Infection control in implantation of cardiac implantable electronic devices: current evidence, controversial points, and unresolved issues

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A significant increase in the implantation of cardiac implantable electronic devices (CIEDs) is evident over the past years, while there is evidence for a disproportionate increase in CIED-related infections. The cumulative probability of device infection seems to be higher in implantable cardioverter defibrillator and in cardiac resynchronization therapy patients compared with permanent pacemaker patients. Given that more than a half of CIED infections are possibly related to the operative procedure, there is a need for effective periprocedural infection control. However, many of the current recommendations are empirical and not evidence-based, while questions, unresolved issues, and conflicting evidence arise. The perioperative systemic use of antibiotics confers significant benefit in prevention of CIED infections. However, there are no conclusive data regarding the specific value of each agent in different clinical settings, the value of post-operative antibiotic treatment as well as the optimal duration of therapy. The merit of local pocket irrigation with antibiotic and/or antiseptic agents remains unproved. Of note, recent evidence indicates that the application of antibacterial envelopes into the device pocket markedly decreases the infection risk. In addition, limited reports on strict integrated infection control protocols show a dramatic reduction in infection rates in this setting and therefore deserve further attention. Finally, the relative impact of particular factors on the infection risk, including the type of the CIED, patients’ individual characteristics and comorbidities, should be further examined since it may facilitate the development of tailored prophylactic interventions for each patient.

Keywords
Pacemakers • Implantable cardioverter-defibrillators • Arrhythmia devices • Complications • Infection • Prevention

More than 50 years after the first permanent pacemaker (PPM) implantation, we witness the continuous development and growing clinical application of implantable devices in a wide range of heart rhythm disorders.1–5 Apart from the conventional use of PPMs for the management of bradycardia, more sophisticated devices are increasingly used for cardiac resynchronization therapy (CRT) in heart failure, while the implantable cardioverter defibrillator (ICD) has become established as the most effective treatment against malignant arrhythmias and sudden cardiac death.3,6

Data on temporal trends of implantation rates are sparse, but there have clearly been considerable increases over past decades. A recent population-based study showed that the adjusted implantation incidence rates of PPMs increased 2.7-fold over 30 years.7 Despite significant heterogeneity between different European countries, the implantation of cardiac implantable electronic devices (CIEDs), and especially CRT systems, has substantially increased in the past few years.8 Besides the increase in pacing systems, virtually all countries show a significant rise in the use of ICDs as well.9 Potential factors that possibly contribute to the increase in implantation rates of CIEDs include aging of the population, advances in device technology, and the growing number of evidence-based indications.7–9 There is, however, an underuse of ICDs in Europe compared with the USA.8,9

