Review

Treatment and Prevention of Cardiovascular Implantable Electronic Device (CIED) Infections

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ABSTRACT
An expanded role for cardiac implantable electronic devices (CIEDs) in recent decades reflects an aging population and broader indications for devices, including both primary prevention and management of dysrhythmias. CIED infection is one of the most important device-related complications and has a major impact on mortality, quality of life, healthcare utilization, and cost. Unfortunately, the investigation and management of CIED infection remain complex, often

Cardiac implantable electronic devices (CIEDs) are medical devices that regulate cardiac rate and rhythm (eg, pacemakers, implantable cardioverter-defibrillators [ICDs], and cardiac resynchronization therapy [CRT] devices), as well as diagnostic devices such as implantable cardiac monitors. The use of CIEDs increased as a result of a combination of changing population demographics. In 2018-2019, among devices implanted in Canadian hospitals (inpatient or day surgeries), 22,770 were accounted for by pacemakers and defibrillators, including both de novo implants and revision procedures for the 1-year period. Along with the rising implant rates has come the realization that the systems themselves have increased in complexity, moving from single-chamber fixed-rate pacemakers to include multi-chamber, rate-responsive pacemakers that are capable of
necessitating complete and timely removal of the device and leads in order to eradicate the infection. In addition, the translation of knowledge from an extensive literature to a disparate group of medical practitioners has often been inadequate. This review of CIED infection management highlights the significant advances made during the past decade, including diagnostic criteria, advanced imaging, and next-generation sequencing for culture-negative cases or those in which uncertainty remains. We also outline the role and indication for powered lead extraction, the process of antibiotic choice and treatment duration, considerations related to the timing and location for reimplantation, and preimplantation risk stratification and associated interventions to reduce the risk of CIED infection.

cardioversion and defibrillation (ICDs) and/or CRT. Indeed, in recent years, dual-chamber pacing has become much more frequently used than single-chamber pacing, with the major increases in device implantation being driven by ICDs and CRT-capable devices.1,2 Increases in device implantation are being driven by ICDs and CRT-capable devices.1,2 Dual-chamber pacing has become much more frequently used than single-chamber pacing, with the major increases in device implantation being driven by ICDs and CRT-capable devices.1,2

CIED infection has a major impact on mortality, quality of life, healthcare utilization, and costs.2,3 CIED infection increased the risk of in-hospital mortality by more than 2-fold, with an estimated in-hospital 30-day mortality from CIED infection of 5%-8%.4 A retrospective cohort study of all CIED implantations (n = 17,584) between April 2013 and March 2016 in Ontario identified 215 patients (1.2%) who developed infection, including 88 early-onset (day 0-30), 85 mid-onset (day 31-182), and 42 late-onset (day 183-365) infections. The total mean 1-year health costs were highest for late-onset infections ($113,778 in Canadian dollars [CAD]), followed by mid-onset (CAD$85,302), and then early-onset (CAD$75,415) infections; by contrast, the costs for uninfected patients were CAD$25,631.4 A single-centre retrospective analysis of CIED infection-related costs in Quebec demonstrated a median cost of CAD$26,879 per patient.5

A recent worldwide survey demonstrated considerable regional disparities and variable adherence to clinical practice guidelines for the prevention and management of CIED infection.6 The purpose of this document is to provide a synopsis of the current literature and various guideline recommendations relevant to CIED infections. This document is intended for a broad range of clinicians who may encounter patients with a CIED and a clinical presentation compatible with device-related infection. This includes family practitioners, emergency room physicians, internists, cardiologists, cardiac surgeons, and infectious diseases physicians.

Background

Clinical manifestations of cardiac device infections vary from local pocket infection (eg, erythema or frank purulent discharge of the generator-pocket site) and/or cutaneous mechanical erosion of the generator/leads to systemic symptoms due to bloodstream infection or endocarditis. In a recent prophylaxis study conducted mainly in Canada, among 128 patients with CIED infections who required surgical intervention, evidence of pocket infection and/or erosion was seen in 73%, and bloodstream infection and/or endocarditis in 38%.7 Most often, pocket infection develops due to perioperative contamination of the leads or generator,8 or erosion of the generator through the skin. Deeper infection of the transvenous portion of the leads develops due to intravascular tracking from a pocket infection or hematogenous seeding from a remote source.9 Although most CIED infections are believed to result from the device implantation procedure, the recent Prevention of Arrhythmia Device Infection Trial (PADIT) of intensive antimicrobial prophylaxis showed no significant effect on the overall risk of infection over and above that provided by standard preoperative antimicrobial prophylaxis.10 One proposed explanation for this finding is that the proportion of CIED infections that have their onset postimplantation may be greater than previously thought.10

Incidence

In comparison to devices without transvenous leads (eg, leadless pacemakers, subcutaneous ICDs, and loop recorders), those that do have transvenous leads have been associated with a higher incidence of CIED infection, including pacemakers (1.19%), ICDs (1.91%), CRT-pacemakers (2.18%), and CRT-defibrillators (3.35%).11 The incidence rates are also higher with replacement, compared to de novo, CIED implants.3,11 The use of a subcutaneous ICD has been demonstrated to be non-inferior to a transvenous ICD, with respect to device-related complications during a median follow-up of 49 months, including vis à vis infections, which occurred in 0.93% and 1.89% of cases, respectively.12 Recent experience with the Reveal LINQ implantable cardiac monitor (loop recorder; Medtronic, Minneapolis, MN) demonstrated a low infection rate at a median follow-up of 16 months, with 8 cases (0.56%) requiring device explantation, which included 3 with pocket-site erosion among 1420 patients.13 Leadless pacemakers rarely become infected.14,15 In a prospective study of 725 patients implanted with a leadless pacemaker, no systemic infections were documented during a 6-month follow-up period.16 In an observational cohort study involving 6219 patients with a leadless pacemaker and 10,212 patients with a transvenous pacemaker, at 2 years of follow-up, the
incidence of infection was < 0.16% and 0.6%, respectively (see Supplemental Data from El-Chami et al.15).12

**Microbiology**

Coagulase-negative staphylococci (CoNS; 42%-77%, using the number of isolates as the denominator, because polymicrobial infections will result in the total number of cultured organisms exceeding the number of patients studied) account for the majority of CIED infections, followed by *Staphylococcus aureus* (10%-30%), gram-negative bacilli (6%-11%), *Streptococcus* spp. (3%-10%), *Enterococcus* spp. (0.4%-10%), *Catabacterium* spp. (formerly *Propionibacterium* spp.; 0.8%-8%), and fungi (0.4%-1.4%).13 Methicillin-resistant staphylococci (both coagulase-negative and -positive) account for approximately one third of all cases.3 The proportion of patients with CIED infection due to methicillin-resistant *Staphylococcus aureus* (MRSA) was 15% in a large single-centre US study that included 816 consecutive patients undergoing device removal for confirmed infection.14 In contrast, a large, single-centre Italian study identified MRSA as the etiologic agent in only 19 of 1204 consecutive patients (1.6%) undergoing device removal for suspected CIED infection during the same time period.13 Similarly, confirmed CIED infections due to MRSA in the PADIT trial accounted for < 5% of patients in the control arm, with patients enrolled from mainly Canadian and some Dutch centres.13

**Risk factors**

A systematic review and meta-analysis of CIED infection that included 60 studies and 206,528 patients was published in 2015.20 Host-related factors include the following: chronic kidney disease (odds ratio [OR] = 3.02 [95% confidence interval [CI] 1.38-6.64]) or end-stage renal disease (OR = 8.73 [95% CI 3.4-22.3]); previous CIED infection (OR = 7.84, [95% CI 1.94-31.6]); long-term corticosteroid use (OR = 3.44 [95% CI 1.6-7.3]); anticoagulant use (OR = 1.59 [95% CI 1.01-2.4]); diabetes mellitus (OR = 2.08 [95% CI 1.62-2.67]); chronic obstructive pulmonary disease (OR = 2.95 [95% CI 1.78-4.90]); malignancy (OR = 2.23 [95% CI 1.26-3.95]); and heart failure (OR = 1.65 [95% CI 1.14-2.39]).14 Procedure-related factors include the following: postoperative hematoma (OR = 8.46 [95% CI 4.0-17.8]); re-intervention for lead dislodgment (OR = 6.37 [95% CI 2.9-13.8]); device replacement or revision (OR = 1.98 [95% CI 1.46-2.70]); pre-implant temporary pacing (OR = 2.31 [95% CI 1.36-3.92]); and an inexperienced operator, defined as one who has performed less than 100 previous procedures (OR = 2.85 [95% CI 1.23-6.58]).14 Device-related factors include the presence of epicardial leads (OR = 8.09 [95% CI 3.4-18.9]); abdominal generator pocket (OR = 4.0 [95% CI 2.4-6.4]); and positioning of 2 or more leads (OR = 2.02 [95% CI 1.11-3.69]).20

PADIT was a recent, large cluster crossover trial of conventional vs intensive antimicrobial prophylaxis performed in 19,603 patients that identified 5 non-modifiable risk factors for CIED infection. These include the following: younger age; procedure type (ICD, CRT, or revision/upgrade procedure); renal dysfunction; an immunocompromised state; and prior CIED procedures.21 The study generated the novel PADIT infection risk score, which was internally validated.21 Another large, CIED infection prophylaxis study (World-wide Randomized Antibiotic Envelope Infection Prevention Trial [WRAP-IT]) enrolled close to 7000 patients and identified risk factors for infection; these include modifiable procedural factors such as longer procedure time, implant location (non-left pre-pectoral), perioperative glycopeptide antibiotic (vs non-glycopeptide), anticoagulant and/or antiplatelet use, and capsulectomy.22

**Management**

An approach to the diagnosis and treatment of CIED infection is outlined in the management algorithm (Fig. 1).

**Diagnosis**

**Triage and referral**

Patients suspected of having a CIED infection should be evaluated by a multidisciplinary team including a cardiologist and/or cardiac surgeon experienced in CIED infections, and an infectious diseases specialist, with input from imaging specialists.27 This approach is applicable to those who develop symptoms at the generator pocket site and/or unexplained fever or bloodstream infection.28 If uncertainty remains regarding the diagnosis after investigations, then a lead-extraction program clinician should be consulted. The triage and referral process is outlined in the triage algorithm (Fig. 2).

**Clinical assessment**

Although CIED infections are most often encountered during the first 6 months following device implantation, they continue to occur for years beyond that time.29 Infections limited to the device pocket site tend to occur somewhat earlier than those that are systemic. In a recent study that included a 36-month follow-up time, pocket-only and systemic infections occurred a mean of 174 days and 258 days after the procedure, respectively.30 Symptoms and signs associated with CIED infection include those related to the device pocket site (eg, pain, erythema, warmth, swelling, ulceration, and drainage) and/or systemic symptoms (eg, fever, chills), and those related to metastatic sites of infection (eg, left- or right-sided endocarditis, osteomyelitis).29 Laboratory studies should include blood cultures (prior to antibiotic initiation), complete blood counts and differential, and C-reactive protein level. Normal results for these investigations do not exclude CIED infection. Arterial emboli and cutaneous signs of endocarditis are seldom present in CIED-related infection unless left-sided valve involvement is present.

**Considerations for novel CIEDs**

**Leadless pacemakers.** These devices, which have no subcutaneous generator pocket and no transvenous leads, rarely become infected.15 For patients with these devices, blood cultures and echocardiography are required only if symptoms or signs suggest systemic infection (eg, fever, chills).

**Subcutaneous ICDs.** Infections usually occur within the first year and may present with inflammatory changes at the
Figure 1. Management algorithm (adapted with permission from DeSimone and Sohail23 and the American Society for Microbiology). CIED, cardiovascular implantable electronic device; FDG-PET/CT, fluorine-18-fluorodeoxyglucose positron emission tomography-computed tomography; TEE, transesophageal echocardiogram; TTE, transthoracic echocardiogram; WBC SPECT/CT, 99mTc-hexamethylene diphosphonate labeled autologous white blood cell single-photon emission computerized tomography/computerized tomography.a Pocket-site findings: unequivocal signs of pocket infection include discharge, or erosion through the overlying skin. If suspect only superficial infection (eg, cellulitis, stitch abscess), particularly in the 1st month after implantation, then draw blood cultures and consider empiric trial of oral anti-staphylococcal therapy without device removal (see Differential Diagnosis section in text). If the clinical diagnosis of pocket infection is uncertain, then consider FDG-PET/CT or WBC SPECT/CT. b Suspect endocarditis: eg, constitutional symptoms (eg, fevers), septic pulmonary emboli, new regurgitant murmur.c TTE, then do TEE: In addition to providing a new baseline study for future comparison, TTE offers complementary information24 and may shorten the duration needed for a TEE procedure, which in some cases may not be well tolerated. Given the evidence for improved survival associated with early removal of infected devices within 1 week of hospitalization,25 orders for both studies (TTE and TEE) may be submitted simultaneously in order to minimize delays, but with the expectation that the TEE preferably would be done first. This is also consistent with the proposed Canadian benchmark for an urgent echocardiogram within 7 days,26 which in this circumstance is the TEE rather than just the TTE. d Consider other imaging for extent of disease, other source, etc (eg, FDG-PET/CT or WBC SPECT/CT; intracardiac echocardiography). If FDG-PET/CT not available or findings are equivocal, then consider WBC SPECT/CT. FDG-PET/CT can be utilized in both early and late CIED infection.24 e CIED extraction: At device removal, obtain pocket-site tissue (þ/- swabs) for culture, and submit the whole device and leads in a sterile container to the microbiology laboratory for sonication prior to culture. 1 Antibiotic duration: The start is timed from the date of CIED extraction or from the date when blood cultures became negative, whichever occurred last. 2 Lead endocarditis antibiotic duration: (a) Staphylococcus aureus, 4 wk; (b) other bacteria, 2 wk. 3 Pocket-infection antibiotic duration: (i) infection: 10–14 d; or (ii) erosion through skin without purulence or discharge: 7–10 d. Antibiotic intravenously until blood cultures confirmed negative, then complete therapy orally. 1 Consider CIED extraction according to blood cultures:2,28: (i) extract if single blood culture is positive for S. aureus, or Candida spp, or multiple blood cultures are positive for coagulase-negative staphylococcus or Cutibacterium spp. (formerly Propionibacterium spp.) when no other source is identified; (ii) extract if recurrent or persisting bacteremia or fungemia due to any organism when no other source is identified; (iii) consider extraction if blood culture is positive for alpha-hemolytic or beta-hemolytic streptococci, or enterococci; and (iv) retain the CIED for bacteremia due to pneumococcus or gram-negative bacilli, and repeat blood cultures 2 wk later after antibiotic completed. 1 Response to oral antibiotic: For suspected superficial pocket-site infection, a trial of therapy is recommended for 7-14 d with an anti-staphylococcal regimen (see Differential Diagnosis section in text).
pocket site and/or the parasternal lead incision site, but systemic infection is rare. As a result, the diagnostic evaluation of patients suspected to have a subcutaneous-ICD infection does not routinely include blood cultures or echocardiography. A trial of empiric antibiotic therapy should be given to patients with suspected superficial infection and those in whom the diagnosis remains uncertain, before device extraction is considered. Further investigation (eg, a nuclear medicine study) may be needed in order to clarify the diagnosis.

Loop recorders. As for subcutaneous ICDs, infections involving these devices present with inflammatory changes at the pocket site, but they rarely result in systemic infection. Blood cultures and echocardiography are usually not required in the diagnostic evaluation, except for patients at risk of developing infective endocarditis (IE).

Differential diagnosis

Pocket-site infection needs to be clinically differentiated from other causes of inflammation in the vicinity of the device, including superficial skin and soft tissue infection (eg, cellulitis and incisional infection such as a stitch abscess), hematoma, and allergic reactions to dressings, tape, or topical disinfectants, particularly during the first month following device implantation. When superficial infection is suspected, an empiric trial of oral anti-staphylococcal therapy (after blood cultures have been collected) is warranted for 7-14 days. Antibiotic options include cephalaxin monotherapy (or in combination with doxycycline or trimethoprim-sulfamethoxazole), or monotherapy with clindamycin, trimethoprim-sulfamethoxazole, doxycycline, or linezolid. The use of linezolid is often restricted to infectious diseases specialists due to cost, toxicity, and concerns related to the possible development of resistance. Resolution of the superficial inflammation avoids the need for device removal and may be documented with serial photographs; however, close follow-up is needed in order to detect recurrence. If uncertainty continues regarding the presence of pocket-site infection, then a nuclear medicine study should be considered (see Nuclear Medicine section).

Microbiology investigations

At the time of first seeking medical attention for unexplained febrile illness, or possible “lower respiratory tract infection,” patients with a CIED should have a minimum of 2 sets of blood cultures collected prior to initiation of any empiric antibiotic therapy. For those suspected of having CIED infection (eg, pocket-site symptoms), at least 3 sets of blood cultures should be drawn at the initial evaluation, before initiation of any empiric antimicrobial therapy. Any positive blood cultures should be followed up with repeat blood cultures 48-72 hours later, and should be repeated every 48 hours until they are negative.

When the CIED is explanted, generator pocket tissue gram stain and culture should be obtained, rather than just swabs.
The sensitivity for organism recovery from tissue specimens from the pocket site (69%) has been greater than that of pocket swab cultures (31%). The whole explanted device and leads should be submitted to the microbiology laboratory in a sterile container for sonication prior to culture. CIED device sonication disrupts the hardware-related biofilm and has been associated with increased recovery of bacterial isolates. Advance notification of the microbiology laboratory that an explanted device will be submitted for sonication and culture can facilitate processing of the specimen.

If bacterial cultures are negative, then mycobacterial and fungal cultures can be requested along with polymerase chain reaction testing on any residual specimens for organisms missed on routine culture. Recent experience suggests an improved yield on microbiology specimens for a causative organism in 95% of patients with the addition of sonication fluid undergoing both conventional cultures and next-generation sequencing. Next-generation sequencing is most relevant for patients whose conventional cultures remain negative; however, its limitations include restricted availability at reference laboratories, and in some cases, difficulty differentiating true pathogens from false positives due to specimen contamination.

Lead-tip cultures may be positive in patients with isolated pocket infection, given that the leads are withdrawn through an infected pocket site. In the absence of other evidence of lead endocarditis (eg, positive blood cultures, echocardiogram, or nuclear medicine study findings), a positive lead-tip culture does not warrant a prolongation of antibiotic therapy duration.

Percutaneous aspiration of the generator pocket should not be performed as part of the diagnostic evaluation of suspected CIED infection, given the risk of inadvertent pocket-site contamination, in addition to the difficulty of evaluating the significance of organisms that may be skin contaminants from the procedure. Also, collection of a pre-operative culture obtained by passing a swab through a draining sinus may give misleading results and is discouraged.

Imaging

**Echocardiography.** A transthoracic echocardiogram, and then also a transesophageal echocardiogram (TEE), should be obtained for suspected CIED-related endocarditis (eg, positive blood cultures, history of constitutional symptoms, or presentation suggestive of right-sided endocarditis with septic pulmonary emboli). Intracardiac echocardiography has demonstrated high sensitivity for detection of vegetations on cardiac devices and has at times been utilized during lead extraction, but it is not routinely performed. TEE should be done to evaluate the left-sided heart valves, even if transthoracic views have demonstrated lead-adherent masses.

A lead mass is not an uncommon TEE finding, and in the absence of other evidence of infection, it is unlikely to represent IE and should not prompt lead (and CIED) removal. A study of TEE (ordered for various reasons) findings among 153 patients with pacemakers or ICDs showed a device lead mass in 25 patients (16%). IE was diagnosed in 17 patients, of whom 8 (47%) had a lead mass on TEE. No evidence of an infective process was seen in the other 17 patients (72%) who had a demonstrable lead mass by TEE. In the same study, among 136 TEE examinations performed for indications other than suspected IE, lead masses were noted in 13 studies (10%), but only one patient was judged to have IE.

Echocardiography in limited pocket-site infection previously has been considered unnecessary in patients with negative blood cultures (collected prior to antibiotics) and no other clinical suspicion of systemic infection or endocarditis. However, both a transthoracic echocardiogram and a TEE have now been recommended, in a recent international guideline, for all patients with CIED infection. Whether the addition of echocardiography to the management of patients with clinical evidence of infection limited to the pocket site is associated with improved patient outcomes remains unclear. Furthermore, detection of a noninfectious lead thrombus or fibrous adhesion in such patients may result in unnecessarily prolonged antibiotic treatment. Nuclear medicine studies (fluorodeoxyglucose positron emission tomography/computed tomography [FDG-PET/CT] or white blood cell single-photon emission computerized tomography/computerized tomography [WBC SPECT/CT], as outlined below) may help clarify the significance of lead masses detected on echocardiography.

**Nuclear medicine.** The 2 relevant studies for CIED infection are whole-body fluorine-18 (18F)-FDG-PET/CT and 99mTc-hexamethylpropylene amine oxime labeled (99mTc-HMPAO) autologous-WBC SPECT/CT (also referred to as WBC SPECT/CT). 18F-FDG is a glucose analog, with a positron-emitting radionuclide fluorine-18. The accumulation of 18F-FDG in tissue is a marker of the metabolic process of glucose uptake in tissues, which may be increased in various conditions including neoplastic, inflammatory, and infectious diseases. By contrast, radio-labeled leukocytes accumulate at sites of leukocyte recruitment, which is more specific for infection. Performance of FDG-PET/CT is optimized in regard to both sensitivity and specificity by dietary preparation in order to reduce physiologic uptake of FDG by cardiomyocytes. Patients scheduled for an early-morning FDG-PET/CT study should have at least one high-fat/low-carbohydrate meal (dinner) the evening before, followed by a 12-hour fast. For late-morning or early-afternoon studies, a high-fat/low-carbohydrate breakfast should be followed by at least a 4-hour fast beforehand. Prolonged antibiotic use has been associated with reduced sensitivity for both FDG-PET/CT and WBC SPECT/CT.

The advantages of these whole-body functional imaging tools compared to echocardiography or CT are possible earlier diagnosis before the development of anatomic abnormalities and potentially additional information regarding embolism and extracardiac sites of infection. Among patients with suspected CIED infection, the nuclear medicine studies have been most helpful in those for whom diagnostic uncertainty continues following the initial investigations, including echocardiography. For example, when a pocket-site infection is suspected but the clinical findings are inconclusive, or if
systemic symptoms are present with or without bacteremia, but with negative echocardiography and no local findings to indicate pocket infection.

A meta-analysis of 14 studies with $^{18}$F-FDG PET-CT showed a pooled sensitivity and specificity for pocket infections of 96% and 97%, respectively. In contrast, the sensitivity and specificity for lead infection and CIED endocarditis were lower, at 76% and 83%, respectively. However, a number of the studies were not designed specifically to detect IE and lacked the dietary preparation protocol used to ensure suppression of myocardial physiological uptake of $^{18}$F-FDG. Although mild increased physiological uptake of $^{18}$F-FDG related to normal wound healing occurs in the first few months after device implantation, it can be differentiated from infection on the basis of reduced intensity and localization to the junction between the leads and the connector. In contrast, uptake around the generator and over the leads favors a pocket infection.

Timely access to a PET-CT scan is limited in some regions. Although published experience using WBC SPECT/CT for this indication is more limited, it may be more readily available, and in one study, the sensitivity and specificity for detection of CIED infection were 94% and 100%, respectively. A retrospective study limited to 48 consecutive patients being evaluated for CIED infection who had undergone both studies compared the performance of FDG-PET/CT and WBC SPECT/CT. The diagnostic sensitivity, specificity, positive and negative predictive values were, respectively, 80%, 91%, 80%, and 91% for FDG-PET/CT, and 60%, 100%, 100%, and 85% for WBC SPECT/CT. WBC SPECT/CT has lower sensitivity but higher specificity than FDG PET-CT for CIED infection.

In summary, the indication for a nuclear medicine study in suspected CIED infection is for those patients for whom there is diagnostic uncertainty, and who are categorized as “possible” by either the 2019 international CIED Infection criteria or the Duke-Li IE criteria. The preferred investigation, if available, is FDG-PET/CT, given its higher sensitivity, speed, and practicality. The role of WBC SPECT/CT is for use in patients without ready access to FDG-PET/CT, or for whom results are equivocal using FDG-PET/CT.

Other imaging

A chest radiograph should be performed in all patients with suspected CIED infection.

Right-sided endocarditis may present with a clinical picture that mimics pneumonia and/or pleurisy. Pulmonary CT angiography may need to be considered in patients presenting with what appears to be recurrent pneumonia if other investigations are nondiagnostic regarding the possibility of septic pulmonary emboli due to CIED-related endocarditis.

Diagnostic criteria for CIED infection

The Utility of the modified Duke criteria (Duke-Li criteria) for the diagnosis of CIED-related lead infection and/or valvular IE has not been established. Diagnostic classification criteria for CIED infection (pocket, and/or IE) have recently been proposed by an international group convened by the European Heart Rhythm Association (EHRA), as outlined in Table 1. This classification is based on the merging of the modified Duke criteria and the European Society of Cardiology (ESC) 2015 guidelines for the management of IE, but it has yet to be validated.

Antimicrobial Management

Empiric and directed treatment

After collection of blood cultures, vancomycin is usually recommended for empiric treatment of a pocket infection. Daptomycin is an acceptable alternative for patients who cannot tolerate vancomycin. Consideration of empiric antimicrobial coverage for patients with possible CIED infection and a suspected bacteremic presentation should take into account clinical findings and epidemiologic factors and the need for inclusion of coverage for gram-negative bacilli pending blood culture results. Patients who are afebrile, are hemodynamically stable, and have a normal peripheral white blood cell count are unlikely to have bacteremia. Such patients who do not have systemic inflammatory response syndrome (SIRS) criteria (temperature $>$ 38.3°C or $<$ 36°C, pulse $>$ 90/min, respirations $>$ 20/min, white blood cell count $>$ 12.0 or $<$ 4.0 x 10^9/L) or blood pressure with a $<$ 90 mm Hg or $>$ 40 mm Hg drop from baseline may have antibiotic therapy withheld until operative cultures are collected, in order to optimize the intraoperative culture yield. Directed treatment is based upon final culture and susceptibility results.

Duration of treatment

The duration of treatment for the various CIED infection presentations is outlined in Table 2.

Removal of infected CIED

Lead extractions should be performed only in facilities that provide adequate support for a lead-extraction program, including the management of complications. This support includes the immediate availability of a cardiac surgeon and surgical team with equipment to perform a thoracotomy or sternotomy. Recommendations for the requirements for physicians and surgeons regarding training and maintenance of competency for CIED therapies, including device implantation and extraction, have been published by the Canadian Heart Rhythm Society Task Force. Transvenous lead extraction (TLE) is usually accomplished with either the laser sheath technique or a rotating sheath technique. The indications for complete device and lead removal are outlined in Table 3. All patients should have blood cultures collected 48-72 hours after CIED removal.

Improved survival has been associated with prompt removal of the device and leads following determination of the diagnosis of CIED infection. In a recent study, delayed CIED extraction (defined as beyond the 7th hospital day) was associated with increased 1-year mortality for patients with bacteremia or localized pocket infection. Removal of the device and leads is recommended by percutaneous transvenous extraction. However, if lead vegetations are $>$ 20-30 mm, then either an alternate surgical extraction method or
percutaneous aspiration of vegetations prior to transvenous extraction should be considered. CIED removal is not indicated for a superficial or incisional infection without involvement of the device and/or leads.

Coexistent LVAD in patients with CIED infection

Most patients with a left ventricular assist device (LVAD) also have a CIED.53 As for other patients, if the CIED becomes infected, then it should be removed. However, for those with CIED lead IE or valvular IE, the LVAD would presumably also be infected, making it necessary to initiate chronic suppressive antimicrobial therapy for concomitant LVAD infection.53

New CIED Implantation After Removal of an Infected Device

A determination should be made as to whether a continued need for a CIED is present. Up to one half of patients may not require device reimplantation.54 The replacement device implantation should not be ipsilateral to the extraction site. Preferred alternative locations include the contralateral side, epicardial, internal jugular vein, and leadless (bradycardia pacing) or extravascular implantation (defibrillator). The optimal timing for implantation of a new device is outlined in Table 3.

Risk-benefit considerations regarding implantation of a new device should include various risk factors for CIED infection (eg, end-stage renal disease with repeated microbial exposure during intravenous access). Alternative novel devices should be considered in those at particularly high risk. The use of an extravascular (EV) ICD, such as a subcutaneous ICD, avoids the drawbacks related to transvenous leads and may be associated with a reduced risk of life-threatening systemic infection. The infection rate requiring device removal in the Evaluation of Factors Impacting Clinical Outcome and Cost Effectiveness of the S-ICD (EFFORTLESS) study over a 3-year follow-up period was only 2.4%. Leadless pacemakers also have been used successfully in those at high risk for infection, such as dialysis patients.55

Bridging for pacemaker-dependent or ICD-dependent patients

Additional options have been evaluated recently for bridging the time before implantation of a new CIED for patients who are pacemaker-dependent. The traditional temporary transvenous pacing balloon-tipped wire is associated with various complications and largely has been replaced with

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**Table 1. Recommendations for diagnosis of CIED infections and/or IE: the Novel 2019 International CIED Infection Criteria**

| Major criteria Microbiology: |
|-----------------------------|
| A. Blood cultures positive for typical microorganisms found in CIED infection and/or IE (coagulate-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 1 positive blood culture: |
| 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, or intracardiac fistula
   iii. Valvular perforation or aneurysm
   iv. New partial dehiscence of prosthetic valve
E. 18F-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

a. Predisposition such as predisposing heart condition (eg, 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 emboli, infectious (myotic) aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway’s lesions
d. Microbiologic evidence: positive blood culture that does not meet a major criterion as noted above or serologic evidence of active infection with organism consistent with IE or pocket culture or leads culture (extracted by noninfected pocket)

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18F-FDG PET/CT, whole body fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography; CIED, cardiovascular implantable electronic device; HACEK, Haemophilus aphrophilus, (now called Aggregatibacter aphrophilus), Aggregatibacter actinomycetemcomitans, Cardiovascular aerobes, Eikenella corrodens, and Kingella kingae; ICE, intracardiac echocardiography; IE, infective endocarditis; S. aureus, Staphylococcus aureus; WBC SPECT/CT, 99mTc-hexamethypropylene amine oxime labeled autologous white blood cell single-photon emission computerized tomography/computerized tomography.
an active-fixation lead secured through the contralateral internal jugular, axillary, or subclavian vein access attached to an external pulse generator that allows patients to be managed with internal jugular, axillary, or subclavian vein access attached to an external de

blood cultures positive

Table 2. Duration of antimicrobial therapy for CIED infection when the device can be removed

| Extent of infection       | Duration* |
|---------------------------|-----------|
| Pocket site               | 7–14 d    |
| Pocket-site infection     | 10–14 d   |
| CIED erosion through skin without obvious purulence | 7–10 d |
| Blood cultures positive   | 4–6 wk    |
| Valve vegetation          |          |
| Lead vegetation:          |          |
| Uncomplicated             |          |
| Complicated (eg, septic phlebitis, osteomyelitis) | |
| TEE-negative:             |          |
| Staphylococcus aureus     | 4 wk      |
| non-S. aureus             | 2 wk      |

CIED, cardiovascular implantable electronic device; TEE, transesophageal echocardiogram.

* Duration is counted from the date of device explantation or (for those with bacteremia) the date blood cultures became negative, which ever occurred last.28

1 Provided blood cultures collected prior to administration of antibiotics were negative.

2 Treatment can be changed from intravenous to an active oral antibiotic once susceptibility results are available and the infected CIED has been removed.28

3 Blood cultures positive or no blood cultures performed prior to administration of antibiotics.

4 Treatment as for endocarditis.28,35,47

Long-term Indefinite Suppressive Antimicrobial Therapy

Long-term suppressive therapy should be considered for only those patients who have CIED infection and are not candidates for complete device removal. Such patients may have unacceptable risk of device removal, inability to reimplant, loss of CRT, high risk of reinfection related to inadequate source control of infections at other sites, or life expectancy of less than 1 year.28,66 For this approach to be viable, an initial 4-6-week course of intravenous antibiotic therapy should be given, as for prosthetic valve endocarditis associated with clinical improvement and clearance of bacteremia (if present), followed by long-term suppressive oral antimicrobial therapy.3

Prevention

The pre-procedural, peri-procedural, and post-procedural measures for reducing the risk of CIED infection are outlined in Table 4. Among the pre-procedural measures, the benefit of antibiotic prophylaxis was demonstrated in a double-blind, placebo-controlled trial in which the infection rates for cefazolin (1 gm immediately preoperation) and placebo were 0.63% and 3.28%, respectively (risk ratio 0.19, P = 0.016).28 Cefazolin is preferred (intravenously within 1 hour before incision); vancomycin is an alternative (intravenously within 2 hours before incision).28,35 More recently, the PADIT trial evaluated incremental antimicrobial prophylaxis (cefazolin plus vancomycin IV, plus intraprocedural bacitracin pocket wash, plus 2 days of oral cephalaxin post-procedure) vs conventional prophylaxis (cefazolin IV) in a cluster randomized crossover trial in 19,603 patients.7 A lower-than-expected hospitalization rate for infection was observed in the control arm (1.03%), and a trend toward reduced infection was observed in the incremental arm (0.78%) which was not statistically significant (OR = 0.77, 95% CI 0.56 to 1.05; P = 0.10).7

The use of the Medtronic (Minneapolis, MN) TYRX antibacterial-eluting envelope (minocycline and rifampin for at least 7 days into the pocket environment) with CIED implantation was recently evaluated for the prevention of infection in an RCT involving 6983 patients (the WRAP-IT study). The 12-month infection-related event rates were 0.7% and 1.2% for the envelope and control groups, respectively (hazard ratio 0.60, 95% CI 0.36-0.98; P = 0.04).73 The benefit was noted for pocket infections associated with high-powered devices (ICD and CRT-defibrillator). More episodes of bacteremia or CIED-related endocarditis occurred in the envelope group, a difference that was not statistically significant (hazard ratio = 1.57, 95% CI 0.61-4.05).

Antimicrobial prophylaxis for invasive procedures in patients with CIEDs

Antimicrobial prophylaxis is not recommended for dental or other invasive procedures (not directly related to device manipulation) to prevent CIED infection.7 Secondary prophylaxis is only recommended for the incision and drainage of infection at other sites or for replacement of an infected device.74

Microbiological Studies in Cases of CIED Removal for Noninfectious Reasons

Routine microbiological studies should not be conducted on CIEDs that have been removed for noninfectious reasons.28 A number of studies have found positive cultures for various bacteria in specimens obtained from pocket sites or sonication fluid of extracted generator or leads in up to one-third or more of patients who underwent device removal for other indications in the absence of any clinical suspicion of device infection.75,77 However, still unclear is what
Timing considerations for new device implantation

Blood cultures should be repeated after device removal and should be negative for at least 72 h before new device placement.

New device implantation should be delayed for at least 14 d after CIED system removal when there is evidence of CIED-endocarditis. The delay of at least 14 d has been associated with a survival benefit, particularly when a valve vegetation has been demonstrated.

New device implantation should be delayed until any other undrained site of infection has undergone adequate source control (eg, pus abscess).

Conclusion

CIED infections account for considerable morbidity and mortality. Recently, a number of promising diagnostic advances have helped minimize the underdiagnosis and overdiagnosis of CIED infections, both of which are associated with unfavourable consequences. The recent progress in risk stratification and infection prevention measures is particularly important. Optimal management requires the early involvement of clinicians with experience in CIED infection, including those at the regional device-extraction facility. Coordination of care among all providers involved, spanning the range from the primary care provider to the device implantation and extraction clinician, is essential.

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