Cardiovascular Implantable Electronic Device Infections

A Contemporary Review

Catherine G. Bielick, MD, MSc[a,b,*], Christopher J. Arnold, MD[a,1], Vivian H. Chu, MD, MHS[c]

KEYWORDS

• Cardiovascular implantable electronic devices • Infection • Endocarditis
• Pacemaker • Implantable cardioverter defibrillator

KEY POINTS

- Coagulase-negative staphylococci and *Staphylococcus aureus* are the major causative pathogens.
- Diagnosis is based on clinical presentation along with adjunctive tools such as blood cultures, pocket tissue cultures, echocardiography, and in some cases fluorodeoxyglucose PET/computed tomography.
- Complete device extraction is an important component of the management of cardiac device infections.
- Duration of antibiotic therapy and timing of device reimplantation depends on the extent of infection.
- Newer technologies are in development to help reduce the risk of device infection among high-risk populations.

INTRODUCTION

Life-saving cardiac implantable electronic devices (CIEDs) are being placed in a growing number of patients with cardiovascular disease, though related complications can have devastating morbidity and mortality.[1] CIED infection (CDI) is a complication associated with a 1 year mortality rate ranging from 18% to 20% if optimally treated to as high as 66% if untreated.[2,3] Utilizing data from a large inpatient sample in the United States (US), one report found mean hospitalization charges to be US$56,000, with a

[a] Division of Infectious Diseases, University of Virginia, Charlottesville, VA, USA; [b] Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Hospital Medicine, West Span 201, Boston, MA 02215, USA; [c] Division of Infectious Diseases, Duke University Health System, Box 102359, Durham, NC 27710, USA
[1] Present address: 1300 Jefferson Park Avenue 5th Floor, Charlottesville VA, 22903.
* Corresponding author. 337 Washington Street, Somerville MA, 02143.
E-mail address: cgbielick@gmail.com

Infect Dis Clin N Am 38 (2024) 673–691
https://doi.org/10.1016/j.idc.2024.07.004 **id.theclinics.com**

mean length of stay of 17 days and 9.2% of cases resulting in in-hospital mortality.[4] The technology is rapidly evolving with brand new types of devices being placed in this past decade, which can present very differently when infected. It is essential for physicians to be familiar with the clinical presentation, management, and prevention of CDIs to best care for this vulnerable population.

EPIDEMIOLOGY

CIEDs have had a growing number of indications for the placement and complexity of device type resulting in a proportionally increasing number of device infections. The prevalence of people living with CIEDs was estimated to be over 3 million worldwide in the year 2000, and since then rates of device placement have continued to increase.[5,6] While rates of CIED implantation are now actually decreasing, rates of CDI are unfortunately continuing to rise.[7–11] An accurate estimate of CDIs has historically been limited by the need for prolonged follow-up in cohort samples (>3 years), and therefore, the use of national hospitalization data may be the clearest.[12,13] One such report found that in 2006 over 350,000 hospitalizations were related to device-related procedures, with 1.5% related to a device infection. By comparison, in 2012 of nearly 250,000 procedures, 3.4% were related to device infection.[6] Another reference noted that while the estimated number of hospitalizations in the United States involving new CIED implantations declined further in 2016 to 191,610, the estimated number of hospitalizations with a CDI increased further to 8060 (4.2%).[14] Of all CDI-related hospitalizations for that sample, 4.7% were discharged as deceased.[14]

Rates of CDI vary by geography, type of device, focus of infection (endocarditis vs pocket infection), organism involved, and number of comorbid conditions.[15] Population cohort rates of CDI historically ranged between 1 and 2 per 1000 device-years depending on follow-up time. However, a recent population cohort with a 7 year follow-up found a rate of 4.7 per 1000 person-years in 2015.[16–21] One systematic review investigated incidence rates and risk factors for CDIs in the past 20 years, finding that the infection rate overall of de novo implants ranged from 0.1% to 2.1%; with pacemakers (PMs) ranging from 0.1% to 0.5% and cardiac resynchronization therapy (CRT) devices from 0.6% to 8.6%.[22] Many other studies have similarly found the rate of CDIs among CRTs to be 2 to 5 times higher than PMs. This is thought to be related to CRTs being larger devices requiring wider incisions, implantation pockets with more skin tension, longer procedural times, and implantation in patients with more comorbidities.[1,7,16,18,20]

RISK FACTORS

Risk factors for CDIs are commonly categorized into 3 domains: patient-related, procedure-related, and device-related risk factors. Among patient-related risk factors, reports universally find a higher adjusted risk and incidence rate for CDIs among male individuals.[23,24] Other higher risk comorbidities include diabetes mellitus, heart failure, chronic kidney disease, a relatively younger age, and an immunocompromised state when adjusting for other factors.[23,24] Hemodialysis also carries an independent risk for CDI, possibly related to an overall impaired immunity and frequent vascular access procedures predisposing patients toward bacteremia.[1,25]

Risk factors related to the procedure directly and in the postprocedural period have been well described. The strongest risk factor for CDI is the need for a revision or upgrade of the device. Repeated access of the device pocket (such as for generator replacement, lead revision, or hematoma evacuation) also carries a higher risk of infection independent of device revision or upgrade.[2,9,11,13,26–29] Utilizing a bootstrapped

multivariable logistic regression, Birnie and colleagues[23] found that the adjusted odds ratio for device revision/upgrade was 4.01 (95% confidence interval [CI] 2.62–6.13) for a single procedure and 3.43 (2.14–5.48) for having had 2 or greater previous procedures. Prior infection was found to have an adjusted hazard ratio of 1.65 (1.34–2.04) for new CDI among a large Danish cohort over 36 years.[24] Conversely, prophylactic antibiotics lower the risk of postprocedural CDI. In a large systematic review of CDI outcomes, Polyzos and colleagues[1] quantified a pooled odds ratio of prophylactic antibiotics to be 0.32 (0.18–0.55) for infection. Other risk factors for infection included device revision/upgrade 1.98 (1.46–2.69), generator change 1.74 (1.22–2.49), abdominal generator pockets 4.01 (2.48–6.49), and occurrence of a perioperative hematoma 8.46 (4.01–17.86).[2,26] In a more recent systematic review, another group calculated a pooled odds ratio for postimplantation pocket hematoma to be 6.30 (3.87–10.24).[30] As for device-related risk factors, higher device complexity continues to demonstrate higher risk of infection. CRTs carry the highest risk.[11] Olsen and colleagues[24] found an adjusted hazard ratio of 2.2 for the cardiac resynchronization therapy defibrillator (CRT-D) and 1.7 for the cardiac resynchronization therapy pacemaker (CRT-P) compared with the PM reference group, where simple ICDs were 1.3. Newer technologies, such as the leadless PM, which will be further discussed in a later section, have been found to have lower infection rates.

