European Heart Rhythm Association (EHRA) international consensus document on how to prevent, diagnose, and treat cardiac implantable electronic device infections-endorsed by the Heart Rhythm Society (HRS), the Asia Pacific Heart Rhythm Society (APHRS), the Latin American Heart Rhythm Society (LAHRS), International Society for Cardiovascular Infectious Diseases (ISCVID) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS)

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EHRA CONSENSUS PAPER

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Pacemakers, implantable cardiac defibrillators, and cardiac resynchronization therapy devices are potentially life-saving treatments for a number of cardiac conditions, but are not without risk. Most concerning is the risk of a cardiac implantable electronic device (CIED) infection, which is associated with significant morbidity, increased hospitalizations, reduced survival, and increased healthcare costs. Recommended preventive strategies such as administration of intravenous antibiotics before implantation are well recognized. Uncertainties have remained about the role of various preventive, diagnostic, and treatment measures such as skin antiseptics, pocket antibiotic solutions, anti-bacterial envelopes, prolonged antibiotics post-implantation, and others. Guidance on whether to use novel device alternatives expected to be less prone to infections and novel oral anticoagulants is also limited, as are definitions on minimum quality requirements for centres and operators and volumes. Moreover, an international consensus document on management of CIED infections is lacking. The recognition of these issues, the dissemination of results from important randomized trials focusing on prevention of CIED infections, and observed divergences in managing device-related infections as found in an European Heart Rhythm Association worldwide survey, provided a strong incentive for a 2019 International State-of-the-art Consensus document on risk assessment, prevention, diagnosis, and treatment of CIED infections.

Keywords Infection • Endocarditis • Microbiology • Cardiac implantable electronic devices • Implantable cardioverter-defibrillators • Pacemakers • Cardiac resynchronization therapy • Leads • Extraction • Re-implantation • EHRA consensus document

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Introduction

Scope of the consensus document

Pacemakers (PM), implantable cardiac defibrillators (ICDs), and cardiac resynchronization therapy (CRT) devices are life-saving treatments for a number of cardiac conditions. Device-related infection is, however one of the most serious complications of cardiac implantable electronic device (CIED) therapy associated with significant morbidity, mortality, and financial healthcare burden. Although many preventive strategies such as administration of intravenous (i.v.) antibiotic therapy before implantation are well recognized, uncertainties still exist about other regimens. Questions still remain such as the use of CIED alternatives expected to be less prone to infections and how to manage medication, such as anticoagulants during CIED surgery, and the role of minimum quality and volume requirements for centres and operators. The recognition of these gaps in knowledge, reports of new important randomized trials, observed divergences in managing device-related infections,[1] and the lack of international consensus documents specifically focusing on CIED infections provided a strong incentive for a 2019 State-of-the-art Consensus document on risk assessment, prevention, diagnosis, and management of CIED infections. The aim of this document is to describe the current knowledge on the risks for device-related infections and to assist healthcare professionals in their clinical decision making regarding its prevention, diagnosis, and management by providing the latest update of the most effective strategies.

Methodology

This consensus document is an international collaboration among seven professional societies/associations, including the European Heart Rhythm Association (EHRA), the Heart Rhythm Society (HRS), the Asia Pacific Heart Rhythm Society (APHRS), the Latin American Heart Rhythm Society (LAHRS), the European Association for Cardio-Thoracic Surgery (EACTS), the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), and the International Society for Cardiovascular Infectious Diseases (ISCVID). The writing group consisting of 16 Task Force Members, were selected based on their expertise and medical specialty (12 cardiologists with varying subspecialties, 2 infectious disease specialists, 1 imaging specialist, and 1 thoracic surgeon), from 11 countries in 4 continents.

All experts undertook a detailed comprehensive literature search until May 2019 (human research published in English and indexed in major databases such as MEDLINE, EMBASE, the Cochrane Library, and others as required) related to studied patient cohort and CIED infection topics using relevant search terms related to the field and prior guidelines. Systematic reviews of published evidence for management of given conditions and clinical problems were performed. Members were asked to weigh the strength of evidence for or against a particular diagnostic instrument, procedure, or treatment, include estimates of expected health outcomes and assess risk–benefit ratios where data existed. Patient-, device-, and procedure-specific modifiers were considered, as were the results of the international survey on CIED infections conducted for this purpose[1] and of previous registries.[2] Consensus statements were evidence-based, derived primarily from published data and by consensus opinion after thorough deliberations, requiring at least 80% predefined consensus delivered via email by chairs to all expert members for their approval/rejection.

The EHRA user-friendly ranking system, for consensus documents, with 'coloured hearts' providing the current status of the evidence and consequent guidance was used for the coding of the scientific evidence for statements made (*Table 1*). The grading does not have separate levels of evidence, which instead are defined in each of the coloured heart grades. A letter coding 'ROME' defining existing scientific evidence was applied: R for randomized trials, O for observational studies, M for meta-analyses, and E for expert opinion (*Table 1*).

The document was peer-reviewed by official external reviewers representing EHRA, the participating societies, and ESC Committee for Practice Guidelines (CPG). All members of the writing group as well as reviewers have disclosed potential conflicts of interest, at the end of this document.

Since this consensus document includes evidence and expert opinions from various countries and healthcare systems, the medical approaches discussed may include drugs or devices that are not approved by governmental regulatory agencies in all countries. Moreover, the ultimate decision on management must be made by the healthcare provider and the patient in light of individual factors presented.

Background and epidemiology

Over the last decades, there has been a substantial increase in the number and complexity of CIED implantations as a result of expanded indications and progressive aging of the population. Although these devices improve cardiovascular outcomes, they also expose patients to a risk for potential complications.

Infection is one of the most serious complications of CIED therapy and is associated with significant mortality, morbidity, and financial healthcare burden. It is difficult to give a precise rate of CIED infections because of divergent definitions, varied populations, and the range of rates in retrospective and prospective studies. In the Danish registry including 46 299 consecutive patients who underwent pacemaker implantation between 1982 and 2007, the incidence of infection was 4.82/1000 device-years after a primary implantation, and 12.12/1000 device-years after replacement.[3] Greenspon *et al.* found that the incidence of CIED infection in the USA increased from 1.53% in 2004 to 2.41% in 2008[4] and a National Inpatient Sample database study showed an increase from 1.45% to 3.41% ($P < 0.001$) from 2000 through 2012, particularly for CRT devices.[5] Infection rates in prospective observational studies,[6,7] registries[8] and more

recent cross-over cluster PADIT- and randomized WRAP-IT trials,[9,10] were only 0.6–1.3%, as compared to retrospective studies,[11,12] reporting significantly higher rates (2.3–3.4%) in the first year after implantation.

Pathogenesis and microbiology of cardiac implantable electronic device infections

Cardiac implantable electronic device infections occur via two major mechanisms. The most common is contamination of leads and/or pulse generator during implantation or subsequent manipulation.[13] Device erosion late after interventions may either be due to, or result in pocket infection. In either case, contamination and subsequent bacterial colonization result in pocket infection which can spread along the intravascular parts of the leads and progress to systemic infection. The second mechanism is a bloodstream infection.[14] Direct lead seeding can occur during bacteraemia caused by a distant infectious focus, such as a local septic thrombophlebitis, osteomyelitis, pneumonia, surgical site infection, contaminated vascular catheters or bacterial entry via the skin, mouth, gastrointestinal, or urinary tract.

Factors, which play a role in the pathogenesis of CIED infections, can be related to the host, the device, or the microorganism. The patient's own skin flora can be introduced into the wound at the time of skin incision and thereby contaminate the device. Contamination may also occur before implantation via the air in the operating room (both host and staff) or via the hands of anyone handling the device. From a pathophysiological standpoint, device-related factors are those affecting bacterial adherence to the generator or lead and the biofilm formation on these surfaces. Bacterial adherence is facilitated by irregular and hydrophobic surfaces.[15] Of the commonly used polymers, polyvinylchloride and silicone allow better adherence than polytetrafluoroethylene, while polyurethane allows less adherence than polyethylene. Metals also differ in their propensity for bacterial adherence—e.g. titanium has less propensity for bacterial adherence than steel. Normally non-pathogenic microorganisms such as Coagulase-negative Staphylococci (CoNS) may adhere to the CIED and establish a focus of infection. The microorganisms most frequently isolated have been Gram-positive bacteria (70–90%), especially CoNS (37.6% of the isolates) and *Staphylococcus* (S.) *aureus* (30.8%), which are far more prone to adhere to non-biological material than others (*Table 2*).[16,17,19] *Staphylococcus aureus* is the most common cause of bacteraemia and early pocket infections. Altogether, methicillin-resistant staphylococci were isolated in 33.8% of CIED infections (49.4% of all staphylococcal infections),[16] their frequency varied by country, and even hospital.[18,20] Over the past decade the rates of methicillin resistance seem to be greater than those reported earlier.[16] Gram-negative bacteria were isolated in 8.9% while other microbes such as streptococci, anaerobes, and fungi were less often isolated (*Table 2*). Enterobacteriaceae, other Gram-negative rods and fungi were rare (*Table 2*).

Risk factors for cardiac implantable electronic device infection

Risk factors for CIED infection may be divided into patient-related, procedure-related, and device-related factors. These risk factors may

Table 1 Scientific rationale of recommendations

Consensus statement related to a treatment or procedure	Definitions of consensus statement	Statement class	Scientific evidence coding (SEC)	Ref.
Recommended/indicated or 'should do this'	Scientific evidence that a treatment or procedure is beneficial and effective. Requires at least one randomized trial, or is supported by large observational studies and authors' consensus		R	
May be used or recommended	General agreement and/or scientific evidence favour the usefulness/efficacy of a treatment or procedure. May be supported by randomized trials based on small number of patients or not widely applicable		O	
Should NOT be used or recommended	Scientific evidence or general agreement not to use or recommend a treatment or procedure		E	

This categorization for the consensus document should not be considered as being directly similar to that used for official society guideline recommendations which apply a classification (I–III) and level of evidence (A, B, and C) to recommendations.
The 'ROME' coding was applied for each consensus statement, defining existing scientific evidence.
E, expert opinion; M, meta-analyses; O, observational studies; R, randomized trials.

Table 2 Pathogens isolated in patients undergoing interventions for device infection from three large patient cohorts in North America, Europe, and Asia

Pathogen	Percentage of isolates		
	North America[16]	Europe[17]	Asia[18]
Coagulase-negative staphylococci		69	45.2
Methicillin-*resistant*	18.8		
Methicillin-*sensitive*	18.8		
S. aureus		13.8	4.1
Methicillin-*sensitive*	15.8		
Methicillin-*resistant*	15.0		
Streptococcus spp.	2.5		
Enterococcus spp.			
Vancomycin-sensitive	2.8		
Vancomycin-resistant	1.4		
Cutibacterium spp. (previously *Propionibacterium* spp.)		2.5	
Corynebacterium		5	
Gram-negative bacteria	8.9	6.1	9.1
Enterobacteriaceae		3	3.2
Non-fermentative bacilli, incl. *Pseudomonas* spp.		1.5	5.9
Anaerobes	1.6		
Fungi	0.9	1	0.9
Mycobacteria	0.2		

be modifiable or non-modifiable. Identification of modifiable risk factors is important because they may allow for preventive measures to reduce the risk. In patients with non-modifiable risks, alternative approaches may be an option to lower the overall risk. For example, renal dialysis is a non-modifiable patient risk factor. By changing the procedure and/or device and selecting an epicardial or subcutaneous system the risk may be reduced. Several studies have examined large databases for the most common risk factors. A meta-analysis[21] of pooled data including 206 176 patients in 60 studies (of which 21 were prospective and 39 retrospective) is presented in *Table 3*. Other large studies analysing risk factors include device registry data matched with Medicare fee-for-service claims data,[22] the National Inpatient Sample database study with 85 203 device-related infections,[5] and the recent Danish device-cohort study, including 97 750 patients.[23]

A summary of the most important risk factors identified in these trials are listed in *Table 3* (adapted from Polyzos *et al.*[21]) Unfortunately, the importance of risk factors varied from study to study and in some cases findings were contradictory (age as an example).

