, a retrospective study identified the lack of antibiotic prophylaxis as a risk factor for PM infection [34]. However, the antibiotics used were not specified in this study. A retrospective single-centre study found that antibiotic prophylaxis prior to PM implantation had a protective effect (odds ratio [OR] 0.087, 95% CI 0.016–0.48). In this study, cefazolin (in 90% of the cases) or vancomycin were used [29]. A prospective observational multicentre study analysing risk factors for PM and ICD infections found that antibiotic prophylaxis, mostly with beta-lactam antibiotics, was negatively correlated with infection (OR 0.4, 95% CI 0.18–0.86) [33]. However, the timing of application was not specified in these studies. A meta-analysis of randomised trials from 1998 including seven studies with a total of 2,023 patients who received oxacillin, flucloxacillin, cefazolin or cefazedone as antibiotic prophylaxis found a protective effect (OR 0.256, 95% CI 0.1–0.656, $p = 0.0046$) [55]. However, every single study included in this meta-

Table 1: Risk factors for cardiovascular implantable electronic device (CIED) infection.

Risk factor	OR (95% CI)*	Study
Renal disease (CrCl <60 ml/min) High creatinine (Cr ≥1.5 mg/dl) Age Male sex Heart failure Diabetes mellitus Warfarin use Generator exchange	4.8 (2.1–10.7) 4.6 (1.9–10.6) 2.28 (1.3–3.8) 2.26 (1.4–3.8) 2.35 (1.2–4.4) 3.22 (1.5–6.7) 2.76 (1.4–5.4) 2.21 (1.0–4.8)	Bloom et al. 2006. Retrospective single-centre study, univariate analysis, 4,856 PM and ICD patients, infection rate 1.5% [27].
Diabetes mellitus Heart disease Simultaneous other procedure Two leads	3.5 (1.03–12.97) 3.12 (1.13–8.69) 2.23 (0.77–6.45) 4.07 (1.23–13.47)	Herce et al. 2013. Retrospective single-centre study, multivariate analysis, 2,496 patients with 2,868 procedures, infection rate 1.4% per patient [28].
Corticosteroid use Presence of >2 leads vs 2 leads Antibiotic prophylaxis	13.9 (1.27–151.7) 5.41 (1.44–20.29) 0.087 (0.016–0.48	Sohail et al. 2007. Retrospective single-centre study, multivariate analysis, 29 case patients and 58 matched control subjects with PMs [29].
Age >60 years Generator replacement Antibiotic prophylaxis Risk factor for systemic infection: Femoral venous catheter	2.5 (1.2–4.0) 3.8 (1.5–5.5) 0.5 (0.4–0.8) 2.8 (1.2–4.0)	Cengiz et al. 2010. Retrospective single-centre study from Turkey, multivariate analysis of 57 patients with CIED infections and 833 controls, infection rate 2.45% [37].
Previous valvular surgery Cerebrovascular disease Chronic lung disease Renal failure or dialysis Device upgrade, malfunction Adverse events (haematoma, lead dislocation) Warfarin use	1.53 (1.38–1.69) 1.17 (1.08–1.28) 1.22 (1.26–1.31) 1.34 (1.12–1.60) 1.35 (1.20–1.53) 2.69 (2.30–3.15) 1.16 (1.06–1.26)	Prutkin et al. 2014. Registry study, multivariate analysis, 200,909 ICD patients, infection rate 1.7% (CRT/ICD 2%, dual chamber 1.5%, single chamber device 1.4%) [30].
Immunomodulator therapy Haemodialysis Fever Malaise Signs of infection at pocket Leucocytosis	3.79 (1.10–13.04) 3.24 (1.39–7.55) 3.78 (1.93–7.40) 1.87 (1.02–3.41) 0.19 (0.10–0.36) 3.61 (1.51–8.62)	Le et al. 2011. Retrospective single-centre study comparing patients with CIED infective endocarditis (n = 93) with patients with a CIED infection without endocarditis (n = 323), multivariate analysis [32].
Device revision Renal dysfunction (GFR <60 ml/min) Oral anticoagulation	3.6 (1.51–8.96) 4.64 (1.48–14.62) 2.83 (1.20–6.68)	Lekkerker et al. 2008. Nested case-control study of 75 patients with CIED infections and 75 matched controls. Infection rate was 2.2% [57].
Early onset (≤6 months) infection: – Epicardial lead placement – Postoperative wound complication Late onset (>6 months) infection: – COPD Duration of hospitalisation – 1 day – 2 days – ≥3 days	 9.67 (1.13–453.3) 27.22 (4.40–infinity) 9.82 (1.32–infinity) 1 33.11 (4.79–infinity) 49.04 (8.30–infinity)	Sohail et al. 2011. Retrospective single centre study including 68 patients with an ICD infection and 136 matched controls, multivariate analysis [31].
Fever 24 h before procedure Temporary pacing wire *De novo* implantation Antibiotic prophylaxis Early reintervention for haematoma or lead dislodgement	5.83 (2.00–16.98) 2.46 (1.09–5.13) 0.46 (0.24–0.87) 0.40 (0.18–0.86) 15.04 (6.70–33.73)	Klug et al. 2007. Prospective multicentre study including 6,319 CIED recipients, with an infection rate of 0.68% after 12 months. Antibiotics for prophylaxis were mostly beta-lactam antibiotics [33].
Infection later than 365 days, HR (95% CI) Female sex, HR (95% CI) Age, HR (95% CI) 20–49 60–69 70–79 80–89 ≥90 No antibiotic prophylaxis, HR (95% CI) DDD pacing mode, HR (95% CI) Prior procedures, HR (95% CI) 1 2 3 4	0.35 (0.17–0.61) 0.67 (0.57–0.8) 1 0.62 (0.47–0.83) 0.44 (0.34–0.59 0.29 (0.21–0.39) 0.31 (0.06–0.30) 2.27 (1.76–2.91) 1.49 (1.07–2.08) 2.74 (2.27–2.31) 3.76 (2.78–5.08) 5.49 (3.71–8.13) 8.68 (3.63–20.8)	Johansen et al. 2011. Population-based study with all Danish patients with a PM from 1982 to 2007 (n = 46,299), multivariate analysis, infection incidence 1.82 per 1,000 PM years after first implantation, 5.32 per 1,000 PM years after replacement [34].

