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CONSENSUS DOCUMENT

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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Pacemakers, implantable cardiac defibrillators, and cardiac resynchronization therapy devices are potentially lifesaving 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 health care 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, antibacterial envelopes, prolonged antibiotics post-implantation, and others. When compared with previous guidelines or consensus statements, the present consensus document gives guidance on the use of novel device alternatives, novel oral anticoagulants, antibacterial envelopes, prolonged antibiotics post-implantation, as well as definitions on minimum quality requirements for centres and operators and volumes. The recognition that an international consensus document focused on management of CIED infections is lacking, the dissemination of results from new 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 Novel 2019 International State-of-the-art Consensus document on risk assessment, prevention, diagnosis, and treatment of CIED infections.

Keywords Infection • Device • Extraction • Defibrillator • Pacemaker • Leads

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Introduction

Pacemakers, implantable cardiac defibrillators (ICDs), and cardiac resynchronization therapy (CRT) devices are lifesaving 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. The recognition of 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 management of CIED infections.

This consensus document is an international collaboration among seven professional societies/associations with a writing group consisting of cardiologists with varying subspecialties, infectious disease specialists, imaging specialist, and thoracic surgeon, from 11 countries in

Table 1 Scientific rationale of recommendations

Consensus statement related to a treatment or procedure	Definitions of consensus statement	Statement class	Scientific evidence coding	References
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 grading does not have separate levels of evidence, which instead are defined in each of the coloured heart grades.
The 'ROME' coding was applied for each consensus statement, defining existing scientific evidence; R for randomized trials, O for observational studies, M for meta-analyses, and E for expert opinion.

4 continents. A detailed literature search until May 2019 and systematic reviews of published evidence related to CIED infection topics were performed. Results of the international survey on CIED infections conducted for this purpose[1] and of previous registries[2] were considered. Consensus statements were evidence-based, derived primarily from published data and by consensus opinion after thorough deliberations, requiring at least 80% predefined consensus.

The European Heart Rhythm Association (EHRA) 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 document was peer-reviewed by official external reviewers representing EHRA, the participating societies, and European Society of Cardiology (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.

The medical approaches discussed may include drugs or devices that are not approved by governmental regulatory agencies in all countries. The ultimate decision on management must be made by the health care provider and the patient in light of individual factors presented.

Background and epidemiology

Infection is one of the most serious complication of CIED therapy and is associated with significant mortality, morbidity, and financial health care burden. In the Danish registry of 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] 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 to 2012.[5] Infection rates in prospective observational studies,[6,7] registries,[8] and recent cross-over cluster PADIT- and randomized WRAP-IT trials[9,10] were only 0.6–1.3%, when compared with 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 erosions late after interventions may either be due to or result in pocket infection. 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 or bacterial entry via the skin, mouth, gastrointestinal, or urinary tract.

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. Contamination may also occur before implantation via the air in the operating room or via the hands of anyone handling the device. Device-related factors are those affecting bacterial adherence to the generator or lead and the biofilm formation on these surfaces.[15] 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

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

Pathogens	Percentage of isolates		
	North America[16]	Europe[17]	Asia[18]
Coagulase-negative Staphylococci		69	45.2
Methicillin-resistant	18.8		
Methicillin-sensitive	18.8		
Staphylococcus 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		

been Gram-positive bacteria (70–90%), especially CoNS (37.6% of the isolates) and *Staphylococcus 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).[16,18,20]

Risk factors for cardiac implantable electronic device infection

Identification of modifiable risk factors is important because it 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.

A meta-analysis[21] of pooled data including 206 176 patients summarizes the most important risk factors in *Table 3*. In large device registry-, heath care database-, and device-cohort studies,[5,22,23] the importance of risk factors varied from study to study and findings were in some cases contradictory (age as an example).

Of the *patient-related factors*, end-stage renal disease was consistently associated with the highest risk, but not age or gender.[21] Younger age, along with prior device infection were identified as significant risks in the Danish device-cohort study.[23] Others identified malnutrition [odds ratio (OR) 2.44, $P < 0.001$] as a strong risk factor.[5]

Regarding *procedure-related* factors, the presence of a haematoma was associated with an approximately nine-fold increased risk of infection, later confirmed by the prospective BRUISE-CONTROL study.[24] Early reoperation for haematoma or lead dislodgement was identified as strongest risk factors for CIED infection in a device registry data.[5,22] Procedure duration was associated with a multifold increased risk of infection,[21,23] as were implantation of CRT and reoperations. 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. Device complexity and the numbers of leads were significantly associated with increased infection risk on multivariate analysis [hazard ratio (HR) 1.26, 1.67, and 2.22 for ICD, CRT-P, and CRT-D systems, respectively vs. pacemakers, $P \leq 0.002$ for all comparisons].[23]

Risk stratification with risk score calculations could potentially play a role in better identifying patients at risk than individual factors[26,27] but can currently not be recommended because the evidence of their benefit remains weak.

Prevention

Recommended preventive measures are summarized in *Table 4* and *Figure 1*.

Pre-procedural measures

Patient selection

For patients undergoing device removal for infection, up to one half may not require device reimplantation.[39] Implanting an epicardial

Table 3 Pooled effect estimates for potential risk factors predisposing to CIED infection

Factors	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	11 839	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 to 26.73)	0.06
Haematoma	12	14 228	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	10 683	2.31 (1.36–3.92)	0.002	4	8683	3.29 (1.87–5.80)	0.00004
Device replacement/revision/upgrade	26	21 214	1.98 (1.46–2.70)	0.00001	8	8793	0.95 (0.49–1.87)	0.89
Generator change	20	12 134	1.74 (1.22–2.49)	0.002	6	2139	0.91 (0.37–2.22)	0.83
Antibiotic prophylaxis	16	14 166	0.32 (0.18–0.55)[d]	0.00005	11	10 864	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	45 224	1.45 (1.02–2.05)	0.04	7	12 102	1.28 (0.73–2.25)	0.38

Adapted from Polyzos *et al.*[21]
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.
CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; NA, not available; NYHA, New York Heart Association.
[a]Glomerular filtration rate ≤15 mL/min or haemodialysis or peritoneal dialysis.
[b]Glomerular filtration rate <60 mL/min or creatinine clearance <60 mL/min.
[c]<100 previous procedures.
[d]The pooled effect estimate from randomized studies was 0.26 (0.13–0.52).

system may be preferential in high-risk patients.[40] 'Leadless' pacemakers may be less prone to infection and can be used in high-risk patients.[41,42] Subcutaneous ICDs (S-ICDs) are an option in patients requiring sudden death protection.

Lead management

The number of leads and the presence of abandoned leads are associated with increased risk for infection. The decision to abandon or extract a lead must be made on an individual basis weighing all known risks and benefits.[43,44]

Patient factors

A procedure should be delayed until a patient has been afebrile for at least 24 h.[28] Better glycaemic control in the periprocedural period may reduce infections in surgical patients.[45]

Anticoagulation and antiplatelet drugs

A 'bridging' approach with heparin is not recommended.[30] In patients with CHA_2DS_2VASc score <4, holding anticoagulation for the procedure and restarting when the bleeding risk is reduced seems prudent. In higher-risk patients (prior embolic event or mechanical valve) continuing anticoagulation with Warfarin is recommended.

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	35
Topical *Staphylococcus aureus* decolonization may be performed		E	
Pre-procedural skin wash may be performed		E	
Hair removal with electric clippers (not razors) is recommended		O	36
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 programme of infection rates and associated microbiology should be set-up at the level of each implanting centre		E	—
Periprocedural measures			
Surgical preparation with alcoholic chlorhexidine should be used rather than povidone–iodine		R	37,38
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	

Continued

Table 4 ***Continued***

Consensus statement	Statement class	Scientific evidence coding	References
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	
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 post-operative 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 reintervention if possible		E	
Haematoma drainage or evacuation (unless tense, wound dehiscence is present or pain is severe)		O	24,28

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

Preliminary data suggest the same for non-vitamin K antagonist oral anticoagulants.[29] Therapeutic low-molecular-weight heparin should be avoided.[30,32,33] Antiplatelet agents, especially P2Y12 inhibitors should preferably be discontinued for 5–10 days before the intervention.[31]

Appropriate environment

The standards for sterile procedures must be met as for other surgical procedures associated with implants.[34]

Staff training

All staff involved in CIED implantation must be trained in appropriate strict sterile techniques and behaviour in an operating room setting. Operators should be adequately trained.[35]

Nasal swabs/*Staphylococcus aureus* decolonization of patients

For elective procedures, *S. aureus* colonization can be detected by nasal swabs. Nasal treatment with mupirocin and chlorhexidine skin washing has been shown in some surgical studies to reduce the risk for infection.[46]

Pre-procedure skin preparation

Routine pre-surgical washing with an antimicrobial agent cannot be strongly supported.[47] Electric clippers with a single-use head (not razors) should be used for chest hair removal.[36]

Pre-procedure antibiotic therapy

Prophylactic systemic antibiotics are the standard of care[21,48,49] and should at least cover *S. aureus* species. Randomized trials have used

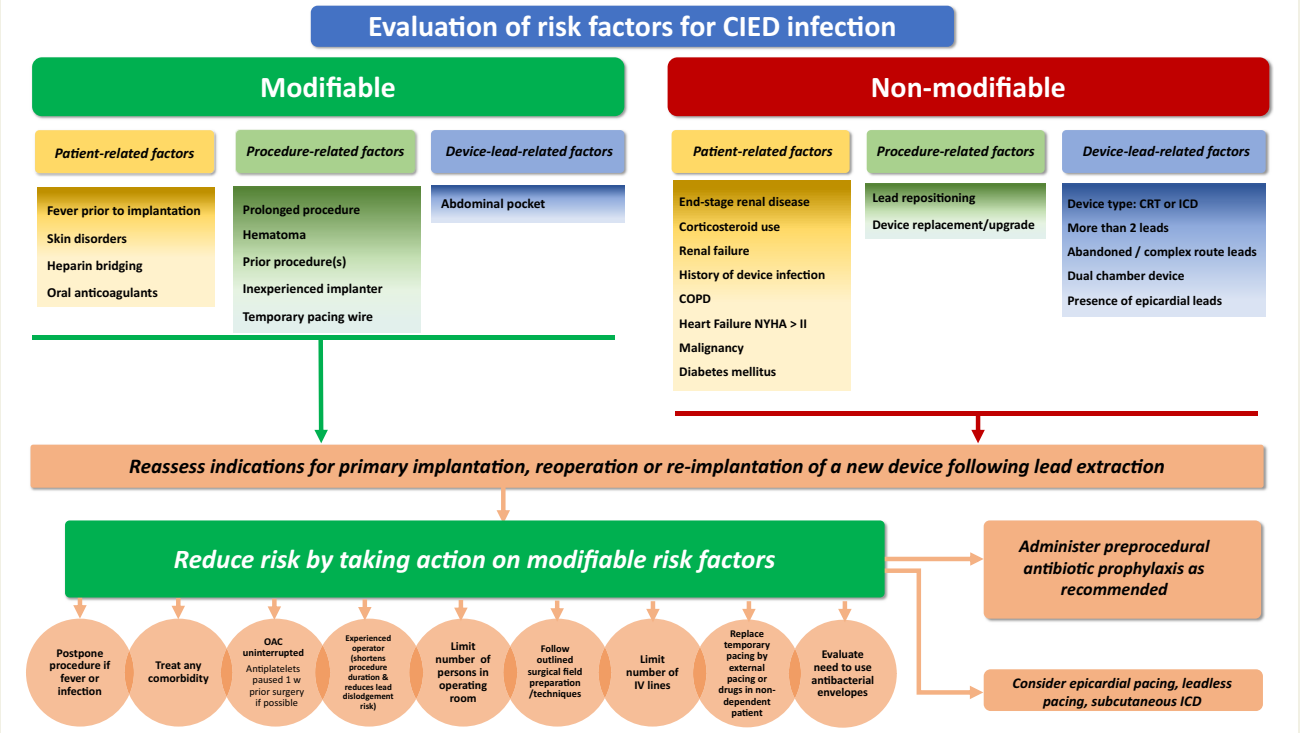

Figure 1 A flowchart indicating how device-related infections can be minimized by targeting modifiable risk factors on various levels. Risk factors ranked in order of strength from top to bottom. CIED, cardiac implantable electronic device; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization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

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.

Periprocedural measures

Patient surgical preparation

Alcoholic 2% chlorhexidine was superior to povidone–iodine for skin preparation prior to surgery[37] or intravascular catheter insertion[38] but no randomized data exist regarding CIED implantation. There is no evidence that adhesive incise drapes reduces infection rates (may increase risk of infection when non-iodophor incise drapes are used[50]).

Good surgical technique

Non-powdered gloves may reduce the risk of infection by reducing local inflammation.[51] 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, ideally performed in an operating room.[24,28]

Antibiotic envelope

An antibacterial mesh envelope (TYRX™, Medtronic, MN, USA), which locally releases minocycline and rifampin, significantly reduced the incidence of CIED infection in high-risk patients (WRAP-IT trial[10]) without a higher incidence of complications. The incidence of primary endpoints (infection resulting in system extraction or revision, long-term antibiotic therapy, or death) within 12 months after the CIED implantation was lower in patients who received the envelope (0.7%) vs. controls (1.2%) (HR 0.60, 95% confidence interval (CI) 0.36–0.98; $P = 0.04$).[10] The number of patients needed to treat to prevent one infection was high. The exclusion of higher-risk patients (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] 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*.

Local instillation of antibiotics or antiseptics

Local instillation of antibiotics or antiseptics is not recommended. The recent PADIT trial demonstrated no benefit.[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] The fibrous capsule inhibits the body's normal defence mechanisms and antibiotic penetration but 'capsulectomy' could also result in more pocket bleeding/haematoma and cannot be recommended as routine practice.[54]

Closure

Closure in layers minimize wound tension and reduces the risk of dehiscence and infection.[55]

Post-procedural measures

Post-procedure antibiotic therapy

The recent PADIT trial,[9] tested the clinical effectiveness of incremental perioperative antibiotics but the primary outcome of 1-year hospitalization for device infection in the high-risk group was not statistically significant. It is therefore not recommended to administer post-operative antibiotic therapy.

Wound care

Pressure dressing may be used for the first 24 h to avoid haematoma.

Reintervention

All measures must be taken to avoid the need of early reintervention which dramatically increases the risk of infection.[19,21,28]

Diagnosis of cardiac implantable electronic device infections and related complications

Clinical findings

A *superficial incisional infection* involves only the skin and the subcutaneous tissue without communication with the pocket.[56,57] Close monitoring of the patient must be pursued in order to recognize a significant pocket infection.

Pocket infection is defined as an infection limited to the generator pocket. Local signs of inflammation may be mild (erythema, warmth, and fluctuation).[14,57] Deformation of the pocket, adherence or threatened erosion are often signs of low grade, indolent infection. 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.[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, and night sweats). Patients with CIED infection may present with embolic involvement of lungs and pleural space[60,61] or with vertebral osteomyelitis and discitis. Procalcitonin test may be of value, especially if positive (≥0.05).[62,63]

The modified Duke criteria[64] and the ESC 2015 criteria[59] for the diagnosis of infective endocarditis are the only available framework for CIED endocarditis diagnosis. In order to increase sensitivity for CIED infection diagnosis, this panel developed the 2019 International CIED Infection Criteria (*Table 5*).

Identification of the causative microorganisms

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 (*Table 6*). In unstable patients with sepsis or septic shock, early empiric antibiotic therapy should be administered following two sets of blood cultures. Blood bottles must be filled properly in order to increase the sensitivity.[17,65] Every positive blood culture, including a single bottle with CoNS or other Gram-positive organisms, should prompt active exclusion of CIED infection with other diagnostic techniques employed (*Figure 2*).[71] In case of negative blood cultures (usually 5 days), the use of biomolecular methods (DNA amplification and/or gene sequencing) to detect fastidious or atypical pathogenes[19] may be considered for CIED endocarditis (*Table 6*).[67] Some Gram-positive microorganisms species may require longer period of incubation, such as *Cutibacterium* (previously *Propionibacterium*) *acnes*.[19]

Tissue or fluid collected from the pocket via an adjacent intact portion of the skin (via a sterile needle or syringe) 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 and generator pocket tissue should be sent for culture (*Table 6*).[71] Culture media suggested are chocolate agar incubated in 5% CO_2, MacConkey agar, blood agar in anaerobic condition, and Sabouraud agar.[72,73] In case of pus, but no growth after 3 days, consider slow growing microorganisms including *C. acnes* and increase incubation duration. Tissue samples and sonication for the recovery of bacteria from CIED leads and tissue may be useful.[68–70]

Imaging

Echocardiography

Transthoracic echocardiography (TTE) and transoesophageal echocardiography (TEE) are both recommended to identify lead vegetations and valvular involvement in suspected CIED infections.[59] Transoesophageal echocardiography is superior for the detection and sizing of vegetations.[74] 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] 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) 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 Recommendations for diagnosis of CIED infections and/or infective endocarditis: the Novel 2019 International CIED Infection Criteria[a]

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 two major criteria or one major + three minor criteria			
'Possible' CIED/IE = presence of either one major + one minor criteria or three 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, *Staphylococcus aureus*) B. Microorganisms consistent with IE from two separate blood cultures: a. Viridans streptococci, *Streptococcus gallolyticus* (*Streptococcus 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 three 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)			

Green text refers to CIED-related infection criteria.
CIED, cardiac implantable electronic device; E, expert opinion; ICE, intracardiac echocardiography; IE, infective endocarditis; M, meta-analysis; O, observational studies; R, randomized trials.
[a]Based on merging of the modified Duke- and ESC 2015 Guidelines criteria, see text.[63,64]

(*Table 5*). Transvenous biopsy, guided by TEE, was shown to be useful to differentiate vegetation from thrombus.[79]

A TEE should be considered after percutaneous lead extraction in order to detect infected material, ghosts,[80] and potential tricuspid valve complications (*Table 7*). 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 (white blood cell, WBC) scintigraphy are complementary tools for the diagnosis of CIED-related infections

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	60,65
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 *Staphylococcus aureus* CIED-related infective endocarditis		E, O	63
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.

and related complications, particularly in the subset of *possible* CIED infections, and may distinguish between early-onset superficial surgical site infection and a true generator pocket infection (*Figure 2*). When patients present with systemic infection without local findings at the generator pocket a PET/CT is 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] White blood cell count 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).[89] In case of CIED-related infective endocarditis, 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.

Positron emission tomography/computerized tomography is particularly useful for the identification of unexpected embolic localizations and metastatic infections.[84,88] 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 after lead extraction, as patients with definite CIED infection without pocket involvement on PET/CT had unfavourable outcome.[101]

The addition of contrast-enhanced CT to standard PET/CT protocol resulted in a high rate of reclassifications from 'possible' to 'definite' infective endocarditis in patients with suspected pulmonary embolism or CIED infections.[84] Pulmonary CT angiography may be useful in patients with recurrent pneumonia.[91] The technical aspects and the interpretation criteria for multimodality imaging has recently been published.[85]

Multidisciplinary team evaluations of imaging results significantly reduced the 1-year mortality[98] from 18.5% to 8.2%.

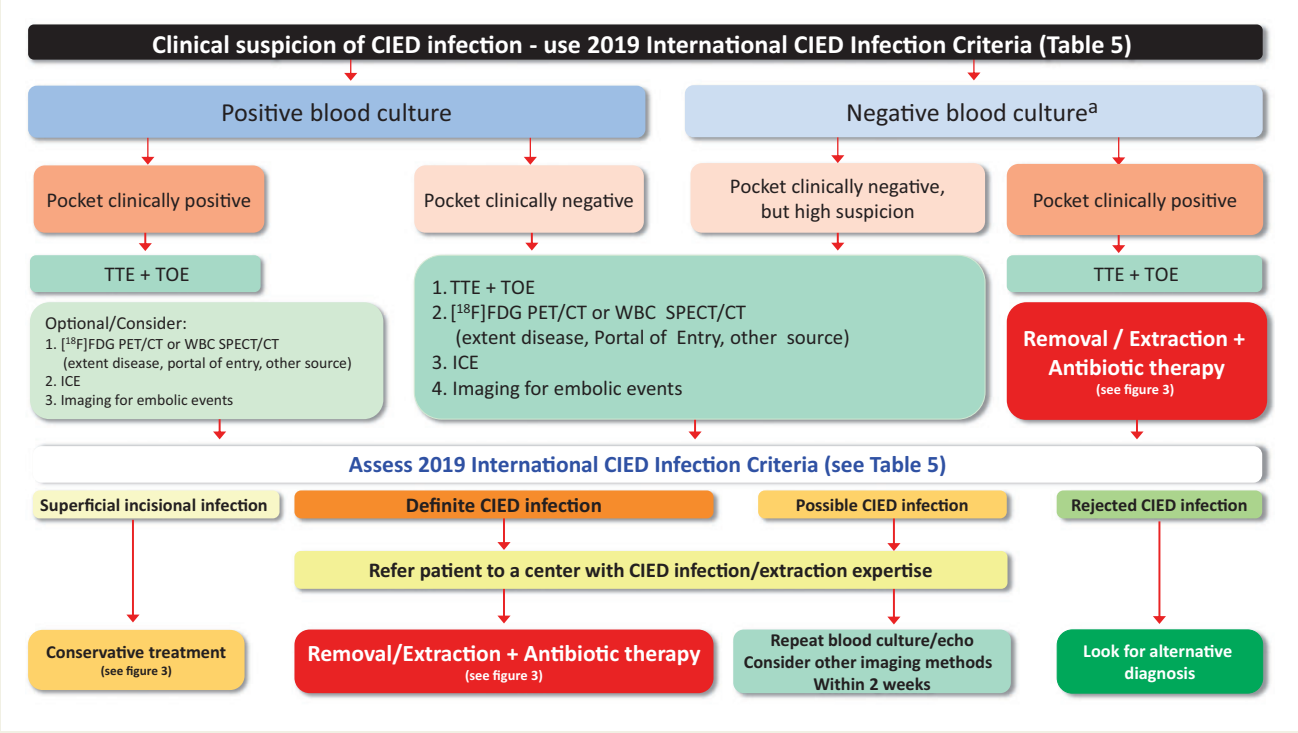

Figure 2 Diagnostic algorithm for diagnosis of suspected cardiac implantable electronic device infections. [a]Ensure sufficient number of blood cultures collected and absence of confounding antibiotic therapy prior to cultures. CIED, cardiac implantable electronic device; [^{18}F]FDG PET/CT, fluorodeoxyglucose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

Management of cardiac implantable electronic device infections

Cardiac implantable electronic device removal

Successful treatment of definite CIED infections (systemic and localized) requires complete removal of all parts of the system and transvenous hardware, including vascular ports or permanent haemodialysis catheter.[81,102,103] Antibiotic therapy without device removal was associated with a seven-fold increase in 30-day mortality 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*, *Table 8*). Transvenous lead extraction within 3 days after hospitalization results in significantly lower in-hospital mortality and shorter hospitalizations in patients with CIED infections.[114] Systemic infection was a predictor for increased all-cause mortality (OR 4.93, 95% CI 2.72–8.93; $P < 0.0001$) in the ELECTRa registry.[2]

Percutaneous transvenous extraction is the method of first choice (*Table 8*) since major complications and mortality are significantly lower compared with open surgical approaches.[105,115] Transvenous extraction procedures are even preferred in the presence of lead vegetations with a diameter of >10 mm (*Table 8*)[116,117] In patients with systemic CIED infection and vegetations larger than approximately 20 mm, open surgical extraction[59,81] or percutaneous aspiration with a veno-venous extracorporeal circuit with an in-line filter may be considered.[106,107] The goal is to reduce the overall 'vegetative' burden and the risk of embolization of infectious material into the pulmonary circulation.

In case of infections of CIED systems with epicardial leads, complete lead removal is recommended in case of definite involvement based on individual risk-risk-analysis.[115] For localized pocket infection without definite involvement of the distal epicardial lead, it is reasonable to leave the distal portion by cutting the lead through a separate incision away from the device pocket.[81] A PET/CT scan may prove helpful.

In cases of occult bacteraemia or fungaemia the results of microbiological examination influence further therapy (*Table 8*). Complete CIED removal is indicated in bacteraemia or fungaemia with *S. aureus*, CoNS, *Cutibacterium* spp. and *Candida* spp., whereas it may be carried out as a second step for other bacteraemia in case of recurrent/continued bacteraemia despite appropriate antibiotic therapy

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

Consensus statement	Statement class	Scientific evidence coding	Reference
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 *Staphylococcus 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* bacteraemia 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.

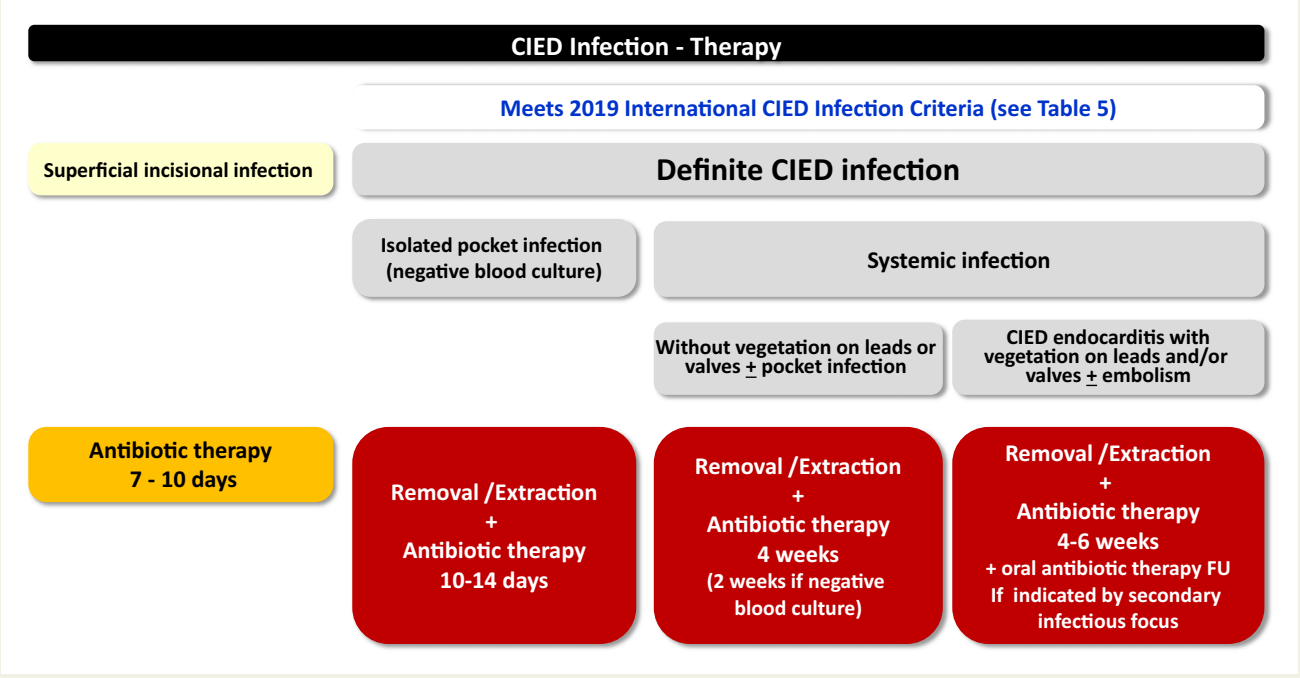

Figure 3 Therapeutic strategies for patients with cardiac implantable electronic device infections. CIED, cardiac implantable electronic device; FU, follow-up; IE, infective endocarditis.

(*Table 8*).[14,72,102,111,112] Complete CIED removal is 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, removal of all non-absorbable suture material and subsequent wound irrigation with sterile saline solution, is crucial.[108]

Cardiac implantable electronic device patients with superficial wound infections early after implantation, device exchange or revision surgery should not undergo device and lead removal.

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.[103] Randomized studies to guide antibiotic choice in CIED infections are lacking.[19,59,65] Successful salvage therapy[103] and long-term suppressive antibiotic therapy have been used in selected cases not candidates for device removal.[118]

Antibiotic treatment recommendations 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*). A switch to oral treatment after device removal is reasonable, 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] Total treatment duration should always be at least 4 weeks. If the TEE performed after device removal shows no signs of valve vegetation, the follow-up blood cultures are negative, the clinical improvement is good and there are no pulmonary abscesses, a 2 weeks treatment duration post-device extraction can be sufficient (*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. 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

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 *Staphylococcus 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

E, expert opinion; M, meta-analysis; NA, not available; O, observational studies; R, randomized trials.

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

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 (amoxicillin–clavulanate standard dose)			
If high MRSA prevalence: Trimethoprim–sulfamethoxazole, Clindamycin, Doxycyclin, Linezolid				
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 *Staphylococcus aureus*:	Vancomycin: 30–60 mg/kg/day i.v. in 2–3 doses (Daptomycin 8–10 mg/kg i.v. o.d.)			
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 o.d.[b]			
To be adjusted after culture result				
If sensitive staphylococcus: Flucloxacillin (1st generation cephalosporin as an alternative)	Flucloxacillin: 8 g/day i.v. in four doses (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/day i.v. in 2–3 doses (Daptomycin 8–10 mg/kg o.d.)			
	+			
+ 3rd generation Cephalosporin (or a broader betalactam antibiotic) or Gentamicin	Cephalosporin: standard dose i.v or Gentamicin 5–7 mg/kg i.v o.d.[b]			
To be adjusted after culture result				
If sensitive staphylococcus: Flucloxacillin iv (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/day i.v. in 2–3 doses (Daptomycin 8–10 mg/kg o.d.)			
	+			
+ 3rd generation Cephalosporin (or a broader betalactam antibiotic) or Gentamicin	Cephalosporin; standard dose or Gentamicin 5–7 mg/kg i.v o.d.[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 two 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 *Staphylococcus 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

E, expert opinion; i.v., intravenous; M, meta-analysis; MRSA, methicillin-resistant *Staphylococcus aureus*; O, observational studies; o.d., once daily; p.o., per oral; R, randomized trials.
[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.