Of the *patient-related factors*, end-stage renal disease was consistently associated with the highest risk, underscoring the importance of a careful clinical evaluation in these patients. In the meta-analysis risk factors included: end-stage renal disease, renal insufficiency, diabetes mellitus, chronic obstructive pulmonary disease, corticosteroid use, history of previous device infection, malignancy, heart failure, pre-procedural fever, anticoagulant drug use, and skin disorders, but not age or gender.[21] However younger age, along with prior device infection were identified as significant risks in the Danish device-cohort study.[23] Others identified malnutrition (OR 2.44, $P < 0.001$) as a strong risk factor.[5]

Regarding *procedure-related* factors, antibiotic prophylaxis was associated with a 70% relative risk reduction in infection and is now the standard of care.[21] The presence of a haematoma was associated with an approximately nine-fold increased risk of infection. These findings were later confirmed by the prospective BRUISE-CONTROL study, which reported data from 659 patients in whom there was a hazard ratio of infection of 7.7 (95% CI 2.9–20.5; $P < 0.0001$) in case of clinically significant haematoma (requiring surgery and/or resulting in prolonged hospitalization ≥24 h, and/or requiring interruption of anticoagulation), with as many as 11% of these patients developing this complication over 1-year follow-up.[24] Early reoperation for haematoma or lead dislodgement were identified as the strongest risk factors for CIED infection in a device registry data matched with Medicare fee-for-service claims data.[22] Haematoma was also one of the strongest risk factors (OR 2.66, $P < 0.001$) in a National Inpatient Sample database study.[5] Procedure duration was associated with a multifold increased risk of infection, although there was significant heterogeneity in the studies.[21] Data from the Danish device registry[23] showed that compared to procedures lasting <30 min, the relative risk [95% CI] of infection for procedures lasting 60–90, 90–120, or >120 min were 1.54 [1.24–1.91], 1.85 [1.36–2.49], and 2.42 [1.77–3.33], respectively. The same registry identified implantation of CRT and reoperations as high and significant risks.[23] Another study confirmed early lead repositioning as a strong predictor of infection although it is as yet unknown whether delaying the re-intervention would reduce risk.[21] Temporary pacing has also been

Table 3 Pooled effect estimates for potential risk factors predisposing to cardiac implantable electronic device infection

Factor	Prospective + retrospective studies				Prospective studies only			
	Studies (*n*)	Total (*n*)	Pooled estimate	*P*-value	Studies (*n*)	Total (*n*)	Pooled estimate	*P*-value
Patient-related factors								
ESRD[a]	8	3045	8.73 [3.42, 22.31]	0.00001	NA			
History of device infection	4	463	7.84 [1.94, 31.60]	0.004	NA			
Fever prior to implantation	3	6652	4.27 [1.13, 16.12]	0.03	2	6580	5.34 [1.002, 28.43]	0.05
Corticosteroid use	10	3432	3.44 [1.62, 7.32]	0.001	3	1349	2.10 [0.47, 9.32]	0.33
Renal insufficiency[b]	5	2033	3.02 [1.38, 6.64]	0.006	NA			
COPD	6	2810	2.95 [1.78, 4.90]	0.00003	2	2393	2.30 [0.97, 5.48]	0.06
NYHA class ≥ 2	3	2447	2.47 [1.24, 4.91]	0.01	2	2393	2.77 [1.26, 6.05]	0.01
Skin disorders	4	6810	2.46 [1.04, 5.80]	0.04	2	6519	2.60 [0.88, 7.70]	0.08
Malignancy	6	1555	2.23 [1.26, 3.95]	0.006	NA			
Diabetes mellitus	18	11839	2.08 [1.62, 2.67]	<0.000001	7	9815	1.88 [1.19, 2.98]	0.007
Heparin bridging	2	6373	1.87 [1.03, 3.41]	0.04	NA			
CHF	6	1277	1.65 [1.14, 2.39]	0.008	NA			
Oral anticoagulants	9	8527	1.59 [1.01, 2.48]	0.04	3	7271	1.18 [0.44, 3.11]	0.75
Procedure-related factors								
Procedure duration	9	4850	9.89 [0.52, 19.25]	0.04	6	4508	13.04 [-0.64, 26.73]	0.06
Haematoma	12	14228	8.46 [4.01, 17.86]	<0.000001	6	9715	9.33 [2.84, 30.69]	0.0002
Lead repositioning	5	1755	6.37 [2.93, 13.82]	0.000003	4	1659	7.03 [2.49, 19.85]	0.0002
Inexperienced operator[c]	2	1715	2.85 [1.23, 6.58]	0.01	2	1715	2.85 [1.23, 6.58]	0.01
Temporary pacing	10	10683	2.31 [1.36, 3.92]	0.002	4	8683	3.29 [1.87, 5.80]	0.00004
Device replacement/revision/upgrade	26	21214	1.98 [1.46, 2.70]	0.00001	8	8793	0.95 [0.49, 1.87]	0.89
Generator change	20	12134	1.74 [1.22, 2.49]	0.002	6	2139	0.91 [0.37, 2.22]	0.83
Antibiotic prophylaxis	16	14166	0.32 [0.18, 0.55][d]	0.00005	11	10864	0.29 [0.13, 0.63]	0.002
Device-related factors								
Epicardial leads	3	623	8.09 [3.46, 18.92]	0.000001	NA			
Abdominal pocket	7	4017	4.01 [2.48, 6.49]	<0.000001	2	2268	5.03 [1.96, 12.91]	0.0008
≥2 leads	6	1146	2.02 [1.11, 3.69]	0.02	NA			
Dual-chamber device	14	45224	1.45 [1.02, 2.05]	0.04	7	12102	1.28 [0.73, 2.25]	0.38

Risk parameters which were statistically significant for retrospective and prospective data are shown. Analyses restricted to prospective data only for the same parameters (if available) are also shown. Adapted from Polyzos *et al.*[21]

CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; NA, not available; NYHA, New York Heart Association.

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

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

[c]<100 previous procedures.

[d]The pooled effect estimate from randomized studies was 0.26 [0.13, 0.52].

shown to increase the risk of infection[21] (and carries a risk of perforation/tamponade). This may be due to deviations in sterility measures due to urgent placement, need for lead re-manipulation and simply as a chronic portal of entry to the bloodstream. Indication for temporary transvenous pacing should therefore be carefully considered, and alternative measures such as backup transthoracic pacing or infusion of rate-accelerating drugs evaluated. Device generator replacement roughly doubles the risk of infection, possibly due to activation of pre-existing bacterial colonization or reduced penetration of antibiotics into the encapsulated generator pocket.[21] As with any procedure, experience has an impact on outcome,[25] and risk of infection may be increased by allocating generator changes to inexperienced operators.

There are fewer *device-related* factors for CIED infection. After restricting analysis to prospective studies, an abdominal pocket was the only significant risk factor,[21] although factors such as patient profile and type of intervention may have confounded the results. Data from the Danish registry[23] showed that device complexity and the numbers of leads were factors significantly associated with increased infection risk on multivariate analysis with a HR of 1.26, 1.67, and 2.22 for ICD, CRT-P, and CRT-D systems, respectively as compared to PMs ($P \leq 0.002$ for all comparisons).

Risk stratification

Considering that CIED infections occur in the presence of multiple host and procedure-related factors, risk scores have been developed to identify patients at low and high risk. Scoring systems could play a role in better identifying patients at risk than individual factors, especially considering the inconsistency of the reported factors in various studies.

A single centre study of 2891 ICD or CRT-D recipients identified a novel composite score of 7 independent risk factors for infection and defined patients as low (1% risk), medium (3.4%), and high (11.1%) risk for infection.[26] Related to its moderate predictive range, the model has not been adopted for risk stratification. Another study identified 10 preoperative risk factors associated with CIED infection for a risk score system that defined score <1 as low risk (1%) and ≥3 as high risk (infection rate 2.4%).[27] Despite the potential practical use of such risk scores, they can currently not be recommended because the evidence behind them remains weak.

Prevention

A summary of recommended preventive measures is shown in *Table 4*. A flowchart that indicates how modifiable risk factors can be minimized on various levels is shown in *Figure 1*.

Pre-procedural measures

Patient selection

The best treatment of device-related infections is prevention. Careful consideration should be given to whether the risks of device implantation, in any individual patient, outweighs the benefit. If there is a significant risk of infection delay of implantation for a period of observation or longer-term antibiotic treatment might be of value. For patients undergoing device removal for infection, one-third to one-half may not require device re-implantation.[38] If the decision is to proceed with an implantation, it is important to 'think before you choose'. Avoiding a transvenous system, and implanting an epicardial system, may be preferential in high-risk patients.[39] There is hope that 'leadless' pacemakers will be less prone to infection and can be used in a similar manner in high-risk patients.[40,41] Subcutaneous ICDs (S-ICD) are an option in patients requiring sudden death protection without requiring pacing. Decisions must be made on an individual basis, weighing all known risks and benefits.

Lead management

The number of leads and the presence of abandoned leads are associated with increased risk for complications, including infection. The decision to abandon or extract a lead can be complex and must be made on an individual basis weighing all known risks and benefits. The increased risk of infection, and increased risk of extraction if an infection occurs, must be considered in this decision.[42,43]

Patient factors

In patients who have fever or signs of active infection, a procedure should be delayed until a patient has been afebrile for at least 24 h.[28] The need for temporary pacing wires increases the risk of infection and should be avoided if possible.[28] Temporary pacing via a jugular route may provide a lower risk of infection than groin access, although this remains to be proven. Studies have demonstrated that better glycaemic control in the peri-procedural period may reduce infections in surgical patients.[44]

Anticoagulation and antiplatelet drugs

The development of a pocket haematoma increases the risk for infection.[24] Studies have demonstrated that a 'bridging' approach with anticoagulation increases the risk of haematoma and is no longer recommended.[30] In patients who are not at high risk for thrombo-embolic events (e.g. CHA_2DS_2VASc score <4), holding anticoagulation for the procedure and restarting when the bleeding risk is reduced seems prudent. In higher-risk patients, such as those with prior embolic event or mechanical valve, continuing anticoagulation with Warfarin is recommended. Preliminary data from the BRUISE-Control 2 study suggests the same may be true for non-vitamin K antagonist oral anticoagulants.[29] Therapeutic low-molecular-weight-heparin (LMWH) should be avoided.[30,32,33] Antiplatelet agents, especially P2Y12 inhibitors (clopidogrel, prasugrel, ticagrelor) significantly increase the risk for bleeding and should (unless clearly indicated) preferably be discontinued for 5–10 days before the intervention, especially if they are combined with oral anticoagulation.[31]

Appropriate environment

Both in operating rooms and Electrophysiology/Catheterization laboratories, the standards for sterile procedures (e.g. cleaning, room design, ventilation, limitation of area traffic, etc.) must be met as for other surgical procedures associated with implants. Minimum standards for the environment for CIED procedures have been published.[41] It is recommended that each centre set up a continuous surveillance program of their infection rates and flora involved. Data must be correlated with patient, procedure, staff, and device information (*Table 4*).

Staff training

All staff involved in CIED implantation must be trained in appropriate strict sterile techniques and behaviour in an operating room setting (scrubbing, set up of tables, patient preparation, and strict limitation to room traffic). Operators should be adequately trained[45] and supervised.

Nasal swabs/*S. aureus* decolonization of patients

For elective procedures, *S. aureus* colonization can be detected by nasal swabs. Nasal treatment with mupirocin and chlorhexidine skin washing can reduce colonization and has been shown in some surgical studies to reduce the risk for infection,[46] but there are no studies relating specifically to CIED interventions.

Pre-procedure skin preparation

In many hospitals, pre-surgical washing with an anti-microbial agent is employed. The data on this practice for general surgical procedures are diverse and a recommendation for its routine use therefore can not be strongly supported.[47] If chest hair needs to be removed,

Table 4 List of recommended preventive measures for CIED infections

Consensus statement	Statement class	Scientific evidence coding	References
Pre-procedural measures			
Confirm indication for CIED		E	
Delay CIED implantation in patients with infection		E	28
Avoid temporary transvenous pacing and central venous lines, which should ideally be removed prior to introducing new hardware, whenever possible		O, M	21
Measures to avoid pocket haematoma are recommended (avoid heparin bridging, discontinue antiplatelets if possible)		R	21,29–31
Periprocedural use of therapeutic low-molecular-weight-heparin		R, M, O	30,32,33
Perform the CIED procedure in an operating room/suite with complete sterile environment as required for other surgical implant procedures		E	34
Procedure should be performed or supervised by an operator with sufficient training and experience (*Table 12*)		O	45
Topical *S. aureus* decolonization may be performed		E	
Pre-procedural skin wash may be performed		E	
Hair removal with electric clippers (not razors) is recommended		O	35
Antibiotic prophylaxis is recommended within 1 h of incision for cefazolin and flucloxacilline, within 90-120 min for vancomycin		R, M	21
A continuous surveillance program of infection rates and associated microbiology should be set-up at the level of each implanting centre		E	–
Peri-procedural measures			
Surgical preparation with alcoholic chlorhexidine should be used rather than povidone-iodine		R	36,37
Allow sufficient time for the antiseptic preparation to dry		E	
Adhesive iodophor-impregnated incise drapes may be used		E	
Perform the procedure with adequate surgical technique—minimize tissue damage, haemostasis, adequate wound closure		E	
Antibiotic envelope in high-risk situations is recommended[a]		R	10
If the operator performs the prepping and draping, glove change/re-scrub or remove outer glove of a double-glove before incision		E	

Continued

Table 4 ***Continued***

Consensus statement	Statement class	Scientific evidence coding	References
Using local instillation of antiseptic and antibiotics in the pocket	♥♥	R, E	9
Use of braided sutures for final skin closure	♥♥	E	
Post-procedural measures			
Use of postoperative antibiotic therapy	♥♥	R	9
Adequate dressing for 2–10 days is recommended	♥	E	
Patient instructions on wound care should be provided	♥	E	
Delay or reconsider indication for re-intervention if possible	♥	E	
Haematoma drainage or evacuation (unless tense, wound dehiscence is present or pain is severe)	♥♥	O	24,28

[a]Candidates are those as defined in the WRAP-IT study population[10] (patients undergoing pocket or lead revision, generator replacement, system upgrade, or an initial CRT-D implantation) and patients with other high risk factors as outlined in *Table 3*, considering also the local incidence of CIED infections.
CIED, cardiac implantable electronic device; E, expert opinion; M, meta-analysis; O, observational studies; R, randomized trials.

