Management of Cardiac Electronic Device Infections: Challenges and Outcomes

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Abstract

Cardiac implantable electronic device (CIED) infection is an increasing problem. Reasons for this are uncertain, but likely relate to an increasing proportion of implantable cardioverter defibrillator (ICD) and cardiac resynchronisation therapy (CRT) devices implanted, as well as implantations in 'higher risk' candidates, i.e. patients with heart failure, diabetes and renal failure. Challenges within the field of CIED infections are multiple with prevention being the most important challenge. Careful prescription of CIED treatment and careful patient preparation before implantation is important. Diagnosis is often difficult and delayed by subtle signs of infection. Treatment of CIED infection includes complete system removal in centres experienced in CIED extraction and prolonged antibiotic therapy. Meticulous planning and preparation before system extraction and later CIED re-implantation is essential for better patient outcome. Future strategies for reducing CIED infection should be tested in sufficiently powered, multicentre, randomised controlled trials.

Keywords

Cardiac implantable electronic device, infection, pacemaker, implantable cardioverter defibrillator, predictors, prevention, management, outcomes

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Cardiac implantable electronic device (CIED) therapy is effective and safe. However, infections related to CIED treatment may have devastating consequences, causing significant morbidity, mortality and generating considerable healthcare costs.^{1–6} Temporal trends in CIED treatment indicate a disproportional increase in CIED infections relative to implantation rates.^{1,7,8} Reasons for this trend are uncertain, but likely relate to increasing proportions of implantable cardioverter defibrillator (ICD) and cardiac resynchronisation therapy (CRT) devices implanted, as well as implantations in 'higher risk' patients, i.e. patients with diabetes, heart failure and renal failure.¹

Challenges within the field of CIED infections are multiple with prevention being the most important one. Diagnosis also poses a challenge with many patients exhibiting only vague symptoms.^{9–12} No international guidelines exist for management of CIED infections; however, an expert consensus statement on lead extractions,¹³ an American Heart Association scientific statement¹⁴ and a British guideline paper¹⁵ are useful for guiding decisions. This review aims to present available data along with identification of challenges and outcomes within the field of CIED infection.

Pathogenesis

Bacterial inoculation often occurs as a result of bacterial colonisation of the operative site at time of CIED implantation. *Staphylococcus* species from the skin, especially, may contaminate the wound, likely during pocket formation, and later cause pocket infection and/or erosion.¹⁶ Most investigators concur that the majority of infections seen within the first year are attributed to this early colonisation and the formation of biofilm on device surfaces. Later, pocket erosion may

also be caused by operative contamination and biofilm formation. Bacteria in biofilm are protected from killing by host defences and antimicrobial agents.¹⁷ Secondary seeding of the CIED may also occur, especially in *Staphylococcus aureus* bacteraemia. Thus, removal of the entire device is necessary when treating CIED infections.

Incidence of Cardiac Implantable Electronic Device Infection

CIED infection rates vary widely depending on definition and follow-up duration. In a large, Danish cohort study, the estimated incidence was 1.82/1,000 device-years and higher within the first 12 months in pacemaker (PM) patients.¹⁸ Infection risk after PM implant is 0.5–1.0 % within the first 6–12 months.^{18–20} With more complex CIED types, infection rates are higher; 0.7–1.2 % in ICD recipients^{21–23} and 1.7–9.5 % in CRT recipients especially with defibrillators (CRT-D).^{24–26} After CIED replacement and system upgrade procedures, infection rates are 2–4 fold higher than after first implant.^{18–21,27–30}

Presentation and Diagnosis

Presentation of CIED infection demonstrates a wide spectrum from subtle complaints of pocket pain to septic shock.^{9,11,12,19,31} The most common presentation of CIED infection is pocket infection, most often seen within the first year.^{4,25,32} Pocket infection, however, may present years later, and any symptom from the CIED pocket should raise suspicion of infection and cause patient referral to a CIED specialist for evaluation. Typical signs are local erythema, warmth, pain and swelling, adherence of skin to device, and erosion of skin with a draining sinus (see *Figure 1*).³³ Erosion is *de facto* infection. Early postoperatively, it may be difficult to distinguish a superficial

Figure 1: Manifestations of Pocket Infections: Adherence Between Skin and Generator (A), Adherence and Perforation (B) and Overt Erosion (C,D)

Table 1: Factors Associated with Increased Cardiac Implantable Electronic Device Infection Risk and Associated Relative Risk

Early CIED re-intervention ^{19,21}	2.7–15.0
Pocket haematoma ^{21,40}	4.0–6.7
CIED replacement ¹⁸	2.7
More complex CIED ^{4,18,21}	1.3–5.4
Temporary pacing ^{4,19}	2.5–5.0
Number of prior CIED procedures ¹⁸	2.7–8.7
Prior CIED infection ³⁷	11.3
Fever/systemic infection ¹⁹	5.8
Renal failure ^{21,37}	1.3
Haemodialysis ³²	8.6
Chronic skin disease ³⁷	10.6
Corticosteroid treatment ⁴	13.9
Chronic obstructive pulmonary disorder ^{21,37}	1.2–9.8
Diabetes ⁸⁵	2.3
Higher Charlson comorbidity index ³⁷	2.7–3.0
Male gender ¹⁸	1.5
Younger age ¹⁸	1.4–4.5
Low operator experience ^{54,55,86}	NA
Longer procedure duration ²⁴	NA

CIED = cardiac implantable electronic device.

wound infection from a pocket infection. Percutaneous puncture with pocket fluid aspiration should be avoided in all cases.