Device-related infections: a growing problem

CIED-related infection represents a devastating complication with a challenging and often difficult management.10–14 Current
recommendations advocate a therapeutic approach of complete removal of the system (generator and leads) and antimicrobial therapy followed, in the majority of cases, by reimplantation at a remote site after some time period.\textsuperscript{10–13} Although older studies had reported remarkably high incidence of device-related infections, current data indicate that the mean incidence of PPM infection is 0.1–0.7% and that of ICD 0.7–1.2%.\textsuperscript{10,15} Of note, a large population-based study of patients with CIEDs reported an incidence of definitive device infection (local signs of inflammation, erosion, or endocarditis plus confirmation from culture samples or gram stain) of 1.9/1000 device-years.\textsuperscript{16} Specifically, the incidence of ICD infection was 8.9/1000 device-years and that of PPM infection 1.0/1000 device-years.\textsuperscript{16} A more recent large Danish cohort reported an incidence rate of 4.82/1000 device-years after first implantation of a pacemaker and 12.12/1000 device-years after pacemaker replacement.\textsuperscript{17} However, a greater incidence of infections has been observed after CRT system implantation (1.7% per year).\textsuperscript{18,19} In keeping with these findings, a recent nationwide study from the USA showed an annual incidence of CIED infections (between 1998 and 2008) in the range of 1.6%.\textsuperscript{20} Notably, a European survey showed great variation in CIED infection rates across different centres.\textsuperscript{15} Specifically, 27% of centres reported infection incidence <0.5%, while 22% of them reported an incidence of >2%.\textsuperscript{21} Most investigators concur that infections occurring within 1 year of implantation are probably due to contamination at the time of surgery, while those occurring thereafter may be due to manipulation of the device such as generator change or due to a blood-borne infection. It has been demonstrated that 25% of CIED infections occur early (0–28 days after device placement), 33% late (29–364 days after device placement), and 42% delayed (>364 days after the device placement).\textsuperscript{22} More recent evidence supports this view showing that 45% of patients with CIED pocket infection presented more than 12 months after their last procedure.\textsuperscript{23} These data imply that more than a half of CIED infections are related to the operative procedure. Interestingly, Sohlai et al. demonstrated a significant difference in the median time from implantation to infection between PPMs and ICDs (415 vs. 125 days, respectively).\textsuperscript{24} An accumulating body of evidence indicates a disproportionate increase in CIED infections compared with implantation rates.\textsuperscript{10,25–27} Potential explanations for this disproportionate increase include increasing comorbidities among CIED recipients, increased survival of patients under contemporary treatments, accomplishment of more complex procedures, and increased awareness and detection of CIED infections.\textsuperscript{15,20–22} Although it seems that the dramatic rise of infections has a temporal relationship with the increase of ICD implantations after the publication of the major primary prevention trials, it remains uncertain whether ICDs implantation per se confers a higher risk of infection than that of PPMs. However, as mentioned above, the cumulative probability of device infection appears to be significantly higher in ICD and CRT patients.\textsuperscript{16,18} Besides the increased complexity of these procedures, this observation could imply underlying differences between the populations of patients.

Taking into account the aforementioned considerations, the implementation of strict and meticulous protocols for prevention of CIED infections is imperative. In general, recommendations from major professional societies and experts have mainly focused on the management and much less on prevention strategies.\textsuperscript{11,12} Very recently, specific guidelines on CIED infections including specific prevention strategies were reported by British scientific societies.\textsuperscript{28} In addition, novel data on this topic are continuously accumulating.\textsuperscript{29–32} However, as will be discussed below, many of the current recommendations are empirical and not evidence-based, while questions, unresolved issues, and conflicting evidence arise.\textsuperscript{33,34}

### Systemic antibiotic prophylaxis in device implantations

Antibiotic administration around the time of CIEDs implantation is a common practice intended to reduce the risk of infection.\textsuperscript{35} The scientific rationale for antibiotic prophylaxis in this setting is well established, but several specific aspects of this practice have not been adequately elucidated. Of note, a meta-analysis published in 1999\textsuperscript{36} included seven prospective randomized trials examining the value of antibiotics in this setting.\textsuperscript{37–43} Six of these studies enrolled 100–500 patients who received either no antibiotic or an anti-staphylococcal β-lactam drug (five studies: flucloxacillin/ cloxacillin; two studies: cephalosporins) for 1–5 days perioperatively. Only one small underpowered study with 106 patients was double blind and placebo-controlled.\textsuperscript{38} Overall, 2023 patients were analysed with follow-up ranging from 1 month to 4 years, although most patients were not monitored for more than 1 year. Where data were available, no differences were found in comorbidities and other potential predisposing factors between the studied groups. In one study,\textsuperscript{39} both groups of patients additionally received intrapocket antibiotics. With regard to the timing of the antibiotic therapy, in six studies the agent was administered intravenously 1 or 2 h before the procedure, whereas in one study commenced immediately after the procedure.\textsuperscript{36} The duration of the therapy also varied from 6 h to 8 days, while in one study only a single dose before implantation was given.\textsuperscript{36} The time interval between implantation and infection was not recorded in two studies, while in the remaining five it ranged from 5 to 356 days. This meta-analysis demonstrated that systemic antibiotic prophylaxis significantly reduces the incidence of serious infective complications after PPM implantation (OR: 0.256).\textsuperscript{36} These findings indicated that the use of antibiotics at the time of implantation may prevent short-term pocket infection, skin erosion, or septicemia.\textsuperscript{36} Therefore, the majority of implanting physicians have adopted this practice. A much more extensive systematic review on the role of antibiotic prophylaxis was performed by Darouiche et al. who analysed 15 studies including 3970 patients.\textsuperscript{44} This analysis examined several other issues such as efficacy of antibiotic agents, timing and routes of administration, and dosages and duration of therapy. It was clearly evident that the antibiotic regimens varied across the studies, while their quality was poor to moderate.\textsuperscript{44} It was demonstrated that perioperative systematic antibiotics delivered within 1 h before the procedure significantly reduced the incidence of infection compared with no antibiotics (RR: 0.13). Also, this strategy was superior to local antisepsics alone and to solely post-operative antibiotic prophylaxis.\textsuperscript{44} In fact, several observational studies further support the role of antibiotic prophylaxis in CIED implantation\textsuperscript{17,45,46} although some contrary results have been published.\textsuperscript{47}
Other approaches in perioperative antimicrobial prophylaxis and infection control