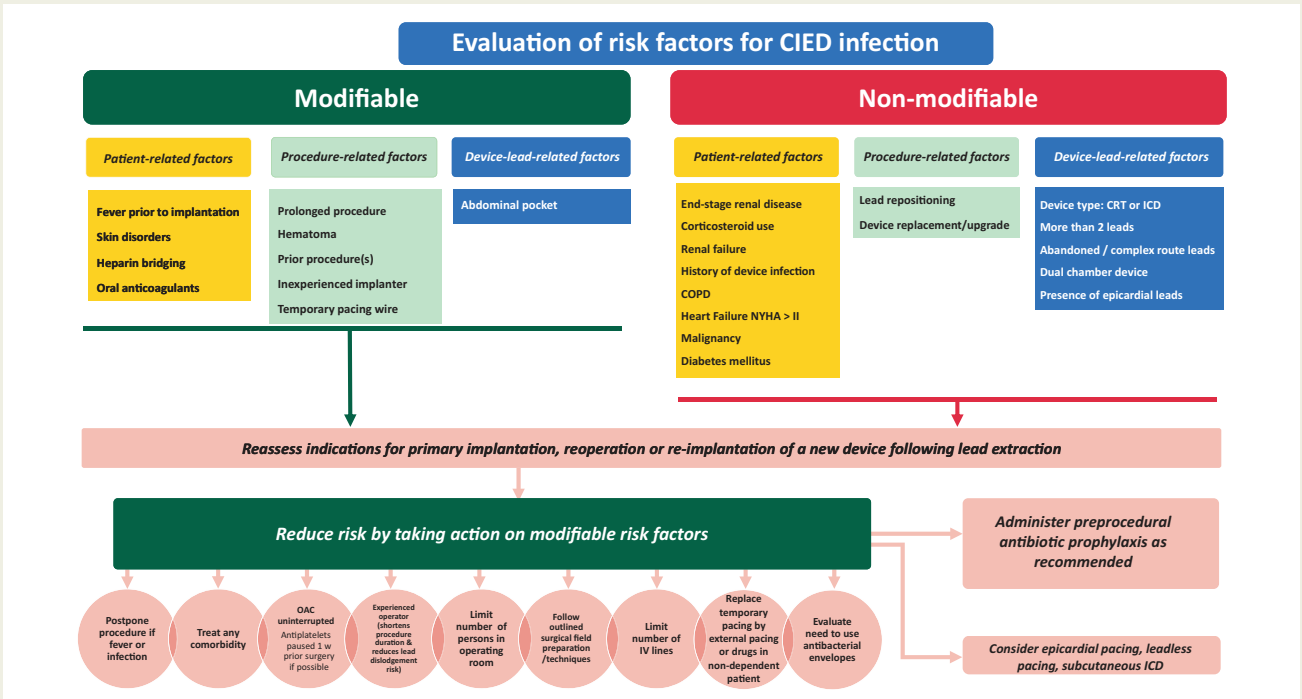

Figure 1 A flowchart indicating how device-related infections can be minimized by targeting modifiable risk factors on various levels. Risk factors ranked in order of strength from top to bottom. CIED, cardiac implantable electronic device; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; ICD, implantable cardiac defibrillator; NYHA, New York Heart Association; OAC, oral anticoagulation; w, week.

electric clippers with a single-use head (and not razors) should be used on the day of the procedure.[35]

Pre-procedure antibiotic therapy

The use of prophylactic systemic antibiotics has been proven to lower infection rates of CIED and is the standard of care.[48,49] It significantly reduces the incidence of device infection, compared with no antibiotic therapy, with a 40–95% relative risk reduction.[21] Antibiotics must be completed within 1 h of incision to ensure adequate tissue levels. *Staphylococcus aureus* is the most common organism involved in acute CIED infections. The degree of methicillin resistance varies. Antibiotics should at least cover *S. aureus* species. Currently, there are no significant data to support routine Methicillin-Resistant *S. Aureus* (MRSA) coverage and its usage should be guided by the prevalence of MRSA in the implanting institution and patient risk. Randomized trials have used i.v. flucloxacillin (1–2 g) and first-generation cephalosporins such as cefazolin (1–2 g).[9,48,49] Vancomycin (15 mg/kg) may be used in case of allergy to cephalosporins and since it should be administered slowly (approximately over 1 h) it needs to be started 90-120 min prior to the incision.

Peri-procedural measures

Patient surgical preparation

Randomized studies have demonstrated alcoholic 2% chlorhexidine to be superior to povidone-iodine (with or without alcohol) for skin preparation prior to surgery[36] or intra-vascular catheter insertion[37] but no randomized data exist regarding CIED implantation. The antiseptic should be allowed to dry completely before incision, in order to provide sufficient time for it to be effective. In addition, alcoholic antiseptic agents may carry a fire hazard with electrocautery, especially if there is pooling. Many operators use adhesive incise drapes, but there is no evidence that it reduces infection rates (and may even increase risk of infection when non-iodophor incise drapes are used[50]).

Good surgical technique

Minimizing tissue damage, strict attention to haemostasis, and adequate wound closure are all important measures to reduce infection. Many operators change gloves (e.g. by double-gloving) when draping the patient and also before handling the generator. Non-powdered gloves may reduce the risk of infection by reducing local inflammation.[51] Pocket haematoma is associated with an increased risk of infection.[24] There are no data supporting the routine use of topical haemostatic agents, although, they may be useful in selected patients. Vigorous pocket irrigation is important to remove devitalized tissue as well as dilute any contaminants.[52] Diagnostic or therapeutic aspiration of a haematoma is contraindicated given the risk of 'inoculating' the pocket and causing an infection.[24,28] Haematoma evacuation should only be undertaken if pain is unmanageable or wound closure is threatened, and should ideally be performed in an operating room.[24]

Antibiotic envelope

An antibacterial mesh envelope [TYRX™, Medtronic, MN, USA] has been developed, which locally releases minocycline and rifampin for a minimum of 7 days to prevent infections and biofilm formation and is fully absorbed in ~9 weeks. The WRAP-IT trial[10] has shown that the envelope significantly reduces the incidence of CIED infection in high-risk patients (undergoing pocket or lead revision, generator replacement, system upgrade, or an initial CRT-D implantation) without a higher incidence of complications. A total of 6983 patients were randomized to receive the envelope or not, with a lower incidence of primary endpoints (infection resulting in system extraction or revision, long-term antibiotic therapy, or death) within 12 months after the CIED implantation in patients who received the envelope vs. controls: 0.7% and 1.2%, respectively (hazard ratio 0.60; 95% confidence interval 0.36–0.98; $P = 0.04$).[10] While the population treated showed benefit, the number of patients needed to treat to prevent one infection was high. The exclusion of higher-risk patients (those treated with immunosuppressive treatments, with vascular access, or on dialysis) may have contributed to a lower-than-expected rate of infections (1.2%) also observed in other prospective studies.[6,7,9] A heightened awareness of infection prevention when participating in prospective trials may also explain such low rates. Higher infection rates (2.3–3.4%), as observed in less-selected retrospective studies,[11,12] would improve the overall cost-effectiveness of the envelope. Recommendation for the use of the antibacterial envelope is outlined in *Table 4*. The use should be individualized based upon presence of risk factors (*Table 3*) and the local incidence of CIED infections.

The use of other 'envelopes' (bioscaffold or pericardium patches) for stabilization, antibiotic soaked gauze, etc. has not been rigorously studied and cannot be supported.

Local instillation of antibiotics or antiseptics

While vigorous pocket irrigation is recommended the use of local installation of an antibiotic or antiseptic is not. The recent PADIT trial demonstrated no benefit (see below).[9]

Capsulectomy

Even in the absence of signs of clinical infections, cultures taken at the time of generator change demonstrate a significant incidence of colonization.[53] In addition, the fibrous capsule inhibits the body's normal defence mechanisms and antibiotic penetration. Theoretically, 'capsulectomy' mitigates these issues but could also result in more pocket bleeding/haematoma, and therefore cannot be recommended as routine practice.[54]

Closure

Wound dehiscence or superficial infection can lead to a frank pocket infection. Closure in layers minimize wound tension and reduces the risk of dehiscence and infection.[55] Skin closure can be with a subcuticular absorbable suture, non-absorbable suture, surgical staples, or surgical adhesive. If non-absorbable material is used, it must be removed in a timely manner when clinically appropriate (usually 7–14 days). Absorbable sutures must be placed with care to allow for absorption and avoidance of a 'stitch abscess' especially at the site of the knot. Although there are no data indicating that the type of suture material impacts the risk of infection, many operators prefer non-

braided monofilament sutures for skin closure as they may avoid bacterial adhesion (see Pathogenesis and microbiology of cardiac implantable electronic device infections section). Some sutures are impregnated with antibiotics, but since there is no evidence that it reduces infection, it cannot be recommended over standard sutures.

Post-procedural measures

Post-procedure antibiotic therapy

Some physicians administer post-implant antibiotics from a single dose to a week i.v. and oral administration.[1] The recent PADIT trial,[9] with its cluster cross-over design, tested the clinical effectiveness of incremental perioperative antibiotics to reduce device infection. The conventional treatment was a single-dose preoperative cefazolin infusion vs. a combination of pre-procedural cefazolin plus vancomycin, intra-procedural bacitracin pocket wash, and 2-day postoperative oral cephalexin in almost 20 000 patients undergoing CIED implantation. The primary outcome of 1-year hospitalization for device infection in the high-risk group was not statistically significant (non-significant 20% reduction of infection). The device infection rates were low. As there are no data supporting this practice, it is not recommended to administer postoperative antibiotic therapy.

Wound care

An appropriate dressing should cover the incision at the end of the operation (except in the case of surgical adhesive). Clinical practice varies with the dressing being left on for 2–10 days. Pressure dressing may be used for the first 24 h to avoid haematoma. It is not necessary to change the dressing, unless it becomes impregnated. Some dressings are waterproof and allow the patient to shower. Patients should be advised to avoid soaking the wound (e.g. by swimming) until it is entirely healed (which usually takes approximately a month). They should also be instructed to seek medical attention in case of signs of local infection.

Re-intervention

It is well known that early re-intervention dramatically increases the risk of infection,[19,21,28] so all measures must be taken to avoid this need (i.e. avoid haematoma, lead dislodgment, etc.). Some operators delay re-intervention by weeks (e.g. for lead repositioning) in an attempt to reduce this risk. This strategy may also alleviate the pain associated with early re-intervention, but further research is needed to determine whether this effectively reduces the risk of infection.

Diagnosis of cardiac implantable electronic device infections and related complications

Clinical findings

A *superficial incisional infection* should be differentiated from a pocket infection, as it involves only the skin and the subcutaneous tissue without communication with the pocket (and hence does not require CIED system extraction).[56,57] Close monitoring of the patient must be pursued in order to recognize early recurrence that may be a sign of a significant pocket infection.

Pocket infection is defined as an infection limited to the generator pocket. It is clinically associated with local signs of inflammation that may be mild and characterized by erythema, warmth, and fluctuation.[14,57] Deformation of the pocket, adherence or threatened erosion are often signs of low grade, indolent infection. Symptoms and signs of an infected surgical wound may fluctuate and although it can be difficult to recognize initially it is not recommended to take a sample of pocket material. Once a wound dehiscence occurs, a purulent drainage or a sinus is established, and a pocket infection is clearly present. If the generator or proximal leads are exposed, the device should be considered infected, irrespective of the results of the microbiology. Material from the pocket may be used for culture, recognizing the potential for contamination. Pocket infections may be associated with lead infections and CIED systemic infections and/or infective endocarditis. The actual rates depend on the definitions used in different studies.[58]

The diagnosis of *CIED systemic infection and infective endocarditis without local infection* may be more challenging (*Table 5*). Symptoms may be non-specific (fever, chills, night sweats) and a long period of time may elapse between CIED implantation and symptom onset as well as diagnosis. Patients with CIED infection may present with embolic involvement of lungs and pleural space, frequently misdiagnosed as pulmonary infections.[61,62] Cardiac implantable electronic device infections may also be revealed by other distant foci as vertebral osteomyelitis and discitis. C-reactive protein (CRP) may be helpful although non-specific and procalcitonin (PCT) test may be of value, especially if positive (≥0.05) due to the high specificity for pocket infection compared to no infection and in case of embolic phenomena and *S. aureus* endocarditis.[63,64]

There is no standardized diagnostic tool for CIED endocarditis. At present, the modified Duke criteria[60] and the ESC 2015 criteria[59] for the diagnosis of infective endocarditis are the only available framework for CIED endocarditis diagnosis. However, none represent a validated and standardized tool for diagnosis in this specific setting. In order to increase sensitivity for CIED infection diagnosis, this panel recommends additional criteria and to merge the modified Duke criteria[60] and the ESC 2015[59] criteria. As a result, the 2019 International CIED Infection Criteria have been developed, and are detailed in *Table 5*.