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, antibiotic therapy should be chosen according to culture results.[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-sulfametoxazole, clindamycin, or doxycyclin are alternatives. Linezolid is not suitable for long-term treatment. Rifampicin and fusidic acid are not suitable as single therapy. A combination suppressive therapy is generally not preferred.

Preventive strategies after cardiac implantable electronic device implantations, reimplantations, and alternative novel devices

Early follow-up in a clinical setting and patient educational programmes should be conducted for early identification of CIED-related infectious complications, including video consultations for wound inspections.

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]

No part of the removed CIED system should be reimplanted. The venous access sheath used for percutaneous removal should not be used for reimplantation 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 reimplantation should always be re-evaluated after a CIED removal.[39,122] There are no randomized trials guiding appropriate timing of reimplantation and therefore such decision must be individualized. Reimplantation 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*).[39,123,135] In pacemaker dependent patients, an active-fixation lead ipsi-laterally implanted (preferably not through the vein used for extraction) and connected to an externalized pacemaker could safely delay reimplantation[124–127] by preserving the contralateral side for definitive device reimplantation.[57,81,128]

Leadless pacemakers (LPMs) may represent a valid solution. In selected high-risk patients, the risk of infection with LPM appears low.[42,129] The device also seems safe and feasible in patients with pre-existing CIED infection and after extraction of infected leads.[129,130,136]

In selected patients, the reimplantation of an S-ICD significantly reduced the risk of new infections while still providing an effective defibrillation system.[132,133,137] While they do not offer complete protection against infection, their removal is simpler

Table 10 Recommendations for preventive strategies after device implantation and for new reimplantations including alternative novel devices

Consensus statement	Statement class	Scientific evidence coding	References
After device extraction, reassessment of the indication for reimplantation is recommended		O	39,122
Whenever possible, reimplantation may be avoided or delayed until symptoms and signs of systemic and local infection have resolved		O	39,123
A temporary pacemaker with ipsilateral active fixation strategy may be considered in pacemaker-dependent patients requiring appropriate antibiotic treatment before reimplantation		O	124–127
Preferred access sites for replacement device are the contralateral side, the femoral vein, or epicardially		E, O	39,128,129
Temporary pacing in patients who are not pacemaker dependent		O	28
Replacement device implantation ipsilateral to the extraction site		E	39
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 a 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 defibrillator.

and most often does not result in a life-threatening systemic infection.[138] While randomized trial data are still forthcoming, data from the European EFFORTLESS Registry found an infection rate (requiring device removal) of 2.4% over 3 years of follow-up.[139] For patients with a high risk of sudden cardiac death, a wearable defibrillator (LifeVest, Zoll) is an option as a bridge to reimplantation.

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] The mortality is higher for patients with significant comorbidities, with CIED endocarditis rather than pocket infection,[114] and for patients who do not undergo complete removal of CIED hardware.[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. Patients with infective endocarditis[144,145] and females have a higher long-term mortality rate than males,[146] when adjusted for comorbid factors. The presence of end-stage renal failure confers a particularly poor prognosis.[147] Patients 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)

Elderly patients needing a pacemaker or ICD pose additional risk and considerations for infection prevention.[150,151] In several studies, age *per se* is not an independent predictor of infection when adjusted for other comorbidities.[5,22,28,152,153] Frailty, observed in CIED patients with decreased activity and common in the elderly, is associated with worse cardiovascular outcomes.[154–156] In a National Cardiovascular Device Registry–ICD (NCDR-ICD) study, 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.[81,157] which may be prevented using a sub-muscular approach.[158]

In multivariate analysis, age under 20 years had a 40% higher risk for infection[3] which may be due to their higher number and

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; E, expert opinion; ICD, implantable cardiac defibrillator; M, meta-analysis; O, observational studies; PM, pacemaker; R, randomized trials; S-ICD, subcutaneous ICD.

complexity of device-related procedures.[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 are 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 with median follow-up of 6 years, the lead failure rate was 15% and the reported infection rate after lead replacement was 1.9%.[163]

Data from the NCDR-ICD notes low (0.2%) acute infection rates in adults with congenital heart disease (CHD) patients.[164] 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).[3,159,165–167]

The approach to device implantation poses special challenges in children and CHD patients.[168–173] Pooled data from the EFFORTLESS registry and the US FDA IDE trial reported no infections in the 19 CHD patients with an S-ICD compared with 1.5% system infections in the remaining 846,[174] confirming other favourable reports.[175–179]

Recommendations for prevention of infections in these patient groups are outlined in *Table 11*.

Minimum quality requirements concerning centres and operator experience and volume

For implantation of pacemakers, an operator experience <100 procedures was associated with higher risk of infection in the pre-prophylactic antibiotic era.[180,181] Less than 100 procedures were also associated with a higher risk of any complication.[182] Pocket haematoma was more common in patients implanted by operators with <100 procedures experience.[183] Close supervision of operators with less than approximately 100 procedures experience seems reasonable (*Table 12*).

An operator volume <29 ICD implantations per year was associated with adjusted OR for infection of 2.47 (95% CI 1.18–5.17) vs. higher volume operators.[184] An operator volume <60 ICD procedures per year was associated with a highly increased risk of any complication [HR 10.4 (1.32–82.14)],[185] while an operator volume >40 pacemaker procedures per year resulted in fewer complications.[186] Annual operators volume <50 procedures was associated with higher risk of CIED infection (1.7% vs. 0.5%, $P = 0.02$).[187] An annual minimum operator volume of approximately 50 CIED procedures is therefore recommended (*Table 12*).

While infection rates were not related to centres volumes in some registries,[187,188] others clearly indicated an inverse relationship between infection risk for procedures and centre procedure volume.[7,189] 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 increasing incidence of CIEDs infections, exceeding the device implantation rates[4,153,190] has important implications for the health care systems in view of induced health care costs.[4,6,191] Estimates of the costs of CIED infection are limited, with reported values of €20 623 to €23 234 in France, €36 931 in the UK, and €15 516 to €337 886 in the USA.[6,11,192] Any added day of in-hospital stay has huge costs.[193]

In Europe, reimbursement practices usually are based on diagnosis related groups and show an important variability for device

Table 12 Recommendations on minimum volume requirements of 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.

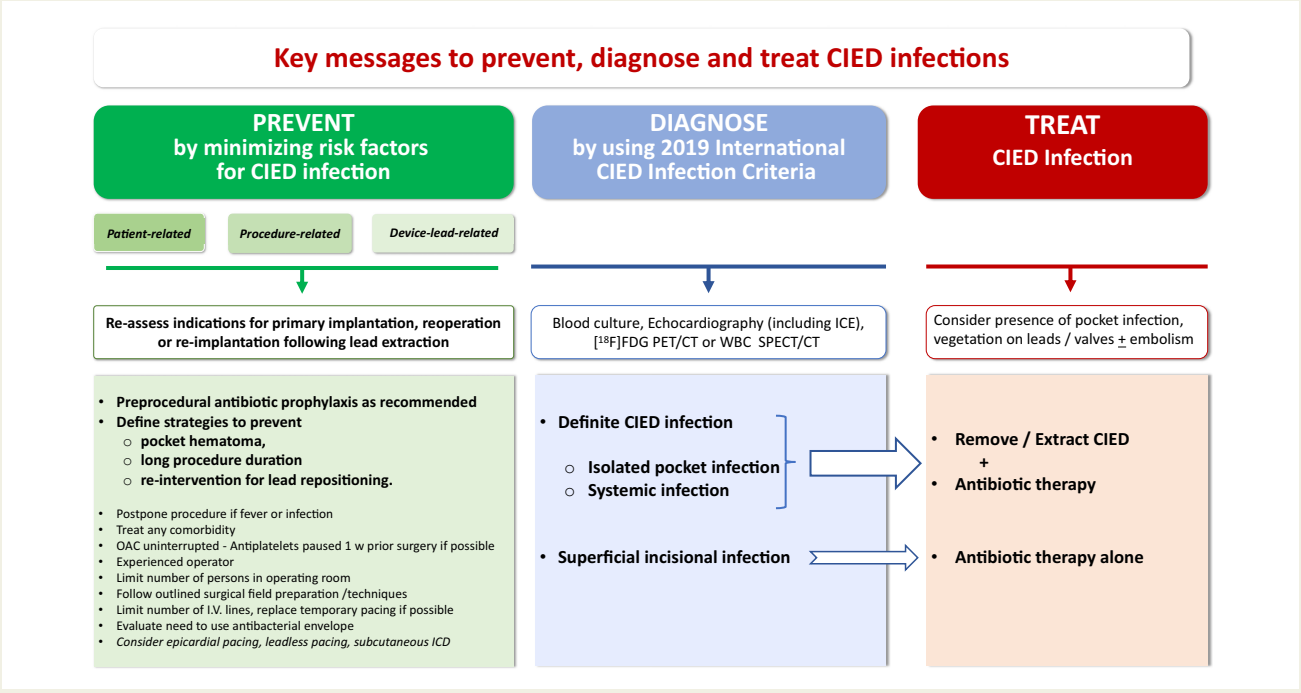

Figure 4. Summary of key messages for prevention, diagnosis, and management of cardiac implantable electronic device infections. CIED, cardiac implantable electronic device; [^{18}F]FDG PET/CT, fluorodeoxyglucose positron emission tomography-computed tomography; ICD, implantable cardiac defibrillator; ICE, intracardiac echocardiography; OAC, oral anticoagulation; w, week; WBC SPECT/CT, white blood cell single-photon emission computed tomography-computed tomography.

procedures,[194] with a substantial risk of suboptimal care.[195] Health technology assessment,[196,197] and registries are of crucial importance for optimization of care, coupling effectiveness with appropriate use of resources.[2,195]

Conclusion

The lack of international consensus documents specifically focusing on CIED infections,[19,59,65,81,198] the gaps in knowledge, new important randomized trials, and observed divergences in managing device-related infections[1] provided a strong incentive for a 2019 International State-of-the-art Consensus document on the prevention, diagnosis, and management of CIED infections. The use of standardized terminology,[199–201] continuous surveillance programme of device infection rates at implanting centres, and improved adherence to guideline recommendations are strongly warranted (*Figure 4*).

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