Male sex, adjusted HR (95% CI) Age, adjusted HR (95% CI) <20 20–49 50–59 60–69 70–79 ≥80 Number of previous CIED infections, adjusted HR (95% CI) 1 2 >3 Replacement, adjusted HR (95% CI) High volume centre (>200 per year), adjusted HR (95% CI)	1.68 (1.37–2.05) 1.84 (1.02–3.32) 1 1.16 (0.77–1.76) 0.58 (0.38–0.86 0.59 (0.41–0.87) 0.60 (0.40–0.90 1.32 (0.96–1.81) 2.86 (1.77–4.61) 3.79 (2.16–6.64) 1.97 (1.54–2.52) 0.54 (0.36–0.80)	Lin et al. 2014. Population-based study including all Taiwanese patients with a CIED from 1997 to 2010 (n = 40,608), Cox proportional hazard analysis, infection rate 2.45 per 1.000 CIED-years [42].
Age Biventricular device	0.96 (0.94–0.98) 7.57 (2.4–23.7)	Margey et al. 2010. Retrospective single-centre study including 39 CIED infections, infection rate 1.25%. Multivariate analysis [38].
Abdominal device New implant New leads placed	5.5 (1.6–19.3) 0.3 (0.1–0.8) 0.2 (0.1–0.6)	Marschall et al. 2007. Unmatched 1:3 case-control single-centre study including 19 surgical site infections with pacemaker or ICD procedures [44].
More than one procedure	4.7 (2.1–10.6)	Catanchin et al. 2007. Retrospective single centre study including 1,481 procedures and 24 CIED infections, infection rate 1.6% [43].
Haematoma	6.72 (1.32–34.04)	De Oliveira et al. 2009. Randomised controlled trial to compare cafazolin 1 g with placebo for prophylaxis. Included were 649 patients. Multivariate analysis [56].
Physician with a low volume of implants	2.47 (1.18–5.17)	Al-Kathib et al. 2005. Retrospective study analysing Medicare files including 9,853 patients and 1,672 physicians who implanted ICDs [36].
Risk factor for CIED infective endocarditis: ICD vs PM Presence of prosthetic heart valve	 13.3 (2.1–84.9) 6.8 (1.1–43.4)	Uslan et al. 2010. Retrospective single.centre study including 62 patients with an CIED and *Staphylococcus aureus* bacteraemia, of whom 22 (36%) had CIED infection (12 with endocarditis). 12 of 20 (60%) ICD patients (60%) vs 10 of 42 (24%) PM patients had CIED infections. Univariate analysis [48].
ICD vs PM	12.6 (10.8–14.4)	Obeid et al. 2012. Retrospective single centre study including 30 CIED patients with *Staphylococcus aureus* bacteraemia from a primary focus other than the CIED. 9 out of 11 (81.8%) ICDs vs 2 out of 11 (18.2%) PMs got infected. Univariate analysis [47].
Infection rate ICD vs PM per 1,000 device years Infection, *Staphylococcus* bacteraemia vs Gram negative bacteraemia, n (%)	8.9 (95% CI 4.2–18.6) vs 1.0 (95% CI 0.5–2.2) p <0.001 12 of 22 (55%) vs 3 of 25 (12%), p = 0.004	Uslan et al. 2007. Retrospective population-based study including 1,524 patients with CIEDs [50].
Haematoma, infection vs no infection, n (%) Povidone-iodine, infection vs no infection, n (%)	5 of 22 (22.7%) vs 17 of 1722 (0.98%) 13 of 22 (59.1%) vs 764 of 1722 (44.4%) p = 0.003	Uslan et al. 2012. Prospective multicentre study including 1,744 patients in 72 sites undergoing CIED replacement. Infection rate was 1.3% [35].
Device replacement vs new implant, % Prior lead dislodgement, % Dual/triple chamber vs single, %	56% vs 27%, p = 0.007 24% vs 7%, p = 0.02 72% vs 43%, p=0.038	Nery et al. 2010. Retrospective single-centre study including 24 patients with CIED infections and 72 controls, infection rate 1%, univariate analysis [39]
Dialysis, HR (95% CI) Procedure time, HR (95% CI) Reintervention, HR (95% CI) CRT-D vs CRT-PM, HR (95% CI)	13.39 (2.73–65.62) 1.03 (1.01–1.05) 7.99 (1.83–34.98) 10.45 (1.75–62.45)	Romeyer-Bouchard et al. 2010. Single-centre study including 316 patient with CRT, of whom 13 developed infection. Multivariate analysis [40].
COPD, HR (95% CI) Device replacement, HR (95% CI)	2.18 (1.00–4.75) 2.04 (1.1–4.09)	Landolina et al. 2011. Multicentre study including 3,253 CRT-D patients, of whom 30 had an infection, infection rate 1% per year [41].

*If not otherwise indicated, the numbers represent odds ratio (OR) and 95% confidence interval (CI).
COPD = chronic obstructive pulmonary disease; CrCl = creatinine clearance; CRT = cardiac resynchronisation therapy; CRT-D = CRT with defibrillation function; CRT-PM = CRT pacemaker without defibrillation function; GFR = glomerular filtration rate; HR = hazard ratio; ICD = implantable cardioverter defibrillator; PM = pacemaker

analysis was not powered enough to show a significant difference itself. Finally, in a randomised controlled double-blinded single-centre trial from Brazil in 2009, a single dose of 1 g cefazolin or placebo was given immediately before the surgical procedure. The study was terminated by the safety committee after 26.5 months because of a significant difference in the infection rate between the two groups (11 of 335 [3.28%] receiving placebo vs 2 of 314 [0.64%] receiving cefazolin, p = 0.016) [56]. The effect of antibiotic prophylaxis was also demonstrated in 2012 by a meta-analysis of studies in which mostly beta-lactams were used (risk ratio 0.13, 95% CI 0.05–0.36) [58]. American guidelines recommend prophylaxis with an antibiotic that has *in-vitro* activity against staphylococci: cefazolin should be given 1 hour before the start of the procedure. If vancomycin is used – in centres with a high prevalence of oxacillin-resistant staphylococci – it should be given 90 to 120 minutes before the start of the procedure [17]. British guidelines recommend teicoplanin as the first-line agent so that CNS and meticillin-resistant *Staphylococcus aureus*

(MRSA) are covered, with or without gentamicin depending on local Gram-negative infection rates because it can be given as a bolus rather than a longer infusion as in the case of vancomycin [59]. But no studies evaluated teicoplanin as prophylaxis for CIED infections, and teicoplanin was inferior to cefazolin in the setting of cardiac surgery in preventing deep and superficial surgical site infections; postoperative urinary tract infection and tracheobronchitis was more common in the teicoplanin group. Moreover, all bacteraemias in the teicoplanin group were caused by *Staphylococcus epidermidis*, a known causative pathogen of CIED infections. This was shown in a multicentre randomised double-blind study performed in Canada. The authors state that teicoplanin is highly protein bound, drug concentration levels are low in presternal subcutaneous fat, and is more slowly bactericidal compared with beta-lactams, which could be the reason for inferiority [60]. In contrast, vancomycin was not inferior or even superior to cefazolin in cardiac and neuro-surgery: in a double-blind randomised trial including 321 cardiac surgery patients and performed in the USA, there were 3.7% surgical site infections in the vancomycin group versus 12.3% in the cefazolin group [61]. In a recent prospective cohort study from Israel including 2,637 patients undergoing cardiac surgery, surgical site infection rate was similar in the cefazolin and vancomycin group [62]. In another study analysing patients undergoing cerebrospinal shunt placement in an Italian hospital with a high prevalence of MRSA, shunt infections were significantly less likely in patients on vancomycin than on cefazolin prophylaxis (4% vs 14%) [63]. However, there are no studies that compare vancomycin with cefazolin in prevention of CIED infections. The importance of timing of antibiotic prophylaxis was shown by a study evaluating the association of timing of prophylactic 1.5 g cefuroxime prior to surgery with rates of surgical site infection. Multivariable logistic regression showed a significant increase of infection rates when cefuroxime was administered less than 30 minutes (adjusted OR 1.95, 95% CI 1.4–2.8) or 60 to 120 minutes (adjusted OR 1.74, 95% CI 1.0–2.9) before incision as compared with the reference interval of 30 to 59 minutes [64]. However, there are no such studies in the setting of CIED procedures.

Antibiotic prophylaxis for invasive procedures at distant sites in patients with a CIED in place is not recommended, since no reports on haematogenic CIED infections from dental, gastrointestinal, genitourinary, dermatological or other sites have been published. Moreover, staphylococci infrequently cause transient bacteraemia related to these procedures. Furthermore, no data support the prophylactic administration of antibiotics postoperatively [1, 17].

Third, the use of local antiseptics has been studied with mixed results. Use of povidone-iodine as a preoperative topical antiseptic was associated with more CIED infections than chlorhexidine in one large database [35]. This is in line with a randomised multi-centre trial that compared povidone-iodine with chlorhexidine-alcohol for surgical site antisepsis in 849 subjects undergoing abdominal, thoracic, gynaecological or urological surgery. The overall rate of surgical-site infections was significantly lower in the chlorhexidine-alcohol group than in the povidone-iodine group (9.5% vs 16.1%, p = 0.004); a limitation was that no CIED procedures were included in the study [63]. In contrast, a retrospective analysis from the Cleveland Clinic that was very recently published demonstrated no difference in CIED infection rates in 2,792 patients who underwent either chlorhexidine-alcohol or povidine-iodine skin preparation [66]. Despite these latter findings, chlorhexidine-alcohol is currently preferred to povidone-iodine [59]. The use of topical antibiotics after wound closure did not show significant benefit in a randomised placebo-controlled single-centre trial comparing povidone-iodine ointment, neomycin ointment, nonadherent pad and non-antibiotic, non-antiseptic placebo maintained for 72 hours after wound closure [67].

Fourth, double-gloving was effective in reducing the incidence of postoperative shunt infections in neurosurgical patients by 50% [68]. Thus, double-gloving might also be effective in the prevention of CIED infections, but no studies exist in this setting to date.

Fifth, postoperative haematoma and oral anticoagulation were identified as risk factors for CIED infection [27, 30, 35, 37, 56, 57]. Thus, efforts to reduce the occurrence of postoperative haematoma should be made. A recent study randomised patients with a high risk for thromboembolism receiving therapy with warfarin into two patient groups. One continued warfarin treatment; the other bridged anticoagulation therapy with heparin during CIED surgery. Clinically significant device-pocket haematomas occurred more often in the heparin-bridging group (54 of 338; 16%) compared with the continued-warfarin group (12 of 343; 3.5%, relative risk 0.19, 95% CI 0.1–0.36). Major surgical and thromboembolic complications were rare and did not differ between the two groups [69]. Thus, high-risk patients for thromboembolism (i.e., mechanical valve: mitral valve replacement, two or more mechanical valves, non-bileaflet aortic valve replacement, aortic valve replacement with other risk factors for thromboembolism; nonvalvular atrial fibrillation: prior stroke or embolic event, cardiac thrombus, CHADS2 score ≥4; venous thromboembolism within the previous 3 months or severe thrombophilia [70]) in whom anticoagulation cannot be interrupted, should continue oral anticoagulation, and should not be bridged with heparin. The higher risk of bleeding was also shown in another study, in which bridging with low-molecular-weight heparin (LMWH) was associated with development of haematoma, and the avoidance of LMWH was associated with a reduction in haematoma rates [71]. however, there are no studies including CIED surgery patients treated with new oral anticoagulants. There are several interventions that have been used to prevent haematomas during procedure, although there are no data: bleeding sites can be meticulously cauterised. The application of topical thrombin to stop bleeding may be helpful. Irrigation of the pocket is useful to remove debris and may reveal bleeding. The use of a monofilament suture for closure of the subcuticular layer and a pressure dressing applied for 12 to 24 hours after skin closure may further decrease the risk of haematoma formation [17].

Thus, extensive training in surgical techniques, including pocket formation and wound management to diminish the risk of complications, is an important component of electrophysiology fellowship programmes [1].

Sixth, local application of antibiotics has been advocated. Packing the pocket with antibiotic-soaked sponges to provide tamponade while leads are being placed has been done, but not systematically studied. Also, irrigation with an antimicrobial-containing solution for pocket cleansing has been used. An antibacterial mesh envelope (Aigis™) was approved in 2008 by the USA Food and Drug Administration. Two types of this mesh are available, a resorbable and a nonresorbable type. It can be placed in the device pocket prior to closure and elutes rifampin and minocycline for 7–10 days, providing surgical site coverage. One multicentre observational study enrolled consecutively 621 high-risk patients for infection who received Aigis™. During a mean follow up of 1.9 months, 3 (0.48%) infections were recorded [72]. In a retrospective study including patients with ≥2 risk factors for CIED infection, 1 of 260 (0.4%) in the Aigis™ group vs 19 of 639 (3%) in the control group developed an infection within a minimum follow up of 90 days [73]. Another retrospective single-centre study compared a cohort of patients who received a CIED before with the cohort who received the device after the implementation of Aigis™. Within a follow-up of 6 months, infection occurred in 25 of 1,651 (1.5%) before vs 8 of 1,240 (0.6%) after the introduction of Aigis™. However, in only 275 (22%) patients was Aigis™ applied [74]. Preliminary data from a combined cohort of the two ongoing prospective trials with patients with a generator change comparing infection rates with published controls and with case-matched controls (Citadel and Centurion) show low infection rates of 0.1% (1 of 1,000 patients with Aigis™) after 90 days and 0.2% after 180 days [75]. Thus, antibacterial mesh envelopes might be an effective method for reducing infection rates, and their use in high-risk patients might be expected after publication of the final results of the Citadel and Centurion trials. It will be important also to evaluate the impact, if any, of antibacterial mesh envelopes on the selection of antibiotic resistance among infecting and colonising bacteria.