Identification of the causative microorganisms

Identification of the causative microorganisms for a CIED infection is pivotal for effective antibiotic therapy (*Table 2*). Therefore, every effort should be made to obtain cultures prior to the institution of antibiotic therapy. Blood cultures should be repeated in patients with CIED and fever without clear signs of local infections and infective endocarditis. Three sets of blood cultures should be taken (at least 30 min in between) prior to starting antibiotic therapy (*Table 6*). Multiple blood cultures at different time intervals enable a distinction between transient and persistent bacteraemia and increases sensitivity. In stable patients, a 2–3 days washout period free from antibiotic therapy may increase precision of microbiological diagnosis. In unstable patients with sepsis or septic shock, early empiric antibiotic therapy should be administered following two sets of blood cultures thus not delaying start of antibiotic therapy. Blood bottles must be filled

Table 5 Recommendations for diagnosis of CIED infections and/or infective endocarditis: the Novel 2019 International CIED Infection Criteria

Consensus statement	Statement class	Scientific evidence coding	Reference
'Definite' CIED clinical pocket/generator infection = generator pocket shows swelling, erythema, warmth, pain, and purulent discharge/sinus formation OR deformation of pocket, adherence and threatened erosion OR exposed generator or proximal leads			
'Definite' CIED/IE = presence of either 2 major criteria or 1 major + 3 minor criteria			
'Possible' CIED/IE = presence of either 1 major + 1 minor criteria or 3 minor criteria			
'Rejected' CIED/IE diagnosis = patients who did not meet the aforementioned criteria for IE			
Major criteria		E	59
Microbiology	A. Blood cultures positive for typical microorganisms found in CIED infection and/or IE (*Coagulase-negative staphylococci*, *S. aureus)* B. Microorganisms consistent with IE from 2 separate blood cultures: a. Viridans streptococci, *Streptococcus gallolyticus* (*S. bovis*), HACEK group, *S. aureus*; or b. Community-acquired enterococci, in the absence of a primary focus C. Microorganisms consistent with IE from persistently positive blood cultures: a. ≥2 positive blood cultures of blood samples drawn >12 h apart; or b. All of 3 or a majority of ≥4 separate cultures of blood (first and last samples drawn ≥1 h apart); or c. Single positive blood culture for *Coxiella burnetii* or phase I IgG antibody titre >1:800		
Imaging positive for CIED infections and/or IE	D. Echocardiogram (*including ICE*) positive for: a. CIED infection: i. Clinical pocket/generator infection ii. Lead-vegetation b. Valve IE i. Vegetations ii. Abscess, pseudoaneurysm, intracardiac fistula iii. Valvular perforation or aneurysm iv. New partial dehiscence of prosthetic valve E. [^{18}F]FDG PET/CT (caution should be taken in case of recent implants) or radiolabelled WBC SPECT/CT detection of abnormal activity at pocket/generator site, along leads or at valve site F. Definite paravalvular leakage by cardiac CT		
Minor criteria		E	59
a. Predisposition such as predisposing heart condition (e.g. new onset tricuspid valve regurgitation) or injection drug use			
b. Fever (temperature >38°C)			
c. Vascular phenomena (including those detected only by imaging): major arterial emboli, septic pulmonary embolisms, infectious (mycotic) aneurysm, intracranial haemorrhage, conjunctival haemorrhages, and Janeway's lesions			
d. Microbiological evidence: positive blood culture which does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with IE or pocket culture or leads culture (extracted by non-infected pocket)			

Based on merging of the modified Duke and ESC 2015 Guidelines criteria, see text.[59,60] Green text refers to CIED-related infection criteria.
CIED, cardiac implantable electronic device; CT, computerized tomography; E, expert opinion; ICE, intracardiac echocardiography; IE, infective endocarditis; M, meta-analysis; O, observational studies; R, randomized trials; SPECT, single-photon emission tomography; WBC, white blood cell.

properly in order to increase the sensitivity.[17,65] An aseptic technique for blood culture is mandatory since bacteria mostly considered as skin contaminants often are the causative agents of CIED infections. Every positive blood culture, including a single bottle with CoNS or other Gram-positive organisms, should be carefully evaluated and prompt active exclusion of CIED infection with other diagnostic techniques employed (*Figure 2*).[71] In case of negative blood cultures (usually 5 days), increased incubation time (10–14 days) and the use of biomolecular methods (DNA amplification and/or gene sequencing) to detect fastidious or atypical pathogenes[19] may be considered for CIED endocarditis and persistent negative blood cultures (*Table 6*).[67] Among Gram-positive microorganisms there are species that may require longer period of incubation, such as *Cutibacterium* (previously *Propionibacterium*) *acnes*, especially in anaerobic

Table 6 Recommendations for diagnosis of CIED infections by clinical findings and microbiology

Consensus statement	Statement class	Scientific evidence coding	References
At least three sets of blood cultures should be acquired in case of clinically suspected CIED endocarditis		E, O	19,65
Samples from the pocket should be cultured but only if acquired during removal and not passing through the sinus		E, O	19,65
Suspect CIED infections in case of vertebral osteomyelitis and/or embolic pneumonia (clinical signs and symptoms of CIED systemic infections may be difficult to recognize as only fever may be present)		E, O	61,65
Cultures of extracted CIED should be performed		E, O	66
PCT may be useful in case of infective endocarditis and embolism and/or in case of *S. aureus* CIED-related infective endocarditis		E, O	64
Increased incubation time (10–14 days) for slowly-growing microorganism may be considered in case of CIED-related infective endocarditis and persistent negative blood cultures		E	67
The usefulness of sonication of CIED to enhance microbial detection during removal/extraction is still under evaluation but may be used with caution when interpreting results		E, O	68–70
Cultures from the sinus of the CIED pocket or from parts of the device exposed		E	19

CIED, cardiac implantable electronic device; E, expert opinion; M, meta-analysis; O, observational studies; PCT, procalcitonin; R, randomized trials.

condition.[19] It has been postulated that *S. aureus* may be associated with earlier infections and with infective endocarditis compared to other pathogens, but data are still inconsistent. More severe cases may be due to *S. aureus* and Gram-negative rods.

Swabs collected from the chronic draining sinus or fistula for culture are discouraged (*Table 6*). Instead, tissue or fluid collected from the pocket via an adjacent intact portion of the skin (via a sterile needle or syringe) is encouraged avoiding passing through the sinus. This approach should only be used to make a bacterial diagnosis, not to determine the presence of a pocket infection. Entering an intact pocket should be avoided to avoid inoculation with bacteria.

During an extraction procedure, distal and proximal lead fragments, lead vegetation if present and generator pocket tissue should be sent for culture (*Table 6*).[71] Gram stain is still encouraged and biomolecular methods are increasingly used and may be more specific. Culture media suggested are chocolate agar incubated in 5% CO_2 for 48–72 h, MacConkey agar incubated for 48 h, blood agar in anaerobic condition for 48–72 h, and Sabouraud agar incubated for 5 days.[72,73] A close collaboration with the local Microbiology Laboratory is important to increase diagnostic yield. In case of pus, but no growth after 3 days, consider slow-growing microorganisms including *C. acnes* and increase incubation duration. In addition to swabs, tissue samples and sonication for the recovery of bacteria from CIED leads and tissue, may be useful in patients with clinical signs of infection although the method merits further investigational study.[68–70]

Imaging

Echocardiography

Echocardiography should be the first imaging tool in the assessment of patients with CIED in order to identify lead vegetations and valvular involvement.[59] Transthoracic- (TTE) and transoesophageal echocardiography (TEE) are both recommended in case of suspected CIED infections. While TTE better defines pericardial effusion, ventricular dysfunction, and pulmonary vascular pressure, TEE is superior for the detection and sizing of vegetations[74] especially in the right atrium-superior vena cava area and in regions less well visualized by TTE. In the absence of typical vegetations of measurable size, both TTE and TEE may be false negative in CIED-related infective endocarditis. Lead masses in asymptomatic CIED carriers may be observed on TTE/TEE and do not predict CIED-related infective endocarditis over long-term follow-up.[75,76] Therefore, once a lead mass is identified, careful clinical assessment to rule out either infection or non-bacterial lead-thrombotic endocarditis is needed, including serial TTE/TEE or additional imaging tests.

Intracardiac echocardiography (ICE) is effective and has a high sensitivity for the detection of vegetations in cardiac devices.[77,78] Therefore, a vegetation seen with ICE may be considered a major criterion for diagnosis (*Table 5*). Recently, transvenous biopsy, guided by TEE, was shown to be useful to differentiate vegetation from thrombus.[79]

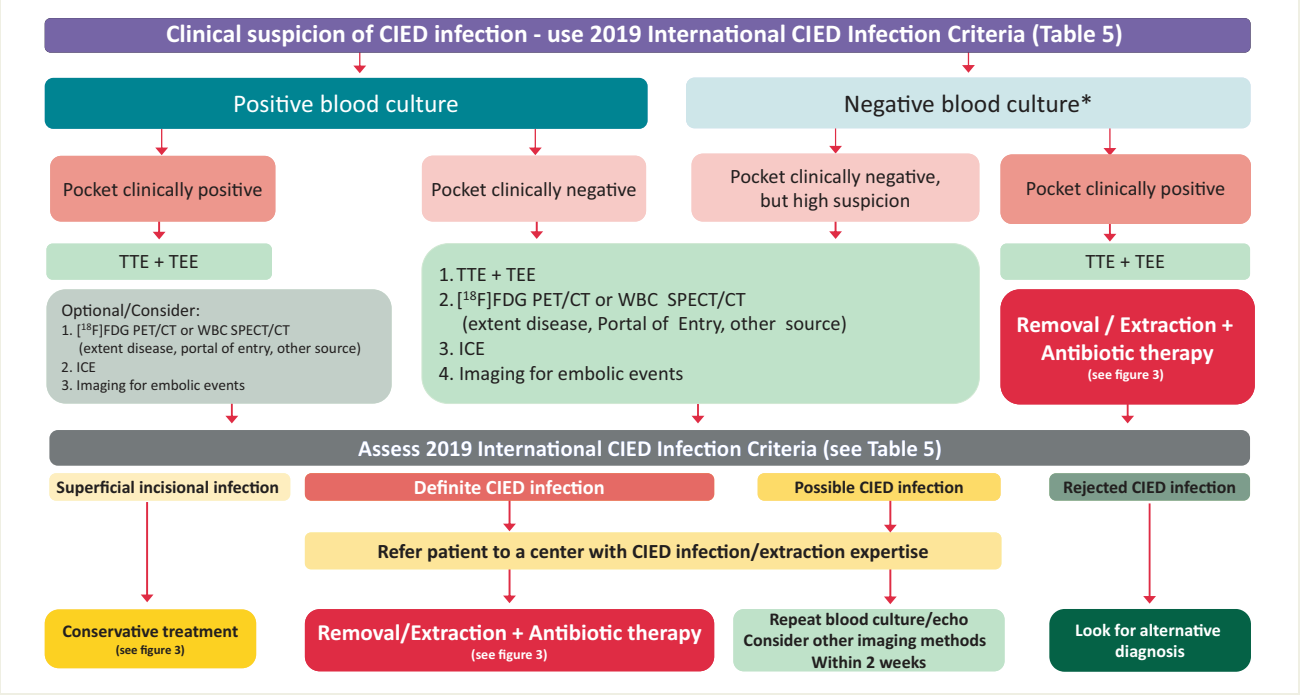

Figure 2 Diagnostic algorithm for diagnosis of suspected CIED infections. *, ensure sufficient number of blood cultures collected and absence of confounding antibiotic therapy prior to cultures. CIED, cardiac implantable electronic device; [^{18}F]FDG PET/CT, fluorodeoxyglucose positron emission tomography—computed tomography; ICE, Intracardiac echocardiography; IE, infective endocarditis, TEE, transoesophageal echocardiography; TTE, transthoracic echocardiography; WBC SPECT/CT, white blood cell single-photon emission computed tomography—computed tomography.

In patients with CIED infections treated with percutaneous lead extraction, a TTE before hospital discharge is recommended to detect retained segments of the pacemaker lead, and to assess tricuspid valve function, right ventricular function, and pulmonary hypertension. A TEE (and additional imaging tests) should be considered after percutaneous lead extraction in order to detect infected material, ghosts,[80] and potential tricuspid valve complications, particularly in patients with persistent sepsis after extraction (*Table 7*). It is important to remember a normal echocardiography does not rule out CIED-related infective endocarditis.

Radiolabelled leucocyte scintigraphy, positron emission tomography, and computerized tomography

Fluorine-18-fludeoxyglucose ([^{18}F]FDG) positron emission tomography/computerized tomography (PET/CT) scanning and radiolabelled leucocyte (WBC) scintigraphy are complementary tools for the diagnosis of CIED-related infections and related complications in complex cases. Both imaging techniques provide additional diagnostic value, particularly in the subset of *possible* CIED infections, and may distinguish between early-onset superficial surgical site infection and a true generator pocket infection or differentiate between superficial and deep pocket infection. When patients only present with systemic infection without local findings at the generator pocket the diagnosis of device lead infection can be challenging and a [^{18}F]FDG PET/CT is in this situation useful for the diagnosis of local infection [pooled specificity and sensitivity of 93% (95% CI 84–98%) and 98% (95% CI 88–100%), respectively, and AUC of 0.98 at ROC analysis].[85,99] Mild inflammatory changes after device implantation usually do not extend beyond 6 weeks and are easily differentiated from infection after this period. White blood cell scintigraphy including single-photon emission tomography/computerized tomography (SPECT/CT) has high sensitivity and specificity for the detection and localization of CIED-related infections (94% and 100%, respectively, in the largest study).[89] In case of CIED-related infective endocarditis, [^{18}F]FDG PET/CT and WBC are very specific when tracer uptake is visualized (only if applied late after implantation), although a negative result does not completely exclude the presence of small vegetations with low metabolic activity (i.e. limited sensitivity and negative predictive value). Therefore, the diagnostic accuracy for lead infections is lower,[99,100] with overall pooled sensitivity of 65% (95% CI 53–76%), specificity of 88% (95% CI 77–94%), and AUC of 0.861.