An additional strategy for infection control in CIEDs implantation is local antibiotic irrigation. Several irrigation protocols have been proposed using one or more antibiotics. However, no study to date has examined the efficacy of this approach. Another common practice is the application of a local antiseptic such as povidone–iodine on the wound and into the pocket just before the placement of the generator. Of note, a retrospective observational study of 2564 patients subjected to PPM/ICD implantation showed no difference in the pocket infection rates between those who underwent local povidone–iodine irrigation and those who had saline irrigation (0.7% vs. 0.6%, respectively).46 In a very recent placebo-controlled study, the role of topical antiseptics and antibiotics placed after wound closure was investigated.49 The use of these agents after closure did not show any significant benefit.49

A promising approach that markedly decreases CIED infection risk, especially in high-risk patients, is the utilization of an antibacterial envelope.50 – 52 This absorbable envelope encompasses the device and extravascular parts of the leads releasing antibiotics into the pocket for at least 7 days. Despite the financial cost of this device, it seems to be a cost-effective preventive measure if used wisely in high-risk procedures.50

Apart from antibiotic prophylaxis, it should be stressed that the clean and well-ventilated surgical environment, meticulous skin preparation and disinfection, hand antisepsis, and good surgical technique are considered essential for a favourable outcome. In fact, many specific measures regarding patient, operator, and personnel preparation have been proposed to decrease the infection risk, but relative evidence from clinical studies is lacking.11,28,29 Furthermore, the modulation of other modifiable risk factors should be an integral part of infection prophylaxis. These include avoidance of temporary pacing, measures to reduce the incidence of pocket haematoma, avoidance of heparin bridging in anticoagulated patients, and others.11,28,32 Also, complex procedures such as CRT implantation, system upgrades, and lead revisions should be performed by the most experienced implanters in high-volume centres.11,28,32 However, it should be acknowledged that still many of the known risk factors of CIED infection are not modifiable.32

Integrated protocols for infection control

Intensive multilevel protocols for aggressive infection control in CIED implantations seem to exhibit remarkable effectiveness. Borer et al. studied the impact of a strict infection control programme on the incidence of CIED-associated infections.43 This programme included staff education, pre-operative modification of patient risk factors, intraoperative control of strict aseptic technique, surgical scrubbing and attire, control of environmental risk factors, optimization of antibiotic prophylaxis, post-operative wound care, and active surveillance. Remarkably, following this intervention, a complete and sustained prevention was achieved with no infection cases over the 24-month follow-up period.53 However, it should be noted that the relative impact of each aforementioned measure was not clarified. Very recently, Ahsan et al. applied a new protocol for prevention of CIED infections.31 Specifically, methicillin-resistant Staphylococcus aureus screening was performed, and eradication treatment as well as dual-specific antibiotic treatment was used in these patients. Moreover, tailored antibiotic prophylaxis was applied, namely the high-risk patients received two antibiotics (teicoplanin plus gentamicin). Other measures included meticulous skin preparation using double gloves, improved glycaemic control, the use of antibacterial absorbable sutures, the use of diathermy, meticulous check for signs or markers of infection, specific intravenous cannulas, and intact wound dressings for the first 3 post-operative days.31 This specific protocol led to a 54% reduction in CIED infection incidence.31

Controversial and unresolved issues

Several issues regarding infection control during CIEDs implantation are controversial or remain unresolved. First of all, it is evident that there are some differences in the protocols applied for antibiotic prophylaxis across the various studies. These include the administered agent, the timing and duration of treatment, the trial endpoints, the length of follow-up, and the definition of CIED infection. Most patients in the latter studies received a β-lactam antimicrobial agent such as cefazolin. In this context, most experts recommend cefazolin as a first choice and vancomycin, clindamycin, or other anti-staphylococcal agents as second choices.44 Of note, there are no studies reporting direct comparison of different antibiotic agents. Whether these agents are equally effective in this setting or whether there are disparities in terms of periprocedural and patient characteristics remains unknown. For example, it would be reasonable to assume that in high-risk procedures or in patients with several risk factors for infection to provide more intense antibiotic treatment with more potent agents or a combination of two agents. Interestingly, an in vitro study indicated that nebacetin has the best efficacy to toxicity ratio in prevention of pacemaker infections compared with other antibiotics or antiseptics.54 However, no relative clinical data are available.

With regard to the timing of pre-procedural administration of antibiotics, the vast majority of published protocols adopted the intravenous infusion of the agent 1–2 h before the operation.36,44 It seems that with this practice maximal concentrations during the implantation procedure can be achieved.36,44 However, no study has evaluated the relative merit of different timings of antibiotics administration.

The relative value of post-operative antibiotic prophylaxis is still a matter of debate. According to a recent meta-analysis, perioperative antibiotic treatment is superior to isolated post-operative prophylaxis.44 Also, it is uncertain whether the duration of antibiotic therapy after the operation has any meaningful effect on the incidence of device-related infections. The administration of a single dose of antibiotic prophylaxis seems to be a common practice in many centres since in a recent large population survey this scheme was followed in 61% of the cases.46 Unfortunately, the investigators did not mention
if there was any difference between the patients who received ‘a single dose’ and those who received ‘several doses’.46 Also, in the European Heart Rhythm Association (EHRA), survey data on the post-operative use of antibiotics are not reported.51 Of note, the British guidelines point out that repeat dosing of antibiotics after the operation does not seem to have any benefit and therefore is not recommended.28 In the same context, Italian experts recommend no routine use of prophylactic antibiotics beyond the second dose.29 On the other hand, some device experts suggest continuation of antibiotics for 5 days after the procedure.55 In support of this notion, Senaratne et al. demonstrated that post-operative antibiotic treatment leads to a further significant reduction in CIED infection rates.56 In this observational study, a post-operative oral administration of a single antibiotic agent for 4 days following the intravenous pre-operative administration was compared with a simple scheme of two intravenous doses (one administered 30 min before skin incision and the second administered 8 h after the first).56 Data regarding the ideal duration of post-operative antibiotic treatment are very limited. A small randomized prospective study examined two different durations of antibiotic prophylaxis in 178 patients who underwent a first PPM implantation.57 Specifically, all patients received 2 g cloxacillin 2 h before the procedure and then randomized to a triple therapy of ampicillin, cloxacillin, and gentamycin for 2 or 7 days. After a mean follow-up of 9 months, no significant difference in device-related infections was evident.57

With regard to the surgical technique and associated materials, there is evidence that antimicrobial-coated and non-braded sutures are associated with reduced risk of surgical infections.58,59 However, specific data on CIED-related infections are lacking apart from the aforementioned integrated protocol that applied antibacterial absorbable sutures.60 Moreover, the use of plastic adhesive drapes during the operation did not show any significant benefit in terms of surgical infection risk.60

Local symptoms at the pulse generator area represent the most common manifestation of a CIED-related infection.11,32 However, definition criteria and endpoints vary across studies.34,44 In the PEO-PLE study, the impending or frank erosion without apparent infectious manifestations was not included among infectious complications.60 In keeping with this view, some investigators have proposed stricter criteria, namely microbiological confirmation (positive cultures) using samples from the generator pocket, leads, or blood.42,45 Conversely, in the majority of the published studies erosion or impending erosion is considered equivalent to infection. This concept is reinforced by a study that showed that local symptoms at the site of pacemaker implantation are usually associated with infection of the intravascular part of the leads, with a potential risk of progressing to systemic infection.61 Specifically, the incidence of positive intravascular lead cultures in patients presented with local signs of inflammation, impending erosion, frank erosion, and local infection (purulent collection, abscess, fistula) was 83.3, 76.9, 77.7, and 78.3%, respectively.51 Also, lead vegetations were present in one-fifth of patients with local infection and in one-third of those with chronic draining sinus.62 Another poorly studied issue is the classification of localized superficial infections. In one study, cellulitis limited to the epidermis without pocket involvement was classified as a superficial infection that initially treated with antibiotics for 2 weeks.48 In this context, the British guidelines recommend close observation or oral antibiotic therapy for 7–10 days in cases with early post-implantation superficial inflammation.28

As discussed above, the increased risk for infection of ICDs and CRTs needs further investigation.38,46 Also, a particularly increased incidence of infections reaching the level of 7% in 6 months’ time has been observed in patients who undergo upgrade from a single chamber pacemaker to a CRT device.63 It would be reasonable to speculate that an intensified prophylactic strategy would be of particular value in these patients. The potential role of a more aggressive approach in these patients could be further supported by the observation that the median time from implantation to infection seems to be significantly shorter in these patients compared with PPM patients.42 In addition, patients with ICD and CRT devices usually have more comorbidities. For instance, renal dysfunction, which represents a common comorbidity in heart failure patients, has been associated with an increased risk for infection in patients with CIEDs.26,64 Interestingly, an ongoing randomized trial (PADIT trial) investigates whether an intensive strategy of incremental antibiotics before, during, and after device surgery is better than a control antibiotic strategy of a single pre-operative dose in high-risk patients (repeat CIED procedures or CRT procedures).45

The value of eradication of S. aureus in nasal carriers with regard to CIED infection prophylaxis remains speculative since only evidence from surgical patients is available.32 However, the recently released British guidelines recommend the elimination of S. aureus in colonized patients.28 Also, the protective role of capsulectomy of the old pocket during the time of generator change is questionable since it may increase the risk of pocket haematoma.11,29,32,33 Indeed, very recently a prospective randomized study showed that pocket capsule decortication in patients undergoing device replacement is associated with increased incidence of haematoma with no effect on infection rate.56 Finally, the issue of the antiseptic agent used for skin preparation is still a matter of controversy. In the EHRA survey, 57.8% of centres use povidone–iodine solution and the remaining chlorhexidine solution.51 In the REPLACE registry (patients undergoing CIED replacement), participating centres with infection rates > 5% were more likely to use povidone–iodine for local antisepsis.65 In keeping with these findings, a recent systematic analysis indicated the superiority of chlorhexidine for skin preparation in general surgery.68 However, in a very recent cohort including 2840 CIED procedures, no difference in infection rates was found between povidone–iodine and chlorhexidine groups.69 Also, no difference in infection rates was observed between aqueous and alcoholic povidone–iodine solutions.70 Interestingly, a staged bundled antiseptic skin preparation seems to decrease CIED-related infections.71 This strategy includes application of 75% alcohol over the anterior chest and covering with sterile gauzes after taking a shower on the night before the procedure, povidone–iodine at the incision site 10 min before operation, and standard antiseptic preparation before incision.71

Conclusion

The growing implantations of CIEDs as well as emerging evidence of a disproportionate increase in device-related infections underscore the importance of an effective periprocedural prophylactic strategy. The perioperative systemic use of antibiotic agents
significantly reduces the incidence of infections. However, further studies are needed to elucidate the role of post-operative antibiotic prophylaxis, the specific value of each agent in different clinical settings as well as the optimal duration of therapy. On the contrary, the merit of local pocket irrigation with antibiotic and/or antiseptic agents remains unproven. The application of antibiotic envelopes into the device pocket is very promising especially in high-risk patients. Moreover, limited reports on strict integrated infection control protocols show a dramatic reduction in infection rates in this setting and therefore deserve further attention. Finally, the relative impact of particular factors on the infection risk, including the type of the CIED, patients' individual characteristics and comorbidities, should be further examined since it may facilitate the development of tailored prophylactic interventions for each patient.

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**Authors’ contribution**

P.K.: conception of the idea, literature search, manuscript drafting. S.S.: design of the manuscript, literature search, manuscript critical revision. P.D.: design of the manuscript, literature search, manuscript critical revision. K.G.: interpretation of the published data, manuscript critical revision. J.A.G.: interpretation of the published data, manuscript critical revision.

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