Seventh, an *in-vitro* study showed that *Staphylococcus epidermidis* biofilm formation can be decreased by inhibiting the attachment of bacterial cells to trimethylsilane (TMS)-coated surfaces of stainless steel and titanium alloy during the early phase of biofilm development. Moreover, this research group discovered that bacterial cells on TMS-coated surfaces were more susceptible to antibiotics than their counterparts in biofilms on uncoated surfaces. These findings suggest that TMS-coating could result in a surface that is resistant to biofilm development [76]. Thus, coated CIED-surfaces to prevent CIED infections should be evaluated clinically in future.

Finally, the implementation of infection prevention programmes at institutions did reduce the rate of CIED infections. After implementation of an infection control protocol including MRSA screening, antibiotic prophylaxis, double-gloving, chlorhexidine-alcohol instead of povidone-iodine as topical antiseptic, hair removal using electrical clippers, use of teicoplanin and gentamycin as prophylaxis in high-risk patients, glycaemic control, antibacterial vicryl sutures for subcutaneous closure, surgical scrubbing, diathermy, deferral of the procedure in patients with fever or signs of infection, closed venous system intravenous access canulas, body temperature control, and wound dressing, a significant reduction in CIED infections could be achieved within 1 year in one institution in London (1.3% vs 0.6%, $p < 0.01$) [77]. At another institution, infection rates could be lowered from 4.2% to 0% after the implementation of an infection control programme [78].

Areas of uncertainty

In institutions with a high prevalence of oxacillin-resistant staphylococci, especially CNS and MRSA, an active antibiotic such as vancomycin or teicoplanin can be considered as first-line prophylactic agent. However, in contrast to cefazolin, there are no studies that evaluated the effect of vancomycin or teicoplanin to prevent CIED infections. In the case of cephalosporin and glycopeptides allergy, daptomycin or linezolid are considered to be prophylactic options [17]. But, although there is one study that found daptomycin to be a useful antibiotic to treat CIED infective endocarditis [79], there are no studies that evaluated daptomycin or linezolid as prophylactic agents. Although chlorhexidine-alcohol was superior to povidone-iodine, and double-gloving prevented infections in surgical settings [65, 68], these strategies have not been evaluated prospectively for CIED procedures. However, it might be assumed that they are also effective in the prevention of CIED infections. Although the preliminary data of the protective effect of antibacterial mesh envelopes are promising, the results of the two large prospective trials with

Table 2: Strategies for prevention of CIED infections.

Selection of patients	Procedure should be postponed if patients present with signs of infection such as fever or leucocytosis.
Selection of hardware	Careful selection of appropriate device and avoidance of unnecessary hardware
Place of procedure	Procedure should be performed in an operating theatre.
Performing operator	Physicians performing procedures should be adequately trained. Double-gloving should be considered. Other procedures performed simultaneously should be avoided.
Antibiotic prophylaxis	Cefazolin 1 hour before start of procedure In the case of high prevalence of oxacillin resistant staphylococci: Vancomycin 90 to 120 minutes before or Teicoplanin 1 hour before start of procedure
Skin preparation	Electronic clippers to remove hair. Use of chlorhexidine-alcohol as topical antiseptic.
Application of local antibiotics	The use of antibacterial mesh envelopes may be considered in high-risk patients.
Prevention of haematoma	If oral anticoagulation cannot be interrupted in high-risk patients for thromboembolism, oral anticoagulation should be continued, and bridging with heparin should be avoided.
Revision in the case of adverse events	Early reintervention in case of haematoma or lead dislodgement should be avoided
Infection prevention programmes	The implementation of infection prevention programmes reduces infection rates.

a follow-up of 12 months should be awaited before their routine use. However, these studies are not randomised controlled trials. *In-vivo* studies are required to evaluate the effect of coated device surfaces.

In conclusion, CIED infections are a burden on patients and healthcare systems, and can be prevented by antibiotic prophylaxis and by procedure-related strategies. More randomised controlled studies are needed to evaluate prevention strategies, especially skin preparation and antibiotic prophylaxis with glycopeptides.

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