[^{18}F]FDG PET/CT has the ability of whole-body evaluation, so has proven particularly useful for the identification of unexpected embolic localizations and metastatic infections,[84,88] including mycotic aneurysms, spleen and lung embolisms, and spondylodiscitis (not brain emboli). This impacts the Duke criteria, the diagnostic certainty, and therapeutic management. Moreover, the identification of the infection entry site by PET/CT and WBC imaging is critical for the prevention of infective endocarditis relapse.[90] Positron emission tomography/computerized tomography imaging may also contribute to mortality risk stratification assessment after lead extraction. Patients with definite CIED infection without pocket involvement on [^{18}F]FDG PET/CT had unfavourable outcome, suggesting that the presence of an endovascular infection stemming from an unrecognized/distant site is associated with poor prognosis.[101]

Table 7 Recommendations for diagnosis of CIED infections by imaging[59]

Consensus statement	Statement class	Scientific evidence coding	References
TTE is recommended as the first-line imaging modality in patients with suspected CIED-related IE		O	81
A chest X-ray should be performed in all patients with suspected CIED infection		E	
TEE is recommended in suspected CIED infection with positive or negative blood cultures, independent of TTE results before an extraction, to evaluate CIED infection and IE		O	74
Repeat TTE and/or TEE within 5–7 days is recommended in case of initially negative examination when clinical suspicion of CIED-related IE remains high		O	81
TEE should be performed in CIED patients with *S. aureus* bacteraemia		O	82,83
ICE may be considered if suspected CIED-related IE, with positive blood cultures and negative TTE and TEE results		O, E	77,78
[^{18}F]FDG PET/CT scanning or radiolabelled WBC scintigraphy or contrast enhanced CT are recommended if suspected CIED-related IE, positive blood cultures, and negative echocardiography (attention in imaging interpretation early after device implant)		O, M	84,85
[^{18}F]FDG PET/CT should be performed in case of *S. aureus* bacteremia in CIED patients		O, E	86,87
[^{18}F]FDG PET/CT, radiolabelled WBC scintigraphy and/or contrast enhanced CT is recommended for identification of unexpected embolic localizations (i.e. lung embolism) and metastatic infections		O, M	84,88,89
The identification of the infection portal of entry may be considered by [^{18}F]FDG PET/CT and WBC imaging in order to prevent IE relapse		O, E	84,90
Pulmonary CT angiography is recommended in patients with recurrent pneumonia		O, E	91
In patients with CIED infection treated with percutaneous lead extraction, TTE/TEE before hospital discharge are recommended to detect presence of retained segments of pacemaker lead, and to assess tricuspid valve function, RV function, and pulmonary hypertension		O	80,92,93
In case of persistent sepsis after device extraction: - TEE is recommended to identify residual insulation material and local complications - [^{18}F]FDG PET/CT, radiolabelled WBC scintigraphy and/or contrast enhanced CT for better assessment of local extension of the infection and whole body assessment		O, M	84,94–97
A multidisciplinary team (the Endocarditis Team) is recommended for evaluation of imaging results		E	98

[^{18}F]FDG PET/CT, fluorine-18-fludeoxyglucose positron emission tomography/computerized tomography scanning; CIED, cardiac implantable electronic device; E, expert opinion; ICE, intracardiac echocardiography; IE, infective endocarditis; M, meta-analysis; O, observational studies; R, randomized trials; RV, right ventricular; TEE, transoesophageal echocardiography; TTE, transthoracic echocardiography; WBC, white blood cell count.

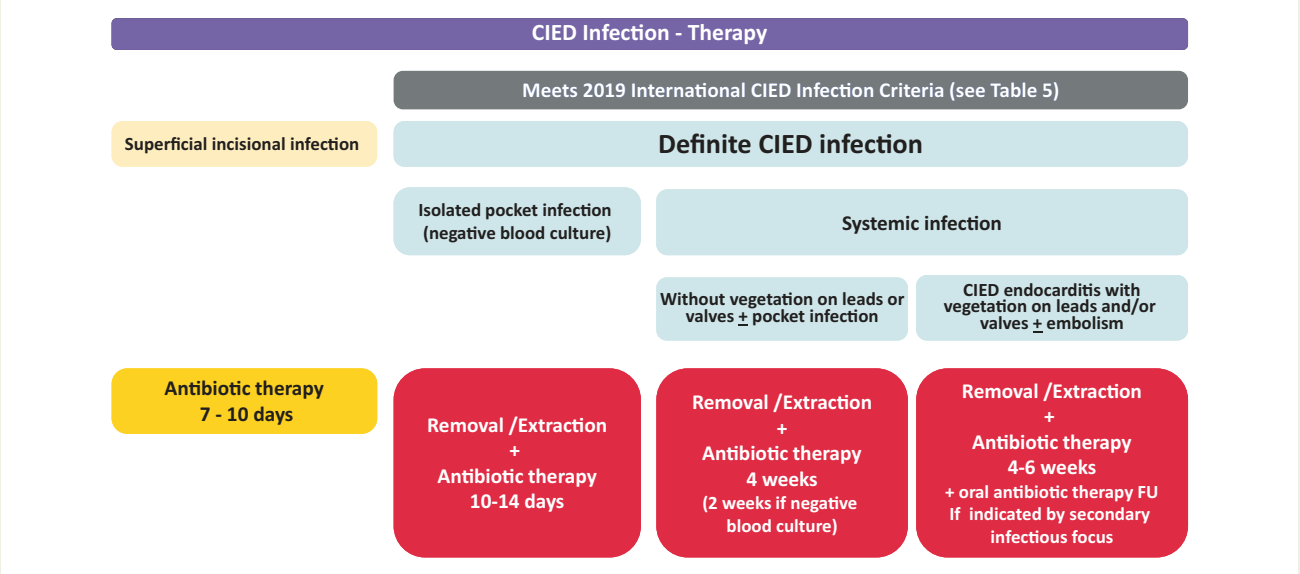

Figure 3 Therapeutic strategies for patients with CIED infections. CIED, cardiac implantable electronic device; FU, follow-up; IE, infective endocarditis.

Contrast-enhanced CT combined with PET may prove useful in selected patients. The addition of contrast-enhanced CT to standard [^{18}F]FDG PET/CT protocol resulted in a high rate of reclassifications from 'possible' to 'definite' infective endocarditis, improving the overall diagnostic accuracy with or without the Duke criteria in a series of patients with suspected pulmonary embolism or CIED infections.[84] Cardiac CT angiography may also add important remote information on vascular complications including mycotic aneurysm, arterial emboli, and septic pulmonary infarcts, which add to the diagnostic criteria and affect the overall treatment strategy. In addition, pulmonary CT angiography may be useful in patients with recurrent pneumonia.[91] A wider use of contrast-enhanced CT is limited by the deleterious impact of contrast agents on kidney function particularly as the patients are exposed to nephrotoxic antibiotic therapy. An extensive description of the technical aspects and the interpretation criteria for multimodality imaging has recently been published.[85]

Multidisciplinary team (the Endocarditis Team) evaluations of imaging results are recommended and have been shown to significantly reduce the 1-year mortality,[98] from 18.5% to 8.2%. *Figure 2* shows the proposed diagnostic flow chart for the use of imaging in patients with suspected CIED infection.

Management of cardiac implantable electronic device infections: when, how, and where

Cardiac implantable electronic device removal

The key aspect to successful treatment of definite CIED infections is complete removal of all parts of the system and transvenous hardware, including the device and all leads (active, abandoned, epicardial as well as lead fragments) as well as vascular ports or permanent haemodialysis catheter.[102,103] This treatment concept applies to systemic as well as localized CIED pocket infections.[81] In a retrospective study of 416 patients with CIED infections, antibiotic therapy without device removal was associated with a seven-fold increase in 30-day mortality (hazard ratio 6.97, 95% confidence interval 1.36–35.60) in multivariate analysis.[104]

The timing of the extraction procedure should be without unnecessary delay after the diagnosis of CIED infection (*Figures 2 and 3*) and should take place at an experienced centre (*Table 8*). The performance of transvenous lead extraction within 3 days after hospitalization results in significantly lower in-hospital mortality and shorter hospitalizations in patients with CIED infections.[114] It is important to note that despite correct treatment with CIED system explantation and adequate antibiotic therapy, the mortality in patients with systemic infection is significantly higher than in patients with local infection. Based on the results of the ELECTRa registry,[2] systemic infection was identified as a predictor for increased all-cause mortality (OR 4.93, 95% CI 2.72–8.93, $P < 0.0001$).

When applicable, percutaneous transvenous extraction techniques are the methods of first choice (*Table 8*), since major complications and mortality at 1 and 12 months in patients undergoing transvenous lead extraction techniques is significantly lower compared to open surgical approaches.[105,115] Transvenous extraction procedures are even preferred in the presence of lead vegetations with a diameter of more than 10 mm (*Table 8*). Small case series have reported good short-term outcomes of transvenous lead extraction procedures in patients with large lead vegetations despite a high percentage of pulmonary embolism. However, long-term outcomes of such patients remain unclear.[116,117] In patients with vegetations larger than ~20 mm open surgical extraction may be considered.[59,81] Even with transoesophageal echocardiography the vegetation size may be difficult to assess. Apart from size, the friability of the vegetation

Table 8 Recommendations for device and lead removal

Consensus statement	Statement class	Scientific evidence coding	References
In patients with definite CIED infection (systemic and local), complete device removal is recommended (including abandoned leads, epicardial leads, and lead fragments)		O	81,102,104
After diagnosis of CIED infection, the device removal procedure should be performed without unnecessary delay (ideally within 3 days)		O	104
The recommended technique for device system removal is percutaneous, transvenous extraction technique. Epicardial leads require surgical removal		O	105
In patients with systemic infection and lead vegetations of approximately >20 mm, percutaneous aspiration of vegetations prior to and during transvenous lead extraction or alternatively surgical extraction may be considered		O	105–107
After device removal, meticulous debridement of the generator pocket (complete excision of the fibrotic capsule and complete removal of all non-absorbable suture material) and subsequent wound irrigation with sterile normal saline solution is recommended		E	108
Cultures of extracted CIED should be performed		E, O	66
The following wound closure methods after device removal and debridement of device pocket may be performed: - Primary closure with or without the use of a drain - Delayed closure after negative pressure wound therapy		E	NA
Complete CIED removal is indicated in bacteraemia or fungaemia with *S. aureus*, CoNS, *Cutibacterium* spp., and *Candida* spp		E	109
In bacteraemia with alpha- or beta-haemolytic *Streptococcus* spp. and *Enterococcus* spp., a complete CIED removal may be performed as first-line treatment or in case of recurrent/continued bacteraemia despite appropriate antibiotic therapy as a second step therapy		E	110
In case of bacteraemia with non-pseudomonal/Serratia Gram-negative bacteria or *Pneumococcus* spp., CIED removal should be performed in the case of recurrent/continued bacteraemia despite appropriate antibiotic therapy when there is no other identifiable source for recurrence or continued infection		E	14,72,111,112
Complete CIED removal is recommended in patients with infective endocarditis with or without definite involvement of the CIED system		E	113
Blood cultures should be taken 48–72 h after removal of an infected CIED		E	19

CIED, cardiac implantable electronic device; E, expert opinion; M, meta-analysis; NA, not available; O, observational studies; R, randomized trials.

should be taken into consideration when planning a procedure. A promising concept in patients with systemic CIED infection and very large lead vegetations is percutaneous aspiration of lead vegetations with the help of a veno-venous extracorporeal circuit with an in-line filter.[106,107] The goal of this treatment is to reduce the overall 'vegetative' burden and the risk of embolization of infectious material into the pulmonary circulation, which may be a source of ongoing septic complications.

In case of infections of CIED systems with epicardial leads, complete removal of such leads is recommended in case of definite

involvement based on individual risk–risk-analysis (operative risk of epicardial lead removal vs. infection-related mortality risk).[115] In case of localized pocket infection of a CIED system without definite involvement of the distal portion of an epicardial lead, it is reasonable to leave the distal portion of the epicardial lead in place by cutting the lead through a separate incision away from the device pocket and removing the proximal part of the lead through the pocket.[81] [^{18}F]FDG/PET/CT scan may prove helpful in assessing such special situations.

In cases of occult bacteraemia or fungaemia, the results of microbiological examination influence further therapy. Complete CIED removal is indicated in bacteraemia or fungaemia with *S. aureus*, CoNS, *Cutibacterium* spp., and *Candida* spp. In bacteraemia with alpha- or beta-haemolytic *Streptococcus* spp. and *Enterococcus* spp. complete CIED removal may be carried out as first-line treatment or as a second step in case of recurrent/continued bacteraemia despite appropriate antibiotic therapy. In case of bacteraemia with non-pseudomonal/Serratia Gram-negative bacteria or Pneumococci an appropriate antibiotic therapy is indicated first. In case of recurrent/continued bacteraemia, complete CIED removal should be performed in cases when no other identifiable source for recurrence or continued infection is found.[14,72,102,111,112] Complete CIED removal is furthermore indicated in patients with infective endocarditis without definite involvement of the CIED system.[113]

After device and lead removal a meticulous debridement of the device pocket with complete excision of the fibrotic capsule as well as removal of all non-absorbable suture material and subsequent wound irrigation with sterile normal saline solution is crucial. Irrigation with antibiotic solution does not offer any significant advantage over irrigation with saline solution.[108] Wound closure concepts may be primary closure with or without the use of a drain or alternatively delayed closure utilizing negative pressure wound therapy.