MICROBIOLOGY

Gram-positive bacteria are implicated in the majority of CDI in all reviews, whether involving the generator pocket or the leads directly.[31–34] Coagulase-negative staphylococci (CoNS) and *Staphylococcus aureus* account for 70% to 89% of infections in most studies.[8,17,20,26,31,32,34–38] Among these, the most commonly implicated Gram-positive bacteria are CoNS, which must be carefully evaluated before dismissing as a contaminant.[29,39,40] These species produce biofilm exopolymer, which simultaneously protects from antibody recognition and promotes resistance to phagocytosis.[29,41] The major microbiologic etiologies of cardiac device infection are shown in **Fig. 1**.

When controlling for significant comorbidities each species is associated with similar in-hospital and 1 year mortality risk.[42] However, in survival analysis, *S aureus* was found to be associated with higher probability of repeat infection and overall mortality over time.[34] Bacteremia due to *S aureus* (SAB) alone has been associated in 2 recent studies with definite CDI in 51% to 52% of cases, which is consistent with prior literature.[41,43,44] This finding is likely related to the known strong association of SAB with endovascular infections and is much more likely to present with systemic signs and symptoms of infection than CoNS.[45,41,46] When SAB occurs less than 1 year after device placement, one study found a 75% association with definite CDI—possibly due to a higher likelihood of the CIED as the source of bacteremia. SAB greater than 1 year from device placement had a much lower association, with 28% for definite CDI and 71% for possible CDI; more likely due to secondary seeding from a distant site.[35] *Enterococcus* species are a less common cause of CDI, accounting for approximately 4.8% in a recent prospective cohort. Enterococcal CDI was associated with an overall mortality of 24%.[47] CIED-related infective endocarditis associated with *Enterococcus* species may be as high as 10.7% of cases and 13.8% for *Streptococcus* species, which is another relatively less common gram-positive cause of CDI.[42]

Gram-negative bacilli (GNB) etiologies of CDI are much less common, ranging from 3% for permanent pacemaker (PPM) infections to up to 9% of CDIs in other series.[31,32,35–38,48] CIED-related infective endocarditis (IE) has been associated with

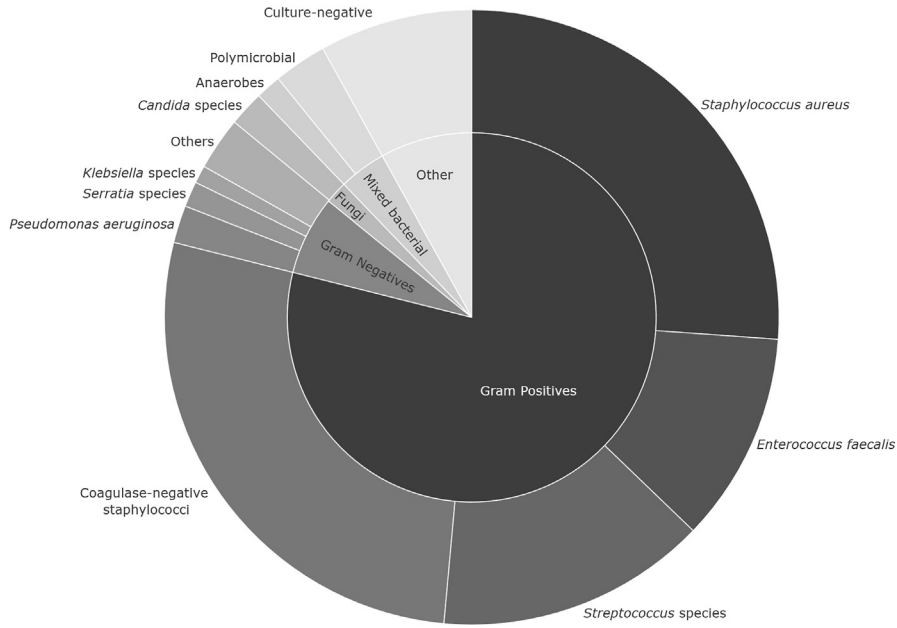

Fig. 1. Distribution of microbiology for cardiovascular implantable electronic device infections. (*Derived from:* Mateos Gaitán R, Boix-Palop L, Muñoz García P, et al. Infective endocarditis in patients with cardiac implantable electronic devices: a nationwide study. EP Europace. 2020;22(7):1062 to 1070. Esquer Garrigos Z, George MP, Khalil S, et al. Predictors of bloodstream infection in patients presenting with cardiovascular implantable electronic device pocket infection. Oxford University Press US; 2019:ofz084.)

GNB bacteremia in 6% to 6.8% of cases.[32,42] In a single-center cohort study, of patients with GNB bacteremia, the proportion of events associated with cardiac device infection for GNB were as follows: 53.8% *Pseudomonas aeruginosa*, 19.4% *Serratia marcescens*, 12.9% Klebsiella species, and 38.7% of other GNB.[39] Other etiologies are even less common, but can still play a significant role including skin flora such as *Cutibacterium acnes* and *Corynebacterium* species, anaerobic species, *Candida* species, and very rarely mycobacteria.[31,42,40,37,49]

CLINICAL PRESENTATION

The clinical presentation for CDIs depends on the location of the infection. Generator pocket infections are the most common location. These can present with tenderness, swelling, purulent drainage, erythema, and in severe cases, bacteremia, which is less common.[37,39,50,51] These signs may be more consistent with an early generator pocket infection in the first year after device placement, but late generator pocket infections can present with dehiscence or erosion of the pocket site.[51,52] When either are complicated by bacteremia in advanced cases, both early and late groups have been found to have similar rates of lead vegetations, but the late group more commonly had valvular vegetations.[45]

CIED-related systemic infection occurs when infection involves the intracardiac lead (eg, with a transvenous cardiac device system or epicardial lead system) usually associated with bacteremia, with or without lead or valve vegetation; rarely infections of the epicardial lead can also lead to mediastinitis or pericarditis due to anatomic proximity.