Infection may track along the leads and cause bloodstream infection and/or endocarditis. In any CIED patient with systemic infection without obvious focus, CIED infection should be suspected. Blood cultures should be obtained before initiating antibiotic treatment. Cultures should be taken of the pocket and leads when the device is removed. Bacteria typical for CIED infections include staphylococcal species, corynebacteria or propionibacteria, and growth of these supports the diagnosis of CIED infection. Cultures are negative in 15 % of these cases.¹⁵ Supplementary diagnostics should include transoesophageal echocardiography to visualise leads, valvular involvement and

vegetation,¹⁵ and in some cases 18-fluorodeoxyglucose positron emission tomography (FDG-PET).^{34,35}

Prevention of Cardiac Implantable Electronic Device Infection

CIED infection is a serious and potentially fatal complication for the patient, and in general necessitates complete CIED system removal. Thus, prevention of CIED infection is the most important issue.

Before Implantation

Careful CIED prescription (i.e. evaluation of indication for CIED implantation including appropriate type of CIED) is essential with assessment of risks and benefits, accounting for individual patient characteristics and comorbidities.³⁶ Several patient-related factors are associated with heightened risk of CIED infection, such as age, gender, renal failure, diabetes, respiratory failure, corticosteroid treatment, chronic skin conditions and higher comorbidity index (see *Table 1*). Since these conditions are largely unavoidable, attention should focus on optimisation before CIED implantation. More complex systems have a higher infection risk and potential benefits from these systems should be weighed against lower infection risk with more simple systems.^{4,18,21}

Meticulous pre-operative preparation is necessary. Fever within 24 hours before implant is associated with a 5–6 fold infection risk, and diagnosis and treatment of ongoing infection before implantation is therefore important.³⁶ It is unsettled whether infected patients who need acute cardiac pacing are best managed with initial temporary transvenous pacing or primary permanent CIED implantation. In most cases, temporary pacing is chosen; however, presence of a temporary pacing lead is also associated with a higher infection risk.^{19,37}

Indwelling lines (e.g. central venous catheters and chest tubes) should be removed before CIED implantation. Most operators prefer >24 hours. Chronic skin conditions are associated with a higher infection risk³⁷ and should be appropriately treated before implant.

Peri-operative

General recommendations for reducing surgical site infections should be applied, including antiseptic skin preparation. Use of chlorhexidine-alcohol as an antiseptic reduces surgical site infections compared with povidone-iodine in clean surgery.^{36,38,39} This effect is thought to be related to a faster and more persistent activity despite exposure to bodily fluids during surgery. Use of transparent films, diathermia or substances to prevent bleeding have not proven beneficial.¹⁵

Pre-operative, systemic antibiotic prophylaxis prior to CIED procedures is mandatory. One randomised controlled trial found infection risk reduced to 0.64 % within 6 months with antibiotic prophylaxis versus 3.28 % with placebo.⁴⁰ Observational data and meta-analyses support this finding.^{4,18,19,41,42} Supporting evidence for using topical antibiotics is lacking;⁴³ however, recently a promising development has been introduced. The TYRX™ Envelope is an antibacterial envelope releasing minocycline and rifampin in the generator pocket after CIED implantation. This envelope eliminates staphylococcal species and prevents biofilm formation on implanted pacing devices in animal studies,⁴⁴ and reduces CIED infections in high-risk patients in observational studies.^{45–47} The most recent version is bio-absorbable and disappears within 9 weeks after implantation. In a single-centre observational study including 1,124 high-risk patients, infection

risk was 0.0 % for the bio-absorbable envelope, 0.3 % for the non-absorbable envelope and 3.1 % for controls with minimum follow-up time of 300 days.⁴⁸ The effect of the bio-absorbable envelope is currently investigated in the Worldwide Randomized Antibiotic Envelope Infection Prevention Trial (WRAP-IT NCT02277990, commenced 2015), aiming to enrol 7,764 patients undergoing a high-risk CIED procedure. Widespread use of this envelope should await the results of this ongoing trial.

Choice of antibiotic prophylaxis differs widely, influenced by local burden of methicillin-resistant staphylococci, local preference and tradition. An ongoing randomised trial enrolling 10,800 patients compares single-dose pre-operative antibiotics (cefazolin or vancomycin) with an antibiotic strategy adding intraoperative wound pocket wash (bacitracin) and post-operative cefalexin/cefadroxil/clindamycin for two days.⁴⁹

Prevention of tissue damage with a meticulous surgical technique assuring haemostasis is important. Some authors advocate capsulectomy during CIED replacement procedures to remove avascular tissue. This strategy has, however, not been tested in controlled studies, and capsulectomy may increase haematoma risk, which is associated with a higher infection risk.^{24,36,40} In anticoagulated patients, continued warfarin use is preferred to heparin bridging because of a lower risk of haematoma (odds ratio [OR] 0.19).⁵⁰ Use of clopidogrel and aspirin increases risk, however, treatment is rarely discontinued. How to handle patients treated with one of the new oral anticoagulants is less clear. A conservative approach when managing haematoma is often advisable, unless particularly tense or painful. Even large haematomas gradually soften and resorb over a few weeks.

Re-operation

Early re-operation is probably the strongest risk factor for later CIED infection.^{19,21,24} In a large, Danish cohort study, number of prior CIED procedures was strongly associated with a higher infection risk (see *Figure 2*).¹⁸ Careful CIED prescription is important to avoid early need for system upgrade, and should include estimation of left ventricular function prior to implantation. Attention should be given to reduce anticipated generator replacements with selection of generators with best reported longevity,⁵¹ and with careful programming to increase generator longevity. Evaluation of change in CIED indication at time of generator replacement is advisable (e.g. development of permanent atrial fibrillation or chronic heart failure). Need for CIED upgrade should be evaluated extremely carefully, given the high infection risk.²¹ Use of active fixation leads should be advocated – with due consideration for a suspected minor increased risk of cardiac perforation – to reduce risk of lead dislodgement and need for re-operation.⁵² Appropriate education and reasonable implant volume for each operator should be assured to decrease risk of lead dislodgements, and complications in general, requiring early re-operations.^{20,52–57}

New Advances

The recently introduced leadless PMs⁵⁸ are likely to bear a lower risk of infection than transvenous systems; however, in the event of infection, extraction risk is unknown especially years after implantation. Confirmation of long-term efficacy and safety that is at least non-inferior to traditional PMs in randomised controlled trials is needed before advocating for their widespread utilisation. Currently, no such studies are underway.

Figure 2: Association Between Number of Prior Device Procedures and Infection Risk

Adapted from Johansen, et al., 2011.¹⁸

Subcutaneous ICD systems⁵⁹ do not bear the risk of blood-stream infection or endocarditis seen with traditional transvenous ICD systems. They could be attractive for patients not needing bradycardia or anti-tachycardia pacing and at particularly high risk of CIED infection. It is unlikely that the pocket infection rate is much lower than for traditional PMs. Again, documentation of at least non-inferiority compared with transvenous ICD systems is needed before expanding this treatment to larger patient-groups. The extraction risk, though, is negligible.

Treatment of Cardiac Implantable Electronic Device Infection

Confirmation of CIED infection regardless of systemic or localised to pocket mandates prompt removal of all CIED hardware, and a prolonged course of intravenous antibiotics. Furthermore, a strategy for re-implantation is warranted. However, in cases of minor incisional abscesses, a few days after implantation, a course of antibiotics and careful follow-up may be sufficient.¹⁵

Planning of Treatment

Planning of timely, correct and complete treatment is of the highest importance for better patient prognosis. Partial procedures such as generator removal and capping of leads are associated with an almost invariable relapse^{10,33,60,61} regardless of clinical presentation. General consensus favours percutaneous removal in centres with procedural volume sufficient to maintain operator skills, and with immediate surgical backup.^{13,14,62}

Management of CIED infection is a multidisciplinary task, and may involve many specialists and various imaging techniques.⁶³ Strategy for antibiotic treatment is often directed by an infection disease specialist. Few data exist in this field, but generally, antibiotics are recommended for 10–14 days after pocket infection, 14 days for bacteraemia and 4–6 weeks for endocarditis.¹⁴ Pacemaker-dependent patients pose a particular challenge, and temporary pacing needs careful planning. Heart failure teams should be involved after CRT device removal when anticipating haemodynamic support. All CIED hardware, including abandoned leads, even if contralateral to infected system, must be removed. In preparation, a chest X-ray is important and computerised

tomography (CT)-scans may be used to visualise suspected perforated leads. Transoesophageal or intracardiac^{64,65} echocardiography is an important part of the evaluation.¹⁴ Large vegetations exceeding 2 cm may indicate surgical explants.^{13,31}

Extraction methodology is beyond the scope of this article.

Re-implantation

Plan for re-implantation is advisable before system extraction. CIED indication must be re-evaluated because some arrhythmia problems may have resolved. Observational studies found that 20–40 % of patients were discharged without CIED re-implantation.^{32,66,67} Some patients have developed indication for more complex CIED treatment while others will need no re-implantation at all (e.g. malignancy in patients with prophylactic ICD). When re-implantation is necessary, this should be done on the opposite side of the chest.

Timing of re-implantation must be individualised, with careful attention to an adequate period of antibiotic therapy. Epicardial placement of PM leads may be considered for those at high risk of re-infection or with limited vascular access. Leadless PM and subcutaneous ICD implantation could also be considered for selected patients. A continued dialogue, beginning pre-operatively, among the electrophysiologist, the surgeon and the infection disease specialist, is critical to ensure individual management plans.

Outcomes of Cardiac Implantable Electronic Device Infection

In general, extraction of all CIED hardware is needed for successful treatment of CIED infections. A series without complete device removal have shown that over half of patients demonstrate relapse.^{10,68,69} In a recent study, it was found that the rate of CIED infection after CIED extraction was higher in patients with incomplete lead removal, 13.5 % versus 3.0 %.⁷⁰ In addition, mortality appears higher without complete removal.^{71–73} One study indicated a threefold higher mortality without system removal.⁷⁴

All-cause mortality following CIED infection is considerable, ranging from 6 % to 35 % at 2 years or longer follow-up, although many deaths are not infection-related.^{10,66,70,74–76} In most of these studies, more than 90 % of patients underwent complete CIED removal. Mortality with

endocarditis is reported between 24.5 % and 29.0 %, ^{31,71,77} and CIED infections with endocarditis have a higher mortality than pocket infection.^{3,78} One study found a 6-month mortality of 10.1 % after system removal in patients with small lead vegetations and 18.4 % in patients with large lead vegetations.³¹

System extraction is associated with a small risk of major complications, particularly vascular lacerations causing haemothorax and death.^{32,70,79–82} Extraction-related mortality rates are 0.1–0.8 % in large experienced centres.^{70,83} In one large, single-centre study, including more than 5,000 lead extractions, 43 % of which were due to infection, risk of major complications was 1.8 %, and minor complications 3.6 %. A total of 11 patients died as a result of the procedure.⁸⁴ Complications are typically more frequent in surgical extractions with open heart surgery.³¹

Conclusion

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 infection is prevention. Careful prescription of CIED treatment and careful patient preparation before implantation is important. Diagnosis is often difficult and delayed by subtle signs of infection. Treatment of CIED infection includes complete system removal in centres experienced in CIED extraction and prolonged antibiotic therapy. Meticulous planning and preparation before system extraction and later CIED re-implantation is essential for better patient outcome. Future strategies for reducing CIED infection should be tested in sufficiently powered and well-designed, multicentre, randomised controlled trials. ■

Clinical Perspective

- Cardiac implantable device (CIED) infection is an increasing problem.
- The key challenge in management of CIED infection is prevention.
- Careful CIED prescription and preparation before implantation is important.
- Diagnosis of CIED infection often is difficult due to subtle signs of infection.
- Treatment of CIED infection includes complete system removal and often prolonged antibiotic therapy.

- Greenspon AJ, Patel JD, Lau E, et al. 16-year trends in the infection burden for pacemakers and implantable cardioverter-defibrillators in the United States 1993 to 2008. *J Am Coll Cardiol* 2011;**58**(10):1001–6. DOI: 10.1016/j.jacc.2011.04.033; PMID: 21867833
- Baman TS, Gupta SK, Valle JA, Yamada E. Risk factors for mortality in patients with cardiac device-related infection. *Circ Arrhythm Electrophysiol* 2009;**2**(2):129–34. DOI: 10.1161/CIRCEP.108.816868; PMID: 19808457
- LE KY, Sohail MR, Friedman PA, et al. Clinical predictors of cardiovascular implantable electronic device-related infective endocarditis. *Pacing Clin Electrophysiol* 2011;**34**(4):450–9. DOI: 10.1111/j.1540-8159.2010.02991.x; PMID: 21208230
- Sohail MR, Usulan DZ, Khan AH, et al. Risk factor analysis of permanent pacemaker infection. *Clin Infect Dis* 2007;**45**(2):166–73. DOI: 10.1086/518889; PMID: 17578774
- Sohail MR, Henrikson CA, Braid-Forbes MJ, et al. Mortality and cost associated with cardiovascular implantable electronic device infections. *Arch Intern Med* 2011;**171**(20):1821–8. DOI: 10.1001/archinternmed.2011.441; PMID: 21911623
- Kuehn C, Graf K, Heuer W, et al. Economic implications of infections of implantable cardiac devices in a single institution. *Eur J Cardiothorac Surg* 2010;**37**(4):875–9. DOI: 10.1016/j.ejcts.2009.10.018; PMID: 19939696
- Cabell CH, Heidenreich PA, Chu VH, et al. Increasing rates of cardiac device infections among Medicare beneficiaries: 1990–1999. *Am Heart J* 2004;**147**(4):582–6. DOI: 10.1016/j.ahj.2003.06.005; PMID: 15077071
- Voigt A, Shalaby A, Saba S. Continued Rise in Rates of Cardiovascular Implantable Electronic Device Infections in the United States: Temporal Trends and Causative Insights. *Pacing Clin Electrophysiol* 2010;**33**(4):414–9. DOI: 10.1111/j.1540-8159.2009.02569.x; PMID: 19793359
- Usulan DZ, Sohail MR, St Sauver JL, et al. Permanent pacemaker and implantable cardioverter defibrillator infection: a population-based study. *Arch Intern Med* 2007;**167**(7):669–75. DOI: 10.1001/archinte.167.7.669; PMID: 17420425
- Klug D, Wallet F, Lacroix D, et al. Local symptoms at the site of pacemaker implantation indicate latent systemic infection. *Heart* 2004;**90**(8):882–6. DOI: 10.1136/hrt.2003.010595; PMID: 15253959; PMCID:PMC1768347
- Sohail MR, Usulan DZ, Khan AH, et al. Infective endocarditis complicating permanent pacemaker and implantable cardioverter-defibrillator infection. *Mayo Clin Proc* 2008;**83**(1):46–53. DOI: 10.4065/83.1.46; PMID: 18174000
- Chambers ST. Diagnosis and management of staphylococcal infections of pacemakers and cardiac defibrillators. *Intern Med J* 2005;**35** Suppl 2:S63–71. DOI: 10.1111/j.1444-0903.2005.00980.x; PMID: 16271062
- Wilkoﬀ BL, Love CJ, Byrd CL, et al. Transvenous lead extraction: Heart Rhythm Society expert consensus on facilities, training, indications, and patient management: this document was endorsed by the American Heart Association (AHA). *Heart Rhythm* 2009;**6**(7):1085–104. DOI: 10.1016/j.hrthm.2009.05.020; PMID: 19560098
- Baddour LM, Epstein AE, Erickson CC, et al. Update on cardiovascular implantable electronic device infections and their management: a scientific statement from the American Heart Association. *Circulation* 2010;**121**(3):458–77. DOI: 10.1161/CIRCULATIONAHA.109.192665; PMID: 20048212
- Sandoe JA, Barlow G, Chambers JB, et al. Guidelines for the diagnosis, prevention and management of implantable cardiac electronic device infection. Report of a joint Working Party project on behalf of the British Society for Antimicrobial Chemotherapy (BSAC, host organization), British Heart Rhythm Society (BHRS), British Cardiovascular Society (BCS), British Heart Valve Society (BHVS) and British Society for Echocardiography (BSE). *J Antimicrob Chemother* 2015;**70**(2):325–59. DOI: 10.1093/jac/cku383; PMID: 25355810
- Da Costa A, Lelièvre H, Kirkorian G, et al. Role of the preaxillary flora in pacemaker infections: a prospective study. *Circulation* 1998;**97**(18):1791–5. PMID: 9603533
- del Pozo JL, Patel R. The challenge of treating biofilm-associated bacterial infections. *Clin Pharmacol Ther* 2007;**82**(2):204–9. DOI: 10.1038/sj.cpt.6100247; PMID: 17538551
- Johansen JB, Jørgensen OD, Møller M, et al. Infection after pacemaker implantation: infection rates and risk factors associated with infection in a population-based cohort study of 46299 consecutive patients. *Eur Heart J* 2011;**32**(8):991–8. DOI: 10.1093/eurheartj/ehq497; PMID: 21252172; PMCID:PMC3076667
- Klug D, Balde M, Pavin D, et al. Risk factors related to infections of implanted pacemakers and cardioverter-defibrillators: results of a large prospective study. *Circulation* 2007;**116**(12):1349–55. DOI: 10.1161/CIRCULATIONAHA.106.678664; PMID: 17724263

20. Kirkfeldt RE, Johansen JB, Nohr EA, et al. Complications after cardiac implantable electronic device implantations: an analysis of a complete, nationwide cohort in Denmark. *Eur Heart J* 2014;**35**(18):1186–94. DOI: 10.1093/eurheartj/ehf511; PMID: 24347317; PMCID:PMC4012708
21. Prutkin JM, Reynolds MR, Bao H, et al. Rates of and factors associated with infection in 200 909 Medicare implantable cardioverter-defibrillator implants: results from the National Cardiovascular Data Registry. *Circulation* 2014;**130**(13):1037–43. DOI: 10.1161/CIRCULATIONAHA.114.009081; PMID: 25081281
22. Usilan DZ, Sohail MR, Friedman PA, et al. Frequency of permanent pacemaker or implantable cardioverter-defibrillator infection in patients with gram-negative bacteremia. *Clin Infect Dis* 2006;**43**(6):731–6. DOI: 10.1086/506942; PMID: 16912947
23. Baddour LM, Bettmann MA, Bolger AF, et al. Nonvalvular cardiovascular device-related infections. *Circulation* 2003;**108**(16):2015–31. DOI: 10.1161/01.CIR.0000093201.57771.47; PMID: 14568887
24. Romeyer-Bouchard C, Da Costa A, Dauphinaut V, et al. Prevalence and risk factors related to infections of cardiac resynchronization therapy devices. *Eur Heart J* 2010;**31**(2):203–10. DOI: 10.1093/eurheartj/ehp421; PMID: 19875388
25. Palmisano P, Accogli M, Zaccaria M, et al. Rate, causes, and impact on patient outcome of implantable device complications requiring surgical revision: large population survey from two centres in Italy. *Europace* 2013;**15**(4):531–40. DOI: 10.1093/europace/eus337; PMID: 23407627
26. Unsworth JD, Zaidi A, Hargreaves MR. Increased late complex device infections are determined by cardiac resynchronization therapy-defibrillator infection. *Europace* 2015;**17**(1):1708–11. DOI: 10.1093/europace/euw074; PMID: 25883081
27. Nery PB, Fernandes R, Nair GM, et al. Device-Related Infection Among Patients With Pacemakers and Implantable Defibrillators: Incidence, Risk Factors, and Consequences. *J Cardiovasc Electrophysiol* 2010;**21**(7):786–90. DOI: 10.1111/j.1540-8167.2009.01690.x; PMID: 20102431
28. Catanchin A, Murdock CJ, Athan E. Pacemaker infections: a 10-year experience. *Heart Lung Circ* 2007;**16**(6):434–9. DOI: 10.1016/j.hlc.2007.02.097; PMID: 17420155
29. Lekkerkerker JC, van Nieuwkoop C, Trines SA, et al. Risk factors and time delay associated with cardiac device infections: Leiden device registry. *Heart* 2009;**95**(9):715–20. DOI: 10.1136/hrt.2008.151985; PMID: 19036758
30. Landolina M, Gasparini M, Lunati M, et al. Long-term complications related to biventricular defibrillator implantation: rate of surgical revisions and impact on survival: insights from the Italian Clinical Service Database. *Circulation* 2011;**123**(22):2526–35. DOI: 10.1161/CIRCULATIONAHA.110.015024; PMID: 21576653
31. Greenspon AJ, Le KY, Prutkin JM, et al. Influence of vegetation size on the clinical presentation and outcome of lead-associated endocarditis: results from the MEDIC registry. *JACC Cardiovasc Imaging* 2014;**7**(6):541–9. DOI: 10.1016/j.jcmg.2014.01.015; PMID: 24813965
32. Tarakji KG, Chan EJ, Cantillon DJ, et al. Cardiac implantable electronic device infections: presentation, management, and patient outcomes. *Heart Rhythm* 2010;**7**(8):1043–7. DOI: 10.1016/j.hrthm.2010.05.016; PMID: 20470904
33. Chua JD, Wilkoff BL, Lee I, et al. Diagnosis and management of infections involving implantable electrophysiologic cardiac devices. *Ann Intern Med* 2000;**133**(8):604–8. PMID: 11033588
34. Sarrazin JF, Philippon F, Tessier M, et al. Usefulness of fluorine-18 positron emission tomography/computed tomography for identification of cardiovascular implantable electronic device infections. *J Am Coll Cardiol* 2012;**59**(18):1616–25. DOI: 10.1016/j.jacc.2011.11.059; PMID: 22538331
35. Amraoui S, Tlili G, Sohail M, et al. Contribution of PET Imaging to the Diagnosis of Septic Embolism in Patients With Pacing Lead Endocarditis. *JACC Cardiovasc Imaging* 2016;**9**(3):283–90. DOI: 10.1016/j.jcmg.2015.09.014; PMID: 26897683
36. Usilan DZ, Gleva MJ, Warren DK, et al. Cardiovascular implantable electronic device replacement infections and prevention: results from the REPLACE Registry. *Pacing Clin Electrophysiol* 2012;**35**(1):81–7. DOI: 10.1111/j.1540-8159.2011.03257.x; PMID: 22077194
37. Sohail MR, Hussain S, Le KY, et al. Risk factors associated with early- versus late-onset implantable cardioverter-defibrillator infections. *J Interv Card Electrophysiol* 2011;**31**(2):171–83. DOI: 10.1007/s10840-010-9537-x; PMID: 21365264
38. Dumville JC, McFarlane E, Edwards P, et al. Preoperative skin antiseptics for preventing surgical wound infections after clean surgery. *Cochrane Database Syst Rev* 2013;3:CD003949. DOI: 10.1002/14651858.CD003949.pub3; PMID: 23543526
39. Darouiche RO, Wall MJ Jr, Itani KM, et al. Chlorhexidine-Alcohol versus Povidone-Iodine for Surgical-Site Antisepsis. *N Engl J Med* 2010;**362**(1):18–26. DOI: 10.1056/NEJMoa0810988; PMID: 20054046
40. de Oliveira JC, Martinelli M, Nishioka SA, et al. Efficacy of antibiotic prophylaxis before the implantation of pacemakers and cardioverter-defibrillators: results of a large, prospective, randomized, double-blinded, placebo-controlled trial. *Circ Arrhythm Electrophysiol* 2009;**2**(1):29–34. DOI: 10.1161/CIRCEP.108.795906; PMID: 19808441
41. Da Costa A, Kirkorian G, Chuchrat M, et al. Antibiotic prophylaxis for permanent pacemaker implantation: a meta-analysis. *Circulation* 1998;**97**(18):1796–801. PMID: 9603534
42. Darouiche R, Mosier M, Voigt J. Antibiotics and antiseptics to prevent infection in cardiac rhythm management device implantation surgery. *Pacing Clin Electrophysiol* 2012;**35**(11):1348–60. DOI: 10.1111/j.1540-8159.2012.03506.x
43. Khalighi K, Aung TT, Elmi F. The role of prophylaxis topical antibiotics in cardiac device implantation. *Pacing Clin Electrophysiol* 2014;**37**(3):304–11. DOI: 10.1111/pace.12280; PMID: 24164587
44. Hansen LK, Berg K, Johnson D, et al. Efficacy of local rifampin/minocycline delivery (AIGS(RX)(R)) to eliminate biofilm formation on implanted pacing devices in a rabbit model. *Int J Artif Organs* 2010;**33**(9):627–35. PMID: 20963727
45. Bloom HL, Constantin L, Dan D, et al. Implantation success and infection in cardiovascular implantable electronic device procedures utilizing an antibacterial envelope. *Pacing Clin Electrophysiol* 2011;**34**(2):133–42. DOI: 10.1111/j.1540-8159.2010.02931.x; PMID: 20942819
46. Kolek MJ, Dresen WF, Wells QS, Ellis CR. Use of an antibacterial envelope is associated with reduced cardiac implantable electronic device infections in high-risk patients. *Pacing Clin Electrophysiol* 2013;**36**(3):354–61. DOI: 10.1111/pace.12063; PMID: 23252988; PMCID: PMC3949624
47. Mittal S, Shaw RE, Michel K, et al. Cardiac implantable electronic device infections: incidence, risk factors, and the effect of the AigisRx antibacterial envelope. *Heart Rhythm* 2014;**11**(4):595–601. DOI: 10.1016/j.hrthm.2013.12.013; PMID: 24333543
48. Kolek MJ, Patel NJ, Clair WK, et al. Efficacy of a Bio-Absorbable Antibacterial Envelope to Prevent Cardiac Implantable Electronic Device Infections in High-Risk Subjects. *J Cardiovasc Electrophysiol* 2015;**26**(10):1111–6. DOI: 10.1111/jce.12768; PMID: 26222980; PMCID: PMC4607656
49. Connolly SJ, Philippon F, Longtin Y, et al. Randomized cluster crossover trials for reliable, efficient, comparative effectiveness testing: design of the Prevention of Arrhythmia Device Infection Trial (PADIT). *Can J Cardiol* 2013;**29**(6):652–8. DOI: 10.1016/j.cjca.2013.01.020; PMID: 23702356
50. Birnie DH, Healey JS, Wells GA, et al. Pacemaker or defibrillator surgery without interruption of anticoagulation. *N Engl J Med* 2013;**368**(22):2084–93. DOI: 10.1056/NEJMoa1302946; PMID: 23659733
51. Johansen JB, Nielsen JC, Sandgaard NC. Longevity of implantable cardioverter-defibrillators: still a long way to go. *Europace* 2016;**18**(9):1285–6. DOI: 10.1093/europace/euw029; PMID: 26941342
52. Kirkfeldt RE, Johansen JB, Nohr EA, et al. Risk factors for lead complications in cardiac pacing: A population-based cohort study of 28,860 Danish patients. *Heart Rhythm* 2011;**8**(10):1622–8. DOI: 10.1016/j.hrthm.2011.04.014; PMID: 21699827
53. Freeman JV, Wang Y, Curtis JP, et al. Physician procedure volume and complications of cardioverter-defibrillator implantation. *Circulation* 2012;**125**(1):57–64. DOI: 10.1161/CIRCULATIONAHA.111.046995; PMID: 22095828
54. Al-Khatib SM, Lucas FL, Jollis JG, et al. The relation between patients' outcomes and the volume of cardioverter-defibrillator implantation procedures performed by physicians treating medicare beneficiaries. *J Am Coll Cardiol* 2005;**46**(8):1536–40. DOI: 10.1016/j.jacc.2005.04.063; PMID: 16226180
55. Al-Khatib SM, Greiner MA, Peterson ED, et al. Patient and implanting physician factors associated with mortality and complications after implantable cardioverter-defibrillator implantation, 2002–2005. *Circ Arrhythm Electrophysiol* 2008;**1**(4):240–9. DOI: 10.1161/CIRCEP.108.777888; PMID: 19169382; PMCID: PMC2630252
56. Tobin K, Stewart J, Westveer D, Frumin H. Acute complications of permanent pacemaker implantation: their financial implication and relation to volume and operator experience. *Am J Cardiol* 2000;**85**(6):774–6. A9. PMID: 12000060
57. Eberhardt F, Bode F, Bonnemeier H, et al. Long term complications in single and dual chamber pacing are influenced by surgical experience and patient morbidity. *Heart* 2005;**91**(4):500–6. DOI: 10.1136/hrt.2003.025411; PMCID: PMC1768857
58. Reddy VY, Knops RE, Sperzel J, et al. Permanent leadless cardiac pacing: results of the LEADLESS trial. *Circulation* 2014;**129**(14):1466–71. DOI: 10.1161/CIRCULATIONAHA.113.006987; PMID: 24664277
59. Lambiase PD, Barr C, Theuns DA, et al. Worldwide experience with a totally subcutaneous implantable defibrillator: early results from the EFFORTLESS S-ICD Registry. *Eur Heart J* 2014;**35**(25):1657–65. DOI: 10.1093/eurheartj/ehu112; PMID: 24670710; PMCID: PMC4076663
60. Sohail MR, Usilan DZ, Khan AH, et al. Management and outcome of permanent pacemaker and implantable cardioverter-defibrillator infections. *J Am Coll Cardiol* 2007;**49**(18):1851–9. DOI: 10.1016/j.jacc.2007.01.072; PMID: 17481444
61. Pichlmaier M, Knigina L, Kutschka I, et al. Complete removal as a routine treatment for any cardiovascular implantable electronic device-associated infection. *J Thorac Cardiovasc Surg* 2011;**142**(6):1482–90. DOI: 10.1016/j.jtcvs.2010.11.059; PMID: 21570093
62. Habib G, Lancellotti P, Antunes MJ, et al. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). *Eur Heart J* 2015;**36**(44):3075–128. DOI: 10.1093/eurheartj/ehv319; PMID: 26320109
63. Rizkallah J, Kent W, Kuriachan V, et al. Troubleshooting during a challenging high-risk pacemaker lead extraction: a case report and review of the literature. *BMC Res Notes* 2015;**8**:94. DOI: 10.1186/s13104-015-1034-y
64. Narducci ML, Di Monaco A, Pelargonio G, et al. Presence of 'ghosts' and mortality after transvenous lead extraction. *Europace* 2016; DOI: 10.1093/europace/euw045; PMID: 27025772; epub ahead of press.
65. Narducci ML, Pelargonio G, Russo E, et al. Usefulness of intracardiac echocardiography for the diagnosis of cardiovascular implantable electronic device-related endocarditis. *J Am Coll Cardiol* 2013;**61**(13):1398–405. DOI: 10.1016/j.jacc.2012.12.041; PMID: 23500279
66. Deharo JC, Quatre A, Mancini J, et al. Long-term outcomes following infection of cardiac implantable electronic devices: a prospective matched cohort study. *Heart* 2012;**98**(9):724–31. DOI: 10.1136/heartjnl-2012-301627; PMID: 22523057
67. Bracke FA, Meijer A, van Gelder LM. Lead extraction for device related infections: a single-centre experience. *Europace* 2004;**6**(3):243–7. DOI: 10.1016/j.eupc.2004.01.007; PMID: 15121078
68. Margey R, McCann H, Blake G, et al. Contemporary management of and outcomes from cardiac device related infections. *Europace* 2010;**12**(1):64–70. DOI: 10.1093/europace/eup362; PMID: 19910314
69. del Rio A, Anguera I, Miro JM, et al. Surgical treatment of pacemaker and defibrillator lead endocarditis: the impact of electrode lead extraction on outcome. *Chest* 2003;**124**(4):1451–9. PMID: 14555579
70. Gomes S, Cranney G, Bennett M, Giles R. Long-Term Outcomes Following Transvenous Lead Extraction. *Pacing Clin Electrophysiol* 2016;**39**(4):345–51. DOI: 10.1111/pace.12812; PMID: 26768807
71. Athan E, Chu VH, Tattevin P, et al. Clinical characteristics and outcome of infective endocarditis involving implantable cardiac devices. *JAMA* 2012;**307**(16):1727–35. DOI: 10.1001/jama.2012.497; PMID: 22535857
72. Habib A, Le KY, Baddour LM, et al. Predictors of mortality in patients with cardiovascular implantable electronic device infections. *Am J Cardiol* 2013;**111**(6):874–9. DOI: 10.1016/j.amjcard.2012.11.052; PMID: 23276467
73. Massouire PL, Reuter S, Lafitte S, et al. Pacemaker endocarditis: clinical features and management of 60 consecutive cases. *Pacing Clin Electrophysiol* 2007;**30**(1):12–9. DOI: 10.1111/j.1540-8159.2007.00574.x; PMID: 17241309
74. Le KY, Sohail MR, Friedman PA, et al. Impact of timing of device removal on mortality in patients with cardiovascular implantable electronic device infections. *Heart Rhythm* 2011;**8**(11):1678–85. DOI: 10.1016/j.hrthm.2011.05.015; PMID: 21699855
75. Knigina L, Kühn C, Kutschka I, et al. Treatment of patients with recurrent or persistent infection of cardiac implantable electronic devices. *Europace* 2010;**12**(9):1275–81. DOI: 10.1093/europace/euq192; PMID: 20621894
76. Hamid S, Arujuna A, Ginks M, et al. Pacemaker and defibrillator lead extraction: predictors of mortality during follow-up. *Pacing Clin Electrophysiol* 2010;**33**(2):209–16. DOI: 10.1111/j.1540-8159.2009.02601.x; PMID: 19889182
77. Grammes JA, Schulte CM, Al-Bataineh M, et al. Percutaneous pacemaker and implantable cardioverter-defibrillator lead extraction in 100 patients with intracardiac vegetations defined by transthoracic echocardiogram. *J Am Coll Cardiol* 2010;**55**(9):886–94. DOI: 10.1016/j.jacc.2009.11.034; PMID: 20185039
78. Viganego F, O'Donoghue S, Eldadah Z, et al. Effect of early diagnosis and treatment with percutaneous lead extraction on survival in patients with cardiac device infections. *Am J Cardiol* 2012;**109**(10):1466–71. DOI: 10.1016/j.amjcard.2012.01.360; PMID: 22356796
79. Byrd CL, Wilkoff BL, Love CJ, et al. Intravascular extraction of problematic or infected permanent pacemaker leads: 1994–1996. U.S. Extraction Database, MED Institute. *Pacing Clin Electrophysiol* 1999;**22**(9):1348–57. PMID: 10527016
80. Kennergren C, Bucknall CA, Butter C, et al. Laser-assisted lead extraction: the European experience. *Europace* 2007;**9**(8):651–6. DOI: 10.1093/europace/eum098; PMID: 17597078
81. Maus TM, Shurter J, Nguyen L, et al. Multidisciplinary approach to transvenous lead extraction: a single center's experience. *J Cardiothorac Vasc Anesth* 2015;**29**(2):265–70. DOI: 10.1053/j.jvca.2014.11.010; PMID: 25649700
82. Brunner MP, Cronin EM, Wazni O, et al. Outcomes of patients requiring emergent surgical or endovascular intervention for catastrophic complications during transvenous lead extraction. *Heart Rhythm* 2014;**11**(3):419–25. DOI: 10.1016/j.hrthm.2013.12.004; PMID: 24315967
83. Wazni O, Epstein LM, Carrillo RG, et al. Lead extraction in the contemporary setting: the LExiCon study: an observational retrospective study of consecutive laser lead extractions. *J Am Coll Cardiol* 2010;**55**(6):579–86. DOI: 10.1016/j.jacc.2009.08.070; PMID: 20152562
84. Brunner MP, Cronin EM, Duarte VE, et al. Clinical predictors of adverse patient outcomes in an experience of more than 5000 chronic endovascular pacemaker and defibrillator lead extractions. *Heart Rhythm* 2014;**11**(5):799–805. DOI: 10.1016/j.hrthm.2014.01.016; PMID: 24444444
85. Qintar M, Zardkoohi O, Hammadah M, et al. The impact of changing antiseptic skin preparation agent used for cardiac implantable electronic device (CIED) procedures on the risk of infection. *Pacing Clin Electrophysiol* 2015;**38**(2):240–6. DOI: 10.1111/pace.12514; PMID: 25224666
86. Freeman JV, Wang Y, Curtis JP, et al. The Relation Between Hospital Procedure Volume and Complications of Cardioverter-Defibrillator Implantation From the Implantable Cardioverter-Defibrillator Registry. *J Am Coll Cardiol* 2010;**56**(14):1133–9. DOI: 10.1016/j.jacc.2010.07.007; PMID: 20863954