Cardiac implantable electronic device patients with superficial wound infections early after implantation, device exchange or revision surgery should not undergo device and lead removal. Superficial infections are confined to the skin and the subcutaneous tissue without involvement of any parts of the CIED system. The differentiation between a superficial and a pocket infection can be a clinical challenge. Therefore, it is important to closely watch patients who are under suspicion of having a superficial infection. In such patients, an oral antibiotic therapy (7–10 days) is reasonable.[65]

Antimicrobial therapy including long-term suppressive therapy

Definitive treatment of CIED infection is early and complete removal of all parts of the system and antibiotic therapy is to be seen as a complement to treat associated systemic infection and to cure the remaining infection in native tissues.[103] Randomized controlled studies to guide antibiotic choice in CIED infections are lacking and recommendations are based on cohort studies, case series, expert opinion, and pharmacological considerations.[19,59,65] Access to timely device removal influences antibiotic therapy and treatment regimens also differ between countries depending on the prevalence of MRSA, other differences in antibiotic resistance patterns, and access to specific antibiotics including newer substances. Antibiotic combination therapy with rifampicin targeting biofilm-associated staphylococcal infection is not recommended when the device will be removed unless a concomitant foreign body associated infection, i.e. a prosthetic valve endocarditis that is not amenable to replacement surgery, is present. Antibiotic treatment alone is not recommended for CIED infections but individual patients may not be candidates for device removal. Successful salvage therapy has been reported in a minority of patients.[103] Long-term suppressive antibiotic therapy is also used in selected cases.[118]

Antibiotic treatment recommendations including empirical choices for the three major categories of CIED infections, superficial incisional infection, isolated device pocket infection, and systemic infections, are summarized in *Table 9*. Systemic infections are further divided depending on presence of positive blood cultures and vegetations on leads and/or valves.[65]

For *superficial incisional infection*, a wound culture before initiation of antibiotic treatment is recommended (*Table 9*).

For *isolated pocket infections* empirical i.v. therapy is recommended after blood cultures have been obtained (*Table 9, Figure 3*). Definitive treatment should be given according to culture result with an appropriate antibiotic with a narrow spectrum, if possible a betalactam antibiotic. Combination therapy is not needed. A switch to oral treatment after device removal is reasonable since the remaining infection only involves skin and soft tissue, but evidence-based recommendations are lacking. In pocket erosion with minimal inflammation, delayed antibiotic therapy until after device removal and pocket cultures should be considered.

For *pocket infection with positive blood culture but without vegetation on leads or valves*, the definite treatment follows recommendations given above but the systemic involvement makes a switch to an oral antibiotic regimen inappropriate (*Table 9, Figure 3*). Shorter post-extraction treatment duration is considered possible by some experts.[19]

For *blood culture positive CIED endocarditis with vegetation on lead or valve* the recommendations follow guidelines for infective endocarditis (*Table 9*).[59] If the TEE performed after device removal shows no signs of valve vegetation (i.e. isolated lead vegetation), the follow-up blood cultures are negative, the clinical improvement is good and there are no pulmonary abscesses, treatment duration for 2 weeks post-device extraction can be sufficient but total treatment duration should not be shorter than 4 weeks (*Figure 3*).

For *bacteraemia in a CIED patient without signs of pocket infection or echocardiographic evidence of lead or valve involvement*, the antibiotic treatment follows general recommendations. Due to the risk of undetected device infection, device removal should be considered even in the absence of vegetations, in case of infection with specific pathogens or relapsing bacteraemia without other source, but randomized studies are lacking.[119] The addition of rifampicin is not recommended in patients with *S. aureus* bacteraemia but can be considered in the presence of concomitant non-removable foreign body.[120,121] For *S. aureus*, CoNS, *Cutibacterium* spp., and *Candida* spp., CIED removal is generally recommended. With viridans group and beta-haemolytic *Streptococcus* spp. or *Enterococcus* spp., device removal should be considered as well as prolonged i.v. treatment (4 weeks). Even though Gram-negative bacteria are capable of secondary seeding of a device,[72] concomitant CIED infection is uncommon in non-pseudomonal/Serratia Gram-negative or pneumococcal bacteraemia, and device removal is generally not needed.[14,111,112]

For attempted salvage therapy if complete device removal is not possible, long-term suppressive therapy with i.v. antibiotic following recommendations in prosthetic valve endocarditis for 4–6 weeks is reasonable (*Table 9, Figure 3*). If oral suppressive therapy is planned,

Table 9 International consensus recommendations for antibiotic therapy including long-term suppressive therapy

Consensus statement		Statement class	Scientific evidence coding	References
Superficial incisional infection				
Empirical treatment:			O, R	19,65
Oral antibiotic treatment covering *S. aureus*				
Flucloxacillin oral (amoxicillin-clavulanate is an alternative)	Flucloxacillin p.o. 1 g every 6–8 h			
If high MRSA prevalence: Trimethoprim-sulfamethoxazole, Clindamycin, Doxycyclin, Linezolid	(amoxicillin-clavulanate standard dose)			
To be adjusted after culture result				
Duration: 7–10 days				
Isolated pocket infection (negative blood cultures)				
Empirical treatment:			O, R	19,59,65
Directed at methicillin-resistant coagulase-negative staphylococci (CoNS) and *S. aureus*:	Vancomycin: 30–60 mg/kg/d i.v. in 2–3 doses (Daptomycin 8–10 mg/kg i.v. od)			
Vancomycin (Daptomycin is an alternative)				
If systemic symptoms:	+/-			
For additional Gram-negative coverage, combine with 3rd generation Cephalosporin (or a broader betalactam antibiotic) or Gentamicin	Cephalosporin: standard dose Gentamicin 5–7 mg/kg i.v od**			
To be adjusted after culture result				
If sensitive staphylococcus: Flucloxacillin (1st generation cephalosporin as an alternative)	Flucloxacillin: 8 g/d i.v. in 4 doses or (1st generation cephalosporin standard dose)			
Partial oral treatment often used				
Duration post-extraction: 10–14 days				
Systemic infections				
Without vegetation on leads or valves ± pocket infection				
Empirical treatment: (directed at methicillin-resistant staphylococci and Gram-negative bacteria):			O, R	19,59,65,81
Vancomycin (Daptomycin is an alternative)	Vancomycin: 30–60 mg/kg/d i.v. in 2–3 doses (Daptomycin 8–10 mg/kg od)			
	+			
+ 3rd generation Cephalosporin (or a broader betalactam antibiotic) or Gentamicin	Cephalosporin: standard dose i.v or Gentamicin 5–7 mg/kg i.v. od[b]			
To be adjusted after culture result				
If sensitive staphylococcus: Flucloxacillin i.v. (1st generation cephalosporin i.v. as an alternative)	Flucloxacillin i.v. dosages as above. (1st generation cephalosporin standard dose i.v.)			
Duration post-extraction: 4 weeks (2 weeks if negative blood culture, see text)				
CIED endocarditis with vegetation on leads and/or valves ± embolism				
Empirical treatment:			O, R	59
Vancomycin (Daptomycin is an alternative)	Vancomycin; 30–60 mg/kg/d i.v. in 2–3 doses (Daptomycin 8–10 mg/kg od)			
	+			
+ 3rd generation Cephalosporin (or a broader betalactam antibiotic) or Gentamicin	Cephalosporin; standard dose or Gentamicin 5–7 mg/kg i.v. od[b]			
Adjust to culture result according to ESC endocarditis guidelines 2015				
If prosthetic valve and staphylococcal infection: Rifampicin to be added after 5–7 days	Rifampicin: 900–1200 mg/day orally (or i.v.) in 2 doses			

Continued

Table 9 *Continued*

Consensus statement	Statement class	Scientific evidence coding	References
Duration for native valve infective endocarditis: 4 weeks post extraction, for prosthetic valve endocarditis: (4-) 6 weeks, for isolated lead vegetation: 2 weeks therapy after extraction may be sufficient (in total 4 weeks) except for *S. aureus* infection, see text			
Bacteraemia in a CIED patient without signs of pocket infection or echocardiographic evidence of lead or valve involvement			
According to pathogen specific treatment guidelines, see text		O, R	119,120
Attempted salvage therapy and long-term suppressive therapy			
I.v. antibiotics as in prosthetic valve endocarditis for 4–6 weeks Stop antibiotic therapy under close follow-up or continue individualized long-term suppressive oral therapy, see text		E	103,118

[a]Treatment regimens differ between countries depending on prevalence of MRSA and other circumstances—see text. Dosage recommendation needs to be adjusted for kidney function.
[b]For patients with normal renal function.
d, day; E, expert opinion; H, hour; i.v., intravenous; M, meta-analysis; MRSA, methicillin-resistant *Staphylococcus aureus*; O, observational studies; od, once daily; p.o., per oral; R, randomized trials.

antibiotic therapy should be chosen according to culture results but evidence-based recommendations cannot be made.[103,118] In methicillin-sensitive staphylococci, oral flucloxacillin is considered an option by some experts but is not used by others due to low oral bioavailability. In methicillin-resistant *S. aureus* or CoNS, oral trimethoprim-sulfamethoxazole, clindamycin, or doxycyclin (if sensitive) are alternatives. Linezolid is not suitable for long-term treatment. Rifampicin and fusidic acid are not suitable as single therapy. A combination of suppressive therapy is generally not preferred. The treatment duration needs to be individualized.

Preventive strategies after cardiac implantable electronic device implantations, new re-implantations, and alternative novel devices

Preventive strategies after cardiac implantable electronic device implantations

Since the removal or extraction of CIEDs is usually mandated if infection occurs, prevention of infection is a key goal. While primary prevention measures, including prophylactic antibiotic therapy,[21] appropriate infection control measures, and careful surgical technique, are well established and highly recommended, data supporting the benefits of secondary prophylaxis are relatively scarce and controversial. Early follow-up in a clinical setting and thorough patient educational programs should be conducted for early identification of CIED-related infectious complications, including video consultations for wound inspections. A short period of treatment may prevent progression, but may also mask a pocket infection, delay appropriate treatment, or expose the patient to unnecessary medical therapy.

At present, there is no convincing evidence that microorganisms associated with invasive medical procedures cause infection of non-valvular vascular devices at any time after implantation (*Table 10*). Therefore, antibiotic prophylaxis is not routinely recommended for CIED patients who undergo dental, respiratory, gastrointestinal, genitourinary, or cardiac procedures. Secondary prophylaxis is only recommended for patients when they undergo incision and drainage of infection at other sites or replacement of an infected device.[134]

Re-implantations

All established CIED infections, systemic or localized, mandate complete hardware removal and no part of the removed CIED should be re-implanted. This also applies to the venous access sheath used for percutaneous removal, which should not be used for re-implantation of a new system. Central and peripheral lines and any other removable catheters should also be changed at this time, where feasible.

The indication for re-implantation should always be re-evaluated after a CIED removal.[38,122] A different device than the previous one may be the most optimal choice or there may be no absolute indication for re-implantation at the time of lead extraction. There are no randomized trials guiding appropriate timing of re-implantation and therefore such decision must be individualized. Re-implantation should be delayed until signs and symptoms of local and systemic infection have resolved or postponed until blood cultures are negative for at least 72 h after the extraction if feasible (*Table 10*).[38,123,135] In pacemaker-dependent patients, it seems reasonable to use temporary

Table 10 Recommendations for preventive strategies after device implantation and for new re-implantations including alternative novel devices

Consensus statement	Statement class	Scientific evidence coding	References
After device extraction, re-assessment of the indication for re-implantation is recommended		O	38,122
Whenever possible, re-implantation may be avoided or delayed until symptoms and signs of systemic and local infection have resolved		O	38,123
A temporary pacemaker with ipsilateral active fixation strategy may be considered in pacemaker-dependent patients requiring appropriate antibiotic treatment before re-implantation		O	124–127
Preferred access sites for replacement device are the contralateral side, the femoral vein, or epicardially		E, O	38,128,129
Temporary pacing in patients who are not pacemaker dependent		O	28
Replacement device implantation ipsilateral to the extraction site		E	38
Alternative novel devices as LPM and S-ICD may be considered in selected patients with high infective risk or in patients in whom these devices are considered better options after an CIED infection		O	129–133

CIED, cardiac implantable electronic device; E, expert opinion; LPM, leadless pacemaker; M, meta-analysis; O, observational studies; R, randomized trials; S-ICD, subcutaneous implantable cardiac defibrillator.

pacing until symptoms and signs of systemic infection have resolved before implanting a permanent device. An active-fixation lead ipsilaterally implanted, albeit preferably not through the vein from which the infected lead was extracted, and connected to an externalized pacemaker could be the best strategy in order to safely delay re-implantation[124–127] by keeping the infected extraction side for temporary pacing and preserving the contralateral side for definitive device re-implantation.[57,81,128] Epicardial lead placement has been used for decades as the only reliably strategy for patients at very high risk of re-infection.

Alternative novel devices

Leadless pacemakers (LPM) and S-ICD are excellent alternatives to traditional CIEDs. Currently, two self-contained right ventricular pacemakers implanted by using a femoral percutaneous approach have been developed: Micra™ Transcatheter Pacing System (TPS; Medtronic, Minneapolis, MN, USA) and Nanostim™ Leadless Cardiac Pacemaker (LCP; St. Jude Medical, Sylmar, CA, USA), although only the former is currently available for clinical use. It can pace the right ventricle with a rate response technology and may represent a valid and alternative solution, if indication is appropriate. No infection occurred after a short/mid-term follow-up.[129] In selected high-risk patients, the risk of infection with LPM appears low.[41] The device also seems safe and feasible in patients with pre-existing CIED infection and after extraction of infected leads.[130,136]

Similarly, S-ICD has proven to be safe and effective in many clinical trials in detecting, discriminating, and terminating potentially life-threatening ventricular arrhythmias, even if it is not able to deliver anti-tachycardia pacing and can only provide post-shock ventricular pacing at 50 b.p.m. for 30 s. In selected patients with no need for pacing, ATP or CRT, the re-implantation of a S-ICD significantly reduced the risk of new infections while still providing an effective and safe defibrillation system.[132,133,137] While they do not offer complete protection against infection, their removal is much simpler and most often does not result in a life-threatening systemic infection.[138] While randomized trial data are still forthcoming, data from the 985 patients enrolled into the European EFFORTLESS Registry found an infection rate (requiring device removal) of 2.4% over 3 years of follow-up.[139]

In the near future, the LPM and the S-ICD (Boston Scientific) are expected to integrate wireless intrabody communication between devices to co-ordinate pacing and antitachycardia therapy delivery.[133]

For patients with a high risk of sudden cardiac death on short-term and no need for pacing a wearable defibrillator (LifeVest, Zoll) is an option as a bridge to re-implantation.

Prognosis, outcomes, and complications of cardiac implantable electronic device infections

Cardiac implantable electronic device infection has an in-hospital or 30-day mortality of 5–8%[133,140,141] including mortality from lead

extraction, usually reported as ~0.5%,[2] but which is principally related to the complications of ongoing sepsis. The mortality is higher for patients with significant co-morbidities (e.g. cardiac failure, renal failure, corticosteroid use), with CIED endocarditis rather than pocket infection,[114] and for patients who do not undergo complete removal of CIED hardware.[118] In-hospital morbidity also comprises the complications of lead extraction, usually reported as 2–3%, including emergency thoracotomy for perforation, arterio-venous fistulae, and tricuspid valve damage; septic pulmonary emboli (~1%); arrhythmias; and ongoing sepsis.[2] Following device removal, complications can arise from the re-implantation of a new device, particularly recurrent infection, although uncommon provided appropriate antibiotic treatment and timing of the new implant.

Patients who do not have complete removal of hardware, particularly because they are considered too frail, have a very high mortality in-hospital and over the months following discharge.[118,142] A delay in device removal also leads to a worse prognosis.[114]

The long-term mortality in patients following CIED infection is up to 1.5–2.4 times the mortality rate of non-infected patients,[140,143] which is 6–15% at 1 year and 14–33% at 3 years, the range of estimates reflecting the age and co-morbidities of the patients being studied. Patients with infective endocarditis[144,145] and females have a higher long-term mortality rate than males,[146] when adjusted for co-morbid factors. The presence of end-stage renal failure confers a particularly poor prognosis.[147] However, it is not clear whether the higher long-term mortality is due to the CIED infection itself, or to the presence of poor prognostic factors in the patients who develop CIED infection (e.g. cardiac failure, renal failure, coagulopathy, corticosteroid use, diabetes), or whether a poor outcome reflects inadequate management. There is some indication that patients who have been successfully treated ('cured') with complete removal of hardware and a full course of antibiotics may have a similar prognosis to patients who have never been infected.[148,149]

Special considerations to prevent device-related infections (elderly, paediatrics, adult with congenital heart disease)

Certain patient populations pose additional risks and considerations for infection prevention. One of these populations are the elderly patients needing a pacemaker or ICD.[150,151] In several studies, age per se is not an independent predictor of infection when adjusted for other co-morbidities, such as diabetes, renal failure, heart failure, malignancy, and pulmonary disease.[5,22,28,152,153] Frailty, common in the elderly, is associated with worse cardiovascular outcomes.[154,155] Cardiac implantable electronic device patients with decreased mobility and decreased activity are more likely to be frail.[156] In a study of nearly 84 000 patients followed in the National Cardiovascular Device Registry-ICD (NCDR-ICD), combinations of frailty with other known risk factors for CIED infections were predictive of higher mortality.[155] The elderly are often at greater risk of device erosion due to the loss of subcutaneous tissue and muscle mass.[81,157] Using a sub-muscular approach may provide better protection against erosion in appropriate patients. There are several surgical approaches to the sub-muscular space and implanting physicians should be familiar with these.[158] As in all patients, careful attention to haemostasis is important, as haematoma is a consistent risk factor for infection.[7,24]

Younger age also has been associated with a higher risk of CIED infection. In a study of 46 299 patients enrolled in the Danish Pacemaker Register, 2499 (5%) of patients were under the age of 20 years. In multivariate analysis, age under 20 years was found to have a 40% higher risk for infection (HR 1.41, 95% confidence interval 0.83–2.38).[3] The higher risk of infections may be due to the total number and complexity of device-related procedures that a young person is exposed to over the course of their life.[152,159,160] Colonization of the pocket may lead to higher rates of infections with subsequent generator replacements.[161] The complication rates of procedures involving lead revisions or replacements is reported to be at least twice higher than that of *de novo* implants.[21,22,28,162] In one study of 497 children receiving pacemakers over a 20-year period with median follow-up of 6 years, the lead failure rate was 15%, which occurred in 23% of the patients. Over a quarter (28%) of the patients experienced multiple failed leads. Risk of lead failure was associated with age <12 years at implant, congenital heart disease (CHD), and epicardial lead placement. The reported infection rate after lead replacement in this study was 1.9%.[163]

Data from the NCDR-ICD note low (0.2%) acute infection rates in adults with congenital heart disease (ACHD) patients.[164] As in adults, most infections in paediatric ages and CHD present after longer-term follow-ups and appear to be in a similar range as that reported in adults (~1–5% serious infections).[3,145,151,152,159,165,166] In one retrospective registry study of 443 ICD paediatric or CHD patients, the 30-day and longer than 30-day cumulative infection rate was 4.9%.[165] While lead extraction is reported to have high success in the paediatric and CHD population, nevertheless the serious consequences of CIED-related endocarditis and need for full device system extraction are not trivial.[159,167]

The approach to device implantation poses special challenges in children and CHD patients. Due to small size, abnormal anatomy, and restricted venous access, unusual surgical approaches may be required.[168–173] Epicardial pacing leads and submuscular abdominal positions for the generator are used in the very young with ICD high voltage leads placed in the posterior-lateral pericardial space. As the children grow, transition to transvenous PM and ICD systems can occur if venous access is available. The submuscular (subpectoral) approach for generator placement has been preferred due to smaller size and/or cosmetic reasons.[174] Regardless of specific approach, the young paediatric, CHD, and ACHD patients face a lifetime of device system revisions often resulting in the need for alternative approaches. An alternative approach for older children needing an ICD is the S-ICD. The absence of need for transvenous leads may decrease device-related complications including infection. A report of pooled data from the EFFORTLESS registry combined with the patients enrolled into the US FDA IDE trial showed that no infections occurred in the 19 patients with CHD (age 12–65) compared with 1.5% system infections in the remaining 846. Overall complications were similar (10.5% and 9.6%, respectively) over a follow-up about 2 years.[175] In a report from the Alliance for Adult Research in Congenital Cardiology, 21 patients from 7 centres with ACHD received a S-ICD. At 14 months of follow-up, a single infection was

identified which did not require device removal.[176] Several additional reports have demonstrated favourable use of the S-ICD in these patients.[177–179] Pacemakers that are programmed dedicated bipolar pacing are compatible with the S-ICD system and the combination has been reported in CHD.[180]

Recommendations for prevention of infections related to device implantations in elderly, paediatric patients and patients with ACHD are outlined in *Table 11*.

Minimum quality requirements concerning centres and operator experience and volume

Data on association between centre volume and operator experience and volume and the occurrence of CIED infections are scarce and heterogeneously reported. Some studies date back to the pre-antibiotic era, all are observational in nature, and choice of predictors, statistical adjustments and CIED infection definitions vary widely as do follow-up periods. The recommendations given on centre and operator volumes are approximations based on observational data and expert consensus.

For every surgical procedure a learning curve exists during which complications are expected more frequently. For implantation of cardiac pacemakers, an operator experience <100 procedures was associated with higher risk of infection in the pre-prophylactic antibiotic era.[181,182] Less than 100 procedures were also associated with a higher risk of any complication.[183] Pocket haematoma, known to be associated with higher infection risk, was more common in patients implanted by operators with <100 procedures experience, and haematoma requiring re-intervention were more frequent with operators experience <50 procedures.[184] Based upon these reports, it seems reasonable to recommend close supervision of operators with less than approximately 100 procedures experience.

Several large observational studies have reported complication risk for different operator volumes. For ICD implantations, operator volume <29 procedures per year was associated with adjusted odds ratio for infection of 2.47 (95% CI 1.18–5.17) compared to higher volume operators.[185] Notably, more high-volume operators also had higher volume of pacemaker implantations.[185] Considering any complication, operator volume <60 procedures per year was associated with a highly increased risk of complications [hazard ratio 10.4 (1.32–82.14)] in data from the Ontario ICD database.[186] For cardiac pacemakers, operator volume >40 procedures per year was associated with fewer complications.[187] From a Danish nationwide cohort study of CIED procedures, annual operators volume <50 procedures was associated with a 1.9 (1.4–2.6) adjusted risk ratio of any complication, and higher risk of CIED infection (1.7% vs. 0.5%, $P = 0.02$).[188] Therefore, an annual minimum operator volume of approximately 50 CIED procedures is recommended.

For centre volume, data are even less solid. Centres with lower implantation volume (<250 per year) were reported with higher infection risk for replacement procedures.[7] In historical data from the Danish Pacemaker Registry, infection rates for cardiac pacemakers were similar between high-volume university centres and lower volume centres (<200 procedures per year).[3] From a prospective Danish nationwide cohort, centres with implant volume >750 per year had the lowest risk of any complication, while infections did not differ between centre volumes.[188] However, the smallest centres in this analysis had up to 249 implants per year. In the Dutch FOLLOWPACE registry, including centres with mean annual volumes from 53 to 220 procedures, no association between centre volume and risk of any complication was observed,[189] while a large German nationwide analysis clearly indicated an inverse relationship between risk of any early surgical complications and centre procedure volume.[190] Therefore, any specific recommendation for minimum centre volume will be arbitrarily and consensus based. However, a centre needs ≥2 implanters,

Table 11 Recommendations for prevention of infections related to device implantations in elderly, paediatric patients, and in adults with congenital heart disease

Consensus statement	Statement class	Scientific evidence coding	References
Implanting physicians should be aware of the higher CIED infection risks in frail and elderly patients. Submuscular position of PM or ICD generators is recommended in selected elderly patients with limited subcutaneous tissue to prevent device erosion		O	158
Implanting physicians should be skilled in multiple and alternative surgical approaches performed in paediatric, congenital heart disease, and ACHD patients related to a higher risk of CIED infection due to multiple procedures, lead addition and revisions, and upgrade procedures		M, O	168–172
The entirely S-ICD should be considered as an alternative to transvenous or epicardial approaches in the older child, patients with congenital heart disease, and those with limited or no venous access. Patients with a bradycardia indication, anti-tachycardia pacing, or cardiac resynchronization therapy requirements are not appropriate candidates		O	175–179

ACHD, adults with congenital heart disease; CIED, cardiac implantable electronic device; ICD, implantable cardiac defibrillator; PM, pacemaker; S-ICD, subcutaneous implantable cardiac defibrillator; R, randomized trials; O, observational studies; M, meta-analysis; E, expert opinion.

each performing ≥50–60 procedures. Allowing for training, a minimum centre volume of approximately 150 procedures per year is therefore recommended.[190] The recommendations on minimum quality requirements concerning centres and operator experience and volume are outlined in *Table 12*. Every centre should monitor and report local infection rates to a database.

Health economics for cardiac implantable electronic devices infections and strategies to reduce costs

The incidence of CIEDs infections is increasing at a faster rate as compared with device implantation rates.[4,153,191] This has important implications for the healthcare systems in view of induced healthcare costs, related to a hospitalization usually of 2–4 weeks, with wide use of antibiotics and need for procedures for device removal and lead extraction, as well as CIED re-implantation.[4,6,192] Estimates of the costs of CIED infection are limited, with reported values of €20 623–€23 234 in France, €36 931 (£30 958) in the UK, and values ranging between €15 516 and €337 886 ($16 651 to $362 606) in the USA, with the wide range related to treatment intensity and complexity.[6,11,193] For interpreting these estimates, it is noteworthy to consider that any added day of in-hospital stay has huge costs, ranging from $476–835 in European countries to $4287 (on average) in the USA.[194]

In view of these costs, it is critical that the reimbursement tariffs properly cover the costs due to management of CIED infection patients in all the involved centres. In Europe, reimbursement practices usually are based on Diagnosis Related Groups and show an important variability for device procedures,[195] and if that tariff is inadequate, the reimbursement policy can 'interfere' with physician choices in most complex patients with a substantial risk of suboptimal care.[196]

Health technology assessment is the specific tool for a comprehensive approach to this complex issue, involving all the stakeholders.[197,198] Large national and international registries are of crucial importance for analysing the pattern of referral, the results of lead extraction and the outcomes, in the perspective of optimization of the chain of care, involving many stakeholders, in a 'hub and spoke' organization system which should guarantee expert care, coupling effectiveness with appropriate use of resources.[2,196]

Divergent recommendations from different societies

Strategies for preventing and managing CIED infections vary widely, and the evidence to guide practice is limited. Until now, guidelines on how to prevent, diagnose, and treat CIED infections were published only by the American Heart Association (2010)[65] and by the British Society for Antimicrobial Chemotherapy, British Heart Rhythm Society, British Cardiovascular Society, British Heart Valve Society, and British Society of Echocardiography (2015).[19]

In addition, guidelines for the management of infective endocarditis were published in 2015 by the European Society of Cardiology (ESC)[59] and by the American Heart Association.[199] Recently, the Heart Rhythm Society (HRS) developed a Consensus Statement on Cardiovascular Implantable Electronic Device Lead Management and Extraction providing practical clinical guidance in the broad field of lead management, including lead infectious process.[81] A summary of the main divergent recommendations across these five guidelines is available in *Table 13*.

General definitions and minimal requirements of variables in scientific studies and registries

Cardiac devices registries have been used in many centres around the world; however, a standard dataset definition for patients with CIED infection remains unavailable. A document dedicated to this topic regarding lead extractions has been published.[57] Adopting standardized data elements and a standard terminology is arguably the key to facilitate the exchange of data across studies and to promote interoperability between different electronic health records systems.[200–202] In addition, standardized outcomes measurement will probably open up new possibilities to compare performance globally, providing the medical community with real-world evidence to improve healthcare for patients. A minimum dataset of variables is detailed in *Table 14* to serve as a guide when designing CIED infection

Table 12 Recommendations on minimum volume requirements of cardiac implantable electrical device (CIED) procedures for centres and operators

Consensus statement	Statement class	Scientific evidence coding	References
Operators with less than approximately 100 CIED procedures experience should work under close supervision of more experienced operators		O, E	181–184
An annual minimum operator volume of approximately 50 CIED procedures is recommended for all operators		O, E	185–188

CIED, cardiac implantable electrical device; E, expert opinion; M, meta-analysis; O, observational studies; R, randomized trials.

Table 13 Recommendations/guidelines published by different societies on management of cardiac implantable electronic device infections

Guidelines content	Recommendations	AHA[65] 2010	BHRS[19] 2015	ESC[59] 2015	AHA[199] 2015	HRS[81] 2017	EHRA 2019[a]
Diagnosis							
Transoesophageal echocardiography	TEE should be used for diagnosis since it has higher sensitivity in establishing intravascular related CIED infection than TTE	✓	✓	✓	✓	✓	**7**
[^{18}F]FDG PET/CT/scintigraphy with radiolabelled WBC	[^{18}F]-FDG PET/CT/scintigraphy with radiolabelled WBC should be used as an additive diagnostic tool	NA	Only for research	✓	NA	✓	**7**
Blood cultures	Blood cultures should be taken 48–72 h after removal of infected CIED	NA	✓	NA	NA	NA	**6**
Generator pocket tissue/lead	Percutaneous aspiration of generator pocket should not be performed	✓	NA	NA	NA	NA	**6**
Generator pocket tissue/lead	Tissue should be excised from pocket site and sent for culture	NA	✓	NA	NA	NA	**6**
Radiography	Chest X-ray should be performed if suspected CIED infection	NA	✓	NA	NA	NA	**7**
ceCT/CT pulmonary angiography	ceCT or CT pulmonary angiography should be considered when CIED infection is suspected and echocardiography is non-diagnostic	NA	✓	NA	NA	NA	**7**
Treatment—CIED management							
Early post-implantation inflammation	In superficial or early inflammation, the CIED can initially be left *in situ*.	✓	✓	NA	NA	NA	**8**
Isolated pocket infection/erosion	The CIED must be removed completely within 2 weeks after diagnosis	✓	✓	NA	NA	NA	**8**
CIED lead infection	Complete device system must be removed in CIED lead infection.	✓	✓	NA	NA	✓	**8**
CIED infective endocarditis	Complete removal is mandatory in CIED infective endocarditis	✓	✓	✓	✓	✓	**8**
Occult bacteraemia	Complete device removal is recommended in occult bacteraemia	✓	NA	NA	NA	✓	**8**
Device reimplantation	New transvenous lead implant should be postponed if possible, to allow a few days or weeks of antibiotic therapy	✓	✓	✓	NA	✓	**10**
Device reimplantation	The replacement device implantation should not be ipsilateral to extraction site. Preferred locations are contralateral side, iliac vein, or epicardial	✓	✓	NA	NA	✓	**10**
Treatment—antibiotic strategy							
Early post-implantation inflammation	In early post-implantation inflammation, the use of antibiotic therapy should be determined on a case by case basis	NA	✓	NA	NA	NA	**9**
Uncomplicated pocket infection	In uncomplicated pocket infection, empirical antibiotic therapy can be used	NA	✓	NA	NA	NA	**9**
Complicated pocket infection	Duration of antibiotic therapy should be 10–14 days after CIED removal for pocket-site infection	✓	NA	NA	NA	NA	**9**

Continued

Table 13 *Continued*

Guidelines content	Recommendations	AHA[65] 2010	BHRS[19] 2015	ESC[59] 2015	AHA[199] 2015	HRS[81] 2017	EHRA 2019[a]
Diagnosis							
Complicated pocket infection	Antibiotic treatment options and duration depend on echo findings; if no native valve involvement, treat as uncomplicated generator pocket infection	NA	✓	NA	NA	NA	**9**
CIED lead infection	Duration of antibiotic therapy should be at least 14 days after CIED removal for bloodstream infection	✓	NA	NA	NA	NA	**9**
CIED infective endocarditis	The duration of antibiotic therapy should be at least 4–6 weeks for complicated infection	✓	✓	NA	✓	NA	**9**
Antibiotic prophylaxis	Systemic antibiotic prophylaxis should be used prior to CIED implantation	✓	✓	NA	NA	NA	**4**
Team/reference centre	Complicated infective endocarditis should be referred early and managed in a reference centre with immediate surgical facilities ('Endocarditis Team')	NA	NA	✓	NA	NA	**7**

^{18}F-FDG PET/CT, fluorine-18-fludeoxyglucose ([^{18}F]FDG) positron emission tomography-computerized tomography (PET/CT) scanning; CIED, cardiac implantable electronic device; NA, not available; TEE, transoesophageal echocardiography; TTE, transthoracic echocardiography; ✓, agreed recommendation.
[a]The number refers to the table for the recommendation in the present document where the particular subject was addressed.

Table 14 **Minimal study variables for scientific studies and registries**

Variable group	Data field	Value domain
Hospital characteristics		
	Lead extraction reference centre	Yes/No
	Device implantation volumes	Numbers/year
Demographic factors		
	Age	Date of birth
	Gender	Sex at birth
	Race	Ethnicity per country
	Intravenous drug abuse	Yes/No
	Educational level	Level of schooling completed
Baseline clinical factors		
Comorbidities	Chronic kidney disease	Yes/No
	Diabetes mellitus	Yes/No
	Heart failure	Yes/No
	Valve prosthesis	Yes/No
	Cancer	Yes/No
	HIV infection	Yes/No
Medications	Oral anticoagulants	Yes/No
	Corticosteroids	Yes/No
	Immunosuppressant drugs	Yes/No

Continued

Table 14 *Continued*

Variable group	Data field	Value domain
Specific risk factors	Percutaneous catheters for various indications (infusion, PM, haemodialysis)	Yes/No
CIED characteristics	Type of CIED	
		Pacemaker DDD, SSI
		ICD VR
		ICD DR
		CRT-P
		CRT-D
		ICD-subcutaneous
		Leadless PM
	Pulse generator pocket location	Pectoral/abdominal
	Lead access	Transvenous/epicardial/subcutaneous/hybrid
	Date of CIED implantation	YYYY-MM-DD or estimated
	Total leads number	(number)
	Abandoned leads	Yes/No
	Leads on both sides of the chest	Yes/No
Prior treatments		
	Last CIED procedure	Initial implantation/generator replacement/lead revision/upgrade
	Date of infection diagnosis (time between last CIED procedure and current infection episode)	YYYY-MM-DD or estimated
	Abandoned leads	None/transvenous/epicardial
Admission related to current infection episode		
	Date of admission	YYYY-MM-DD
	Symptoms—fever or hypotension	Yes/No
	Signs of generator pocket infection	Yes/No
	Signs of systemic infection	Yes/No
	Septic shock	Yes/No
Diagnostic methods		
Blood cultures	Microbial pathogens	
TE echocardiogram findings	CIED-related, RA, or RV mass	
	Tricuspid vegetation	
	Left sided vegetation	
Duke-criteria diagnosis	Definite CIED-related infection	
	Suspected CIED-related infection	
[^{18}F]FDG PET/CT findings	CIED-related glycolytic activity	
	Absence of glycolytic activity	
Final diagnosis	Early post-implantation incision inflammation	
	Uncomplicated pocket infection	
	Complicated pulse generator pocket infection	
	CIED-lead infection	
	CIED-associated infective endocarditis	
Treatment	Antibiotic therapy	
	Initial date of antibiotic therapy	YYYY-MM-DD
	Empirical antibiotic therapy	Yes/No
		Antibiotic target
		Dose/route
	Directed (blood culture based) antibiotic therapy	Yes/No
		Antibiotic type
		Dose/route
	Antibiotic therapy length (before CIED removal)	Days
	Antibiotic therapy length (after CIED removal)	Days
	Antibiotic therapy complications	Yes/No
		Type

Continued

Table 14 *Continued*

Variable group	Data field	Value domain
Treatment	CIED removal	
	Date of pulse generator removal	YYYY-MM-DD
	Date of leads removal	YYYY-MM-DD
	Lead extraction procedure	Simple traction, locking stylet, simple mechanical extraction sheath, rotational mechanical extraction sheath, laser sheath, femoral snare approach, internal jugular snare approach, other tools, concomitant percutaneous aspiration of vegetations, surgical extraction without CPB, surgical extraction with CPB
	Lead extraction outcomes	Complete/incomplete, major/minor complications
	Generator pocket tissue culture	Yes/No
		Main findings
	Lead-tip culture	Yes/No
		Main findings
	Wound closure	Primary wound closure—drain, delayed closure—negative pressure wound therapy
Treatment	CIED reimplant	
	Date of re-implantation	YYYY-MM-DD
	Type of CIED	Pacemaker, ICD, CRT
	Pulse generator pocket location	Pectoral/abdominal
	Lead access	Transvenous/epicardial/hybrid/leadless pacemaker/S-ICD
Outcomes		
	Date of hospital discharge	YYYY-MM-DD
	Clinical condition at discharge	Resolved infection/unresolved infection/death
	Need of rehospitalization	Yes/No
	Date of rehospitalization	YYYY-MM-DD
	Recurrent infection	Yes/No
	Death	Yes/No
	Date of death	YYYY-MM-DD
	Cause of death	Lead extraction complications
		CIED infection (sepsis)
		CIED dysfunction
		Refractory heart failure
		Cardiac death—other
		Non-cardiac causes
		Non-detected cause
		Other

CIED, cardiac implantable electronic device; CRT, cardiac resynchronization therapy; ICD, implantable cardiac defibrillator; PM, pacemaker.

registries both in the scientific and clinical settings. The necessity of capturing individual parameters will depend upon the purpose of the study/registry.

Gaps of evidence

(1) The long-term mortality in patients with CIED infection is up to 2.5 times the mortality rate of non-infected patients. It is unclear whether it is related to the CIED infection itself, poor prognostic patient-related factors or inadequate management.
(2) The optimal time for re-intervention (e.g. for lead repositioning) in order to reduce risk for infection is unclear.
(3) The protective role of adhesive antibiotic surgical or other drapes for preventing infections is unclear.
(4) An optimal risk stratification strategy or risk calculator to minimize risk for CIED infection is lacking.
(5) The role of [^{18}F]FDG PET/CT and scintigraphy with labelled leucocytes in the diagnosis and follow-up of occult and manifest CIED infections is of growing evidence of clinical utility but needs clarification.
(6) Duration of postoperative antibiotic therapy following complete CIED system removal for infectious reasons is unclear.
(7) The most optimal salvage strategy in severely ill or frail patients with CIED infections considered too high risk for complete system removal is unknown.
(8) The appropriate timing of re-implantation after CIED infections is unclear.
(9) In PM-dependent patients with CIED infection, the best strategy for permanent pacemaker treatment following lead extraction is unclear; an active-fixation lead ipsilaterally connected to an externalized PM followed by contralateral device implantation, an epicardial lead placement, or a LPM.
(10) In case of a pocket infection with contralateral abandoned lead without systemic infection, it is unclear whether the contralateral abandoned lead should be extracted or not.

Summary of emerging messages and call for scientific evidence

(1) Cardiac implantable electronic device infection rates seem lower (1.2%) in prospective studies[6–10] than in retrospective registries (3.4%),[11,12] which may be related to strengthened adherence to broad infection-preventative behaviours when participating in prospective studies. An assessment of the true infection rates in real-world practice is urgently warranted to more precisely be able to define the benefit of various structured preventive programmes, targeting modifiable risk factors, and developing risk stratification schemes for device implantation and re-implantations.
(2) Although several guidelines and recommendations have been published from various medical societies for managing CIED infections, the EHRA worldwide survey on the clinical practice in managing CIED infections[1] disclosed significant regional differences in current practice, incomplete adherence to guideline recommendations and a lack of profound knowledge in CIED infection management, which underline the need for more widespread and user-friendly international guidelines and implementation programs.
(3) The timing of an extraction procedure should be without time delay after diagnosis of CIED infection since if performed within 3 days after hospitalization it results in significantly lower in-hospital mortality and shorter hospitalizations. Better diagnostic tools are warranted.
(4) The most important procedure-related risk factors for device-related infections are pocket haematoma, long procedure duration, and re-intervention for lead repositioning. Strategies to prevent these risks should be better defined and undertaken more vigorously.
(5) Antibacterial envelope reduces CIED infections in patients with risk factors for device-related infections and is recommended in high-risk patients. Further analysis derived from 'real world' practice will provide more information on its effectiveness and performance in less-selected settings. A risk stratification scheme is warranted to optimize its use.
(6) Postoperative antibiotic is generally not recommended.
(7) Needle aspiration and surgical debridement in cases of pocket infection as an attempt to avoid lead extraction is discouraged. Better diagnostic tools are warranted.
(8) [^{18}F]FDG PET/CT scanning or radiolabelled WBC scintigraphy or contrast-enhanced CT are recommended if suspected CIED-related infective endocarditis, positive blood cultures, and negative echocardiography.
(9) [^{18}F]FDG PET/CT scanning should be performed in case of *S. aureus* bacteraemia in the presence of CIED.
(10) Prudent large national or international non-voluntary user-friendly quality registries of device implantations and its complications with regular monitoring and national requirements of minimal annual operators/centre device volumes may be the ultimate approach to reduce device-related infections.

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