These infections are more likely to present with systemic symptoms related to bacteremia or valvular endocarditis, such as fevers chills in over 80% of patients.[53] Symptoms can also be less specific, including recurrent pulmonary infections (pneumonia, lung abscess, and embolism) or variable chest pain, which can often delay diagnosis.[17,32,40,50] Late infection of a leadless PM is very rare, but presentation has included in case reports chest pain, bradycardia, shortness of breath, and fevers often in the setting of bacteremia due to another cause.[54–56]

These CDIs should be distinguished from postimplantation superficial surgical site infection, which can manifest as a superficial stitch abscess or cellulitis, but do not involve the pocket or device. Postimplantation pocket hematomas can have a similar appearance as a pocket infection and can be difficult to distinguish from infection.

DIAGNOSIS AND TESTING

The diagnosis of pocket infection or CIED-related systemic infection/infective endocarditis is primarily clinical, but several diagnostic tools can assist. Some inflammation over the pocket site is to be expected in 30 days following implantation, but a superficial stitch abscess or persistent mild erythema may indicate an early skin and soft tissue infection (SSTI) related to the procedure without a pocket infection. A postoperative hematoma in the pocket may also be considered, but dehiscence, purulent drainage, discomfort, or deformity should prompt consideration of a true generator pocket site infection. Erosion and exposure of the generator to the environment is diagnostic of at least a pocket infection, in which case systemic signs of infection may be absent if the case is localized, mild, and without bacteremia.[5]

A microbiological diagnosis should always be attempted by obtaining blood cultures.[38] Swab cultures of tissue or hardware exposed to the environment are minimally helpful, as the skin flora will often be cultured, obligate anaerobes will be inherently excluded, and the deeper culprit organism may not be cultured at all.[57] In most cases, the yield of blood cultures ranges from 33% to 40% in CIED and can be as high as 80% in the setting of CIED infective endocarditis.[5,33,51,53] Of note, antibiotic exposure prior to culture collection, unsurprisingly, has been shown to limit blood culture yield. It is critical to distinguish a superficial SSTI from a true generator pocket infection due to differences in management of these 2 entities. In cases of uncertainty for pocket infection, a fluorine-18 fluorodeoxyglucose PET/computed tomography ([18F]FDG-PET/CT) may be used to help support the diagnosis.[25,58–60] Culturing the tip of the device after extraction should be performed, noting, however, that there is a risk of contamination by skin flora during the extraction process.[38]

Systemic symptoms independent of whether a generator pocket site infection is present should prompt echocardiography to evaluate for a lead/valve vegetation and a chest radiography for signs of septic emboli. A diagnosis of systemic CDI is made by the clinical presentation, blood culture microbiology, and by imaging. While all cases with *S aureus* bacteremia raise high concern for systemic CDI, cases with other skin flora such as CoNS and *C acnes* should not be immediately dismissed as a contaminant especially in the setting of high-grade bacteremia.

Numerous studies have shown that a transesophageal echocardiogram (TEE) is more sensitive than transthoracic echocardiography (TTE) for the detection of vegetations.[17,28,35,46,53,61,62] A negative TTE should be followed up with a TEE to more definitively rule out lead and/or valvular vegetations, acknowledging that even with this test the sensitivity is not perfect.[63] A TEE may also identify noninfectious fibrinous material associated with long-standing CIED leads, which can be clinically

difficult to distinguish from infectious vegetation.[64,65] In the updated 2023 Duke-International Society for Cardiovascular Infectious Diseases Criteria for infective endocarditis, identification of abnormal metabolic activity of intracardiac device leads or other prosthetic material by [18F]FDG-PET/CT is now one of the major imaging criteria diagnostic of infective endocarditis.[66] The test has poor sensitivity for native valve endocarditis, but in one meta-analysis, the pooled sensitivity and specificity for prosthetic valve endocarditis was 0.86 (95% CI 0.81–0.89) and 0.83 (95% CI 0.79–0.88), respectively.[67] The use of PET/CT significantly improved all diagnostic metrics when added to use of Duke Criteria in one study evaluating CIED among patients with congenital heart disease.[68] A PET/CT has low rate false negativity for CDI but moderate false positivity.[58,63] It should be performed when there is reasonable clinical suspicion for device infection with the knowledge that a negative test does not rule out CDI (**Fig. 2**).

MANAGEMENT

For either a pocket or systemic CDI, management involves the removal of the entire device and adjunctive antibiotics.[38,25,50,69,70] Early removal of the device has been associated with reduced 1 year mortality when compared with late removal.[71–73] In a retrospective review of 416 patients, one group found a 1 year mortality associated with early removal of 11.4% compared with 43.4% ($P < .001$) for late removal.[74] Another retrospective review, showed a difference in 1 year mortality of 16.9% versus 33.9% ($P = .028$) when comparing those patients who underwent device extraction within 10 days of diagnosis versus those where it was longer than 10 days, respectively.[71] A more recent study found similar results in both pocket and bacteremic CDI groups.[75] Extractions should be performed with cardiothoracic surgery support available in the case of complications.[50,51] Percutaneous removal is less invasive and generally more favored than surgical removal, but surgical removal has been suggested for patients with vegetations larger than 2 cm to minimize risk of pulmonary embolism.[38] Decisions regarding mode of extraction should be individualized.[50]

Treatment with antibiotics alone while retaining the device has been widely associated with higher clinical failure and relapse, but this may be necessary if device removal is infeasible.[40,50,51,76,62] Chronic antibiotic suppression has been offered in cases like this, but is associated with increased mortality related to treatment failure.[38,76] In cases of bacteremia due to *S aureus* in the setting of CIED, device removal with medical management has been shown to have a reduced 1 year mortality with hazard ratios of 0.28 (95% CI 0.08–0.95) in patients without echocardiographic evidence of CDI and 0.17 (95% CI 0.06–0.47) in patients with definite CDI.[43,44] Incomplete device extraction with CDI similarly should be avoided as reinfection rates have ranged in 3 retrospective studies between 21.4% and 50%, compared with 1% and 5.3% with full device extraction (all *P*-values significant).[77–79]

In the absence of definitive microbiological data, empiric antibiotic management should cover the above microbiology and take into consideration individualized patient-level risk factors (see **Fig. 1**). Empiric treatment often includes intravenous vancomycin or daptomycin to treat methicillin-resistant *S aureus* or CoNS.[38] Gram-negative coverage is often included if the patient has risk factors for gram-negative infection, presents with early postoperative infection, or in the setting of systemic inflammatory response. Antibiotics should be narrowed when the causative organism is identified or converted to antifungals if applicable with a high-dose echinocandin or lipid formulation of amphotericin B.[80] Duration varies by extent and site of infection.[37,50,51] For a postoperative SSTI that is definitively not involving the device pocket,

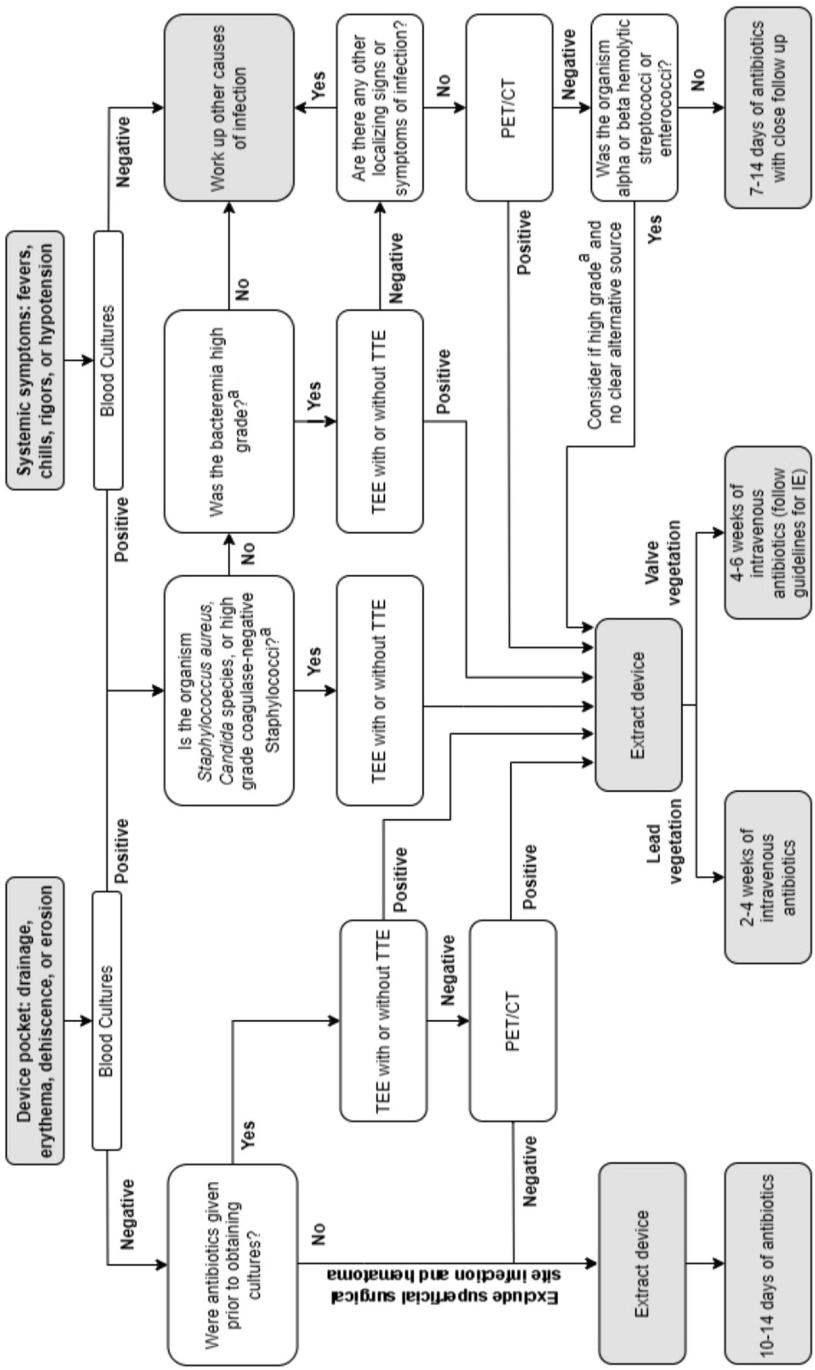

Fig. 2. Approach to management of adults with CDI. [a]High-grade bacteremia: ≥2 separate blood cultures positive.

a short course of 7 to 10 days of oral antibiotics with anti-staphylococcal coverage is appropriate.[37,40,50,61,62] For pocket infections without concomitant bacteremia, treatment after device extraction is generally 10 to 14 days of a targeted regimen. If bacteremia is also present, the duration should be extended to 2 to 4 weeks depending on the extent of infection, clinical severity, or if blood cultures remain positive after device removal. A vegetation in the setting of bacteremia should be treated as infective endocarditis with 4 to 6 weeks of antimicrobial therapy from date of culture clearance.[50,81]

After device extraction the timing of reimplantation is well described in guidelines from the American Heart Association (AHA).[37,25,38] The first consideration is to determine whether there is a continued need for any device placement at all, as at least a quarter of cases have been found no longer to be required.[41] If the device is still needed, then blood cultures should have no growth for 72 hours before replacement is attempted, which should be performed on the contralateral side.[25,38,82] If there is also involvement of a cardiac valve, then experts suggest a delay of 14 days of negative blood cultures prior to reimplantation.[25]

PREVENTION

The cornerstone of CDI prevention is maintenance of sterile technique during implantation and optimization of well-defined patient, procedural, and device-related risk factors listed earlier.[83] Other important areas of prevention are related to periprocedural anticoagulation management, preprocedural antibiotics, and adjunctive technologies aimed at reducing risk of infection.

Prevention of postprocedural pocket hematoma formation has been investigated in several landmark studies over the past decade. Birnie and colleagues[84] demonstrated in the 2013 initial BRUISE CONTROL trial that the continuation of warfarin group had a relative risk of 0.19 (95% CI 0.10–0.36) for pocket hematoma when compared with heparin bridge at the time of procedure. In the 2018 BRUISE CONTROL-2 study, the same investigators compared the strategy of interrupted direct oral anticoagulation (DOAC) 48 hours prior to surgery with DOAC continuation.[85] This study was discontinued early as clinically significant pocket hematoma occurred in 2.1% (interrupted DOAC group) versus 2.1% (DOAC continuation group, $P = .97$) and complications were uncommon. Finally, in a combined analysis of the data from both of these studies, there was a strong association of antiplatelet use versus nonuse with the development of a clinically significant hematoma (adjusted odds ratio 1.9, 95% CI 1.2–3.2).[86] Adjusting for antiplatelet use, there was not a significant difference between continued warfarin and continued DOAC use. Given the aforementioned data, the AHA suggests that continued and interrupted DOAC are both acceptable given the low risk for hematoma and that it is reasonable to perform CIED implantation in patients on chronic warfarin (with a suggested INR 2–3.5).[25]

Prophylactic antibiotics are indicated at the time of device placement with anti-staphylococcal coverage, usually with a first-generation cephalosporin 1 hour before the procedure or vancomycin 2 hours prior if there is a beta-lactam allergy.[27,37,38,40,87,83,88–90] Prophylactic antibiotics with cefazolin were recently compared with an incremental antibiotic regimen in the (Prevention of Arrythmia Device Infection [PADIT]) trial, but the latter was not found to convey any additional benefit.[91] The regimen consisted of preprocedural cefazolin and vancomycin, intraprocedural bacitracin pocket wash, and oral cephalexin until 48 hours after the procedure. Among 19,603 patients in a multicenter clustered randomized trial, infection occurred at 1 year in 1.03% receiving conventional prophylaxis (cefazolin) and in 0.78% receiving

the incremental regimen, odds ratio (OR) 0.77 (95% CI 0.56–1.05). A similar result was found in the high-risk patients OR 0.82 (95% CI 0.59–1.15) and low-risk patients OR 0.77 (95% CI 0.56–1.05). Postprocedural antibiotics and prophylactic antibiotics prior to unrelated dental or genitourinary procedures have not been found to provide any benefit.[38]

Envelopes impregnated with antibiotics have substantial evidence demonstrating a lower risk of CDI and are generally recommended for high-risk patients.[25,83,92,93–96] The (Worldwide Randomized Antibiotic Envelope Infection Prevention [WRAP-IT]) trial randomized nearly 7000 patients at an increased risk of CDI to either use of an antibiotic-impregnated mesh envelope (minocycline and rifampin) wrapped around the CIED or the control group without the envelope.[94] The hazard ratio for CDI among the 0.7% of envelope recipients (n = 25) was 0.60 (95% CI 0.36–0.95) compared with 1.2% of patients in the control group (n = 42). In a study with longer term follow-up of 21 months (±8.3 months), the risk of CDI between groups was maintained (hazard ratio [HR] 0.64, 95% CI 0.41–0.99).[97] The benefit was not sustained in the subgroup analysis comparing low-risk patients; therefore, there have been substantial efforts to develop tools that can systematically identify people at the highest risk.

One systematic review of 6 published risk scores to identify high-risk patients for CDI found a heterogenous mixture of variables across models and consistently low predictive power.[98] Among these, the only score system to utilize a multivariable model was the PADIT group including bootstrapped parameters and external validation using a separate data set. The internal predictive power for CDI was modest, represented by a C-statistic of 0.71 (95% CI 0.67–0.76). External validity among a large registry population found a very modest predictive ability of the PADIT risk score, but another study found high predictive power for reinfection and 1 year all-cause mortality.[99,100] The PADIT score was compared with the (valve prosthesis [P]; arterial hypertension uncontrolled [A]; cancer [C]; elderly [E]; device type [D]; renal failure [R]; antiplatelets [A]; and procedure type [P] [PACE-DRAP]) score in a 2020 study by Slawek-Szmyt and colleagues,[101] finding that both scores had similar specificity but the PACE-DRAP score showed a slightly higher AUC of 0.72 (compared with 0.63 for PADIT) for differentiating high risk and low risk of infection.

Another group compared PADIT with the Ricerca sulle Infezioni Associate a ImpiAnto o sostituzione di CIED (RI-AIAC), Kolek, and Shariff scoring systems.[99] There was variable internal predictive ability, but no reliable success in predicting new CDIs for each of the models. Maclean and colleagues[102] published the (Blood results, Long procedure time, Immunosuppressed, Sixty years old (or younger), Type of procedure, Early re-intervention, Repeat procedure [BLISTER]) score system in 2024 using the PADIT score as a reference. This was an externally validated score derived from a multivariable model stratifying risk factors for CDI to identify patients who may benefit the most from an antibiotic envelope. They found higher predictive value than PADIT for both the standard risk population (AUC 0.82 vs 0.71, $P = .001$) and the high-risk population (AUC 0.77 vs 0.69, $P = .001$), with a number needed to treat of 31 to prevent CDI and encouraging cost-utility analysis results.

Other technologies to prevent CDI include the use of leadless PMs, epicardial leads, subcutaneous ICD (S-ICD) systems, and more, but long-term effectiveness is still under investigation (**Fig. 3**). Leadless PMs are a new technology growing in popularity due to their apparent resistance to infection for a number of reasons.[103] The device consists of a 3 to 4 cm metal cylinder, which is implanted into the myocardium directly to provide electrical impulses locally, obviating extended leads from a generator

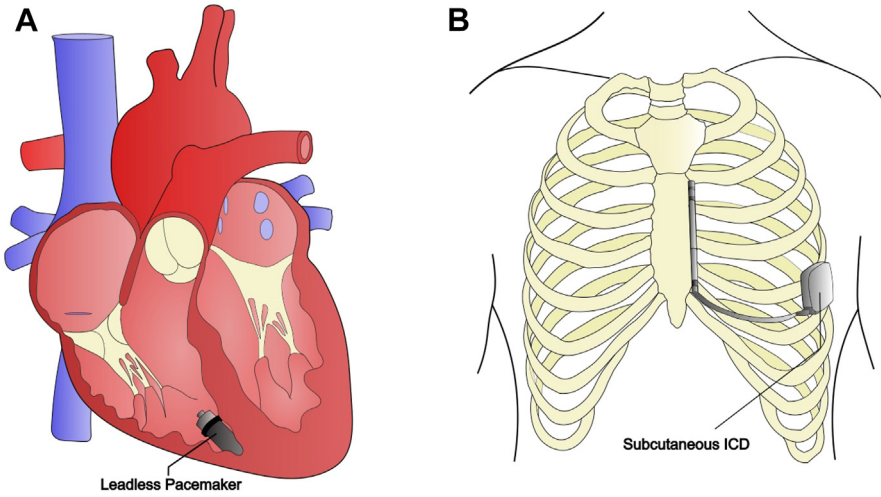

Fig. 3. (*A*) Anatomy of a leadless pacemaker. (*B*) Anatomy of a subcutaneous ICD.

pocket.[104,105] Leadless pacers are often used to minimize the risk of reinfection of transvenous PMs after the extraction of an infected CIED, which can range from 2% to 11% depending on whether hardware is retained.[103] There were no cases of device infection in the preliminary phase I clinical trial, phase II trial, or 1 year follow-up research correspondences.[106–108] Another prospective cohort of 17 patients over a mean follow-up of 16 months found no infections postimplantation; however, some case reports have recently been published demonstrating that infection is possible.[54–56,109] Suggested reasons for why leadless PMs are "resistant" to infection even when placed in the setting of active bacteremia include absence of a subcutaneous pocket or exposure to any skin flora, partial or complete endothelialization of the intracardiac device (similar to a coronary stent or Watchman device), minimal direct handling of the device during placement, and minimal exposure of hardware to circulation.[103] Indications and contraindications for placement have not yet been published into guidelines.

An S-ICD is placed under the skin in the lateral aspect of the chest wall with an electrode extending around and along the sternum to provide a primary and secondary conduction vector for defibrillation.[110,111,112] Systemic infection risk is reduced substantially as the device does not violate the intravascular space, but skin erosions due to localized device infection and sensing problems can occur, which may have severe complications.[113–115] The (Prospective Randomized Comparison of Subcutaneous and Transvenous Implantable Cardioverter Defibrillator Therapy [PRAETORIAN]) trial was a multicenter, prospective, randomized, and controlled study, which demonstrated noninferiority of the S-ICD compared with the transvenous ICD for shock efficacy, but the long-term outcomes are still under investigation.[116] The use of the S-ICD has been recommended as a class IIa recommendation by the European Society of Cardiology and a class I recommendation in the more recent AHA guidelines for patients with complex anatomy or venous access and not requiring PM or resynchronization functionality.[117,118] Some have discussed a possible future of using the leadless PM simultaneously with the S-ICD in patients who require both, but the safety and efficacy of disparate electrical systems potentially in tandem with implantable loop recorder are only in theoretic stages.[119]

SUMMARY

Infections related to CIEDs are increasing and can lead to significant morbidity and mortality. Major risk factors for infection include comorbidities such as diabetes mellitus, heart failure, kidney disease, higher complexity of device, periprocedural hematoma, and lack of prophylactic antibiotics. There have been many attempts at development of a valid scoring system to predict people at highest risk, including the newer BLISTER scoring system. The substantial majority of infections are due to gram-positive bacteria such as CoNS and *S aureus*. The presentation will vary significantly depending on site and extent of infection, but the diagnosis remains clinical. In the setting of a negative workup for CDI (ie, TEE without vegetation) but a reasonable clinical suspicion, a PET/CT can provide diagnostic value, but sensitivity is only moderate. Early and complete device extraction is critical for the management of CDI in tandem with adjunctive antibiotic therapy. Treatment duration varies by the underlying category of infection, but can range from 7 days of oral agents to 6 weeks of intravenous therapy. Sterile technique during device placement, preprocedural antibiotics, and hematoma prevention are cornerstone of CDI prevention measures, but newer technologies such as antibacterial envelopes, leadless PMs, and the subcutaneous ICD have a promising future in groups at the highest risk.

CLINICS CARE POINTS

- Although TTE can provide helpful clinical information, TEE has higher sensitivity and is an important diagnostic imaging test for diagnosing CDI.
- In select cases where TEE is nondiagnostic, FDG PET-CT may be a helpful imaging tool for diagnosis.
- The optimal treatment of CDI is complete CIED extraction.
- Early device removal (eg, within 10 days) is associated with improved outcomes in CDI.
- Patients at high risk for CDI may benefit from the use of antibiotic impregnated envelope, subcutaneous ICD, or leadless PM technologies.
- Scoring systems can help with the identification of patients at highest risk for CDI.

DISCLOSURE

C. Bielick: there are no competing interests, personal financial interests, or other competing interests. Funding support was through the National Institute of Allergy and Infectious Diseases, United States at the National Institutes of Health (grant number T32 AI007046 to C.B.) while employed at the University of Virginia Division of Infectious Diseases and International Health. Christopher Arnold: there are no competing interests, personal financial interests, or other competing interests. Vivian Chu: UpToDate contributor.

REFERENCES

1. Polyzos KA, Konstantelias AA, Falagas ME. Risk factors for cardiac implantable electronic device infection: a systematic review and meta-analysis. Ep Europace 2015;17(5):767–77.
2. Tarakji KG, Wazni OM, Harb S, et al. Risk factors for 1-year mortality among patients with cardiac implantable electronic device infection undergoing transvenous

lead extraction: the impact of the infection type and the presence of vegetation on survival. Europace 2014;16(10):1490–5.
3. Hussein AA, Tarakji KG, Martin DO, et al. Cardiac implantable electronic device infections: added complexity and suboptimal outcomes with previously abandoned leads. JACC: clinical electrophysiology 2017;3(1):1–9.
4. Khaloo P, Uzomah UA, Shaqdan A, et al. Outcomes of patients hospitalized with cardiovascular implantable electronic device–related infective endocarditis, prosthetic valve endocarditis, and native valve endocarditis: a nationwide study, 2003 to 2017. J Am Heart Assoc 2022;11(17):e025600.
5. Chua JD, Wilkoff BL, Lee I, et al. Diagnosis and management of infections involving implantable electrophysiologic cardiac devices. Ann Intern Med 2000;133(8):604–8.
6. Joy PS, Kumar G, Poole JE, et al. Cardiac implantable electronic device infections: who is at greatest risk? Heart Rhythm 2017;14(6):839–45.
7. Prutkin JM, Reynolds MR, Bao H, et al. Rates of and factors associated with infection in 200 909 Medicare implantable cardioverter-defibrillator implants: results from the National Cardiovascular Data Registry. Circulation 2014;130(13):1037–43.
8. Voigt A, Shalaby A, Saba S. Rising rates of cardiac rhythm management device infections in the United States: 1996 through 2003. J Am Coll Cardiol 2006;48(3):590–1.
9. Voigt A, Shalaby A, Saba S. Continued rise in rates of cardiovascular implantable electronic device infections in the United States: temporal trends and causative insights. Pacing Clin Electrophysiol 2010;33(4):414–9.
10. Cabell CH, Heidenreich PA, Chu VH, et al. Increasing rates of cardiac device infections among Medicare beneficiaries: 1990–1999. Am Heart J 2004;147(4):582–6.
11. Greenspon AJ, Patel JD, Lau E, et al. 16-year trends in the infection burden for pacemakers and implantable cardioverter-defibrillators in the United States: 1993 to 2008. J Am Coll Cardiol 2011;58(10):1001–6.
12. Duval X, Suty CS, Alla F, et al. Endocarditis in patients with a permanent pacemaker: a 1-year epidemiological survey on infective endocarditis due to valvular and/or pacemaker infection. Clin Infect Dis 2004;39(1):68–74.
13. Johansen JB, Jørgensen OD, Møller M, et al. Infection after pacemaker implantation: infection rates and risk factors associated with infection in a population-based cohort study of 46299 consecutive patients. Eur Heart J 2011;32(8):991–8.
14. Rennert-May E, Chew D, Lu S, et al. Epidemiology of cardiac implantable electronic device infections in the United States: a population-based cohort study. Heart Rhythm 2020;17(7):1125–31.
15. Deharo J-C. 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). 2020;
16. Uslan DZ, Sohail MR, Sauver JLS, et al. Permanent pacemaker and implantable cardioverter defibrillator infection: a population-based study. Arch Intern Med 2007;167(7):669–75.

17. Carrasco F, Anguita M, Ruiz M, et al. Clinical features and changes in epidemiology of infective endocarditis on pacemaker devices over a 27-year period (1987–2013). Europace 2016;18(6):836–41.
18. Ann HW, Ahn JY, Jeon YD, et al. Incidence of and risk factors for infectious complications in patients with cardiac device implantation. Int J Infect Dis 2015; 36:9–14.
19. Toyoda N, Chikwe J, Itagaki S, et al. Trends in infective endocarditis in California and New York State, 1998-2013. JAMA 2017;317(16):1652–60.
20. Özcan C, Raunsø J, Lamberts M, et al. Infective endocarditis and risk of death after cardiac implantable electronic device implantation: a nationwide cohort study. Ep Europace 2017;19(6):1007–14.
21. Dai M, Cai C, Vaibhav V, et al. Trends of cardiovascular implantable electronic device infection in 3 decades: a population-based study. JACC: Clinical Electrophysiology 2019;5(9):1071–80.
22. Han H-C, Hawkins NM, Pearman CM, et al. Epidemiology of cardiac implantable electronic device infections: incidence and risk factors. EP Europace 2021; 23(Supplement_4):iv3–10.
23. Birnie DH, Wang J, Alings M, et al. Risk factors for infections involving cardiac implanted electronic devices. J Am Coll Cardiol 2019;74(23):2845–54.
24. Olsen T, Jørgensen OD, Nielsen JC, et al. Incidence of device-related infection in 97 750 patients: clinical data from the complete Danish device-cohort (1982–2018). Eur Heart J 2019;40(23):1862–9.
25. Baddour LM, Esquer Garrigos Z, Rizwan Sohail M, et al. Update on Cardiovascular Implantable Electronic Device Infections and Their Prevention, Diagnosis, and Management: A Scientific Statement From the American Heart Association. Circulation 2024;149(2):e201–16.
26. Hussein AA, Baghdy Y, Wazni OM, et al. Microbiology of cardiac implantable electronic device infections. JACC: Clinical Electrophysiology 2016;2(4): 498–505.
27. Tarakji KG, Chan EJ, Cantillon DJ, et al. Cardiac implantable electronic device infections: presentation, management, and patient outcomes. Heart Rhythm 2010;7(8):1043–7.
28. Uslan DZ, Dowsley TF, Sohail MR, et al. Cardiovascular implantable electronic device infection in patients with Staphylococcus aureus bacteremia. Pacing Clin Electrophysiol 2010;33(4):407–13.
29. Le KY, Sohail MR, Friedman PA, et al. Clinical features and outcomes of cardiovascular implantable electronic device infections due to staphylococcal species. Am J Cardiol 2012;110(8):1143–9.
30. Kewcharoen J, Kanitsoraphan C, Thangjui S, et al. Postimplantation pocket hematoma increases risk of cardiac implantable electronic device infection: a meta-analysis. Journal of Arrhythmia 2021;37(3):635–44.
31. Sohail MR, Uslan DZ, Khan AH, et al. Risk factor analysis of permanent pacemaker infection. Clin Infect Dis 2007;45(2):166–73.
32. MASSOURE PL, Reuter S, Lafitte S, et al. Pacemaker endocarditis: clinical features and management of 60 consecutive cases. Pacing Clin Electrophysiol 2007;30(1):12–9.
33. Sohail MR, Uslan DZ, Khan AH, et al. Management and outcome of permanent pacemaker and implantable cardioverter-defibrillator infections. J Am Coll Cardiol 2007;49(18):1851–9.

34. Narui R, Nakajima I, Norton C, et al. Risk factors for repeat infection and mortality after extraction of infected cardiovascular implantable electronic devices. Clinical Electrophysiology 2021;7(9):1182–92.
35. Chamis AL, Peterson GE, Cabell CH, et al. Staphylococcus aureus bacteremia in patients with permanent pacemakers or implantable cardioverter-defibrillators. Circulation 2001;104(9):1029–33.
36. Maskarinec SA, Thaden JT, Cyr DD, et al. The risk of cardiac device-related infection in bacteremic patients is species specific: results of a 12-year prospective cohort. Open Forum Infect Dis 2017;4(3):ofx132.
37. Gandhi T, Crawford T, Riddell J. Cardiovascular implantable electronic device associated infections. Infectious Disease Clinics 2012;26(1):57–76.
38. Baddour LM, Epstein AE, Erickson CC, et al. Update on cardiovascular implantable electronic device infections and their management: a scientific statement from the American Heart Association. Circulation 2010;121(3):458–77.
39. Esquer Garrigos Z, George MP, Khalil S, et al. Predictors of bloodstream infection in patients presenting with cardiovascular implantable electronic device pocket infection. Open Forum Infect Dis 2019;6(4):ofz084.
40. Cacoub P, Leprince P, Nataf P, et al. Pacemaker infective endocarditis. Am J Cardiol 1998;82(4):480–4.
41. Sandoe JA, Barlow G, Chambers JB, et al. Guidelines for the diagnosis, prevention and management of implantable cardiac electronic device infection. J Antimicrob Chemother 2015;70(2):325–59. Report of a joint Working Party project on behalf of the British Society for Antimicrobial Chemotherapy (BSAC, host organization), British Heart Rhythm Society (BHRS), British Cardiovascular Society (BCS), British Heart Valve Society (BHVS) and British Society for Echocardiography (BSE).
42. Mateos Gaitán R, Boix-Palop L, Muñoz García P, et al. Infective endocarditis in patients with cardiac implantable electronic devices: a nationwide study. EP Europace 2020;22(7):1062–70.
43. Chesdachai S, Baddour LM, Sohail MR, et al. Evaluation of European Heart Rhythm Association consensus in patients with cardiovascular implantable electronic devices and Staphylococcus aureus bacteremia. Heart Rhythm 2022;19(4):570–7.
44. Nakajima I, Narui R, Tokutake K, et al. Staphylococcus bacteremia without evidence of cardiac implantable electronic device infection. Heart Rhythm 2021;18(5):752–9.
45. Welch M, Uslan DZ, Greenspon AJ, et al. Variability in clinical features of early versus late cardiovascular implantable electronic device pocket infections. Pacing Clin Electrophysiol 2014;37(8):955–62.
46. Polewczyk A, Janion M, Podlaski R, et al. Clinical manifestations of lead-dependent infective endocarditis: analysis of 414 cases. Eur J Clin Microbiol Infect Dis 2014;33:1601–8.
47. Oh TS, Le K, Baddour LM, et al. Cardiovascular implantable electronic device infections due to enterococcal species: clinical features, management, and outcomes. Pacing Clin Electrophysiol 2019;42(10):1331–9.
48. Chesdachai S, Baddour LM, Sohail MR, et al. Risk of cardiovascular implantable electronic device infection in patients presenting with gram-negative cacteremia. Open Forum Infect Dis 2022;9(9):ofac444.
49. Smith PN, Vidaillet HJ, Hayes JJ, et al. Infections with nonthoracotomy implantable cardioverter defibrillators: can these be prevented? Pacing Clin Electrophysiol 1998;21(1):42–55.

50. Klug D, Lacroix D, Savoye C, et al. Systemic infection related to endocarditis on pacemaker leads: clinical presentation and management. Circulation 1997; 95(8):2098–107.
51. Cengiz M, Okutucu S, Ascioglu S, et al. Permanent pacemaker and implantable cardioverter defibrillator infections: seven years of diagnostic and therapeutic experience of a single center. Clin Cardiol 2010;33(7):406–11.
52. Grammes JA, Schulze CM, Al-Bataineh M, et al. Percutaneous pacemaker and implantable cardioverter-defibrillator lead extraction in 100 patients with intracardiac vegetations defined by transesophageal echocardiogram. J Am Coll Cardiol 2010;55(9):886–94.
53. Athan E. The characteristics and outcome of infective endocarditis involving implantable cardiac devices. Curr Infect Dis Rep 2014;16:1–5.
54. Ellison K, Hesselson A, Ayoub K, et al. Retrieval of an infected leadless pacemaker. HeartRhythm Case Reports 2020;6(11):863–6.
55. Bernardes-Souza B, Mori S, Hingorany S, et al. Late-Onset Infection in a Leadless Pacemaker. Case Reports 2022;4(24):101645.
56. Morita J, Kondo Y, Hachinohe D, et al. Retrieval of an infectious leadless pacemaker with vegetation. Journal of Arrhythmia 2023;39(1):71.
57. Dy Chua J, Abdul-Karim A, Mawhorter S, et al. The role of swab and tissue culture in the diagnosis of implantable cardiac device infection. Pacing Clin Electrophysiol 2005;28(12):1276–81.
58. Salomäki SP, Saraste A, Kemppainen J, et al. 18F-FDG positron emission tomography/computed tomography of cardiac implantable electronic device infections. J Nucl Cardiol 2021;28(6):2992–3003.
59. Sarrazin J-F, Philippon F, Tessier M, et al. Usefulness of fluorine-18 positron emission tomography/computed tomography for identification of cardiovascular implantable electronic device infections. J Am Coll Cardiol 2012;59(18): 1616–25.
60. Juneau D, Golfam M, Hazra S, et al. Positron emission tomography and single-photon emission computed tomography imaging in the diagnosis of cardiac implantable electronic device infection: a systematic review and meta-analysis. Circulation: Cardiovascular Imaging 2017;10(4):e005772.
61. van Hoff RM, Friedman HP. Implantable cardioverter-defibrillator and pacemaker infections. Hospital Medicine Clinics 2015;4(2):150–62.
62. Tarakji KG, Wilkoff BL. Cardiac implantable electronic device infections: facts, current practice, and the unanswered questions. Curr Infect Dis Rep 2014; 16:1–6.
63. Dilsizian V, Budde RP, Chen W, et al. Best practices for imaging cardiac device–related infections and endocarditis: A JACC: Cardiovascular Imaging Expert Panel Statement. Cardiovascular Imaging 2022;15(5):891–911.
64. Downey BC, Juselius WE, Pandian NG, et al. Incidence and significance of pacemaker and implantable cardioverter-defibrillator lead masses discovered during transesophageal echocardiography. Pacing Clin Electrophysiol 2011; 34(6):679–83.
65. Patel NJ, Singleton MJ, Brunetti R, et al. Evaluation of lead-based echodensities on transesophageal echocardiogram in patients with cardiac implantable electronic devices. J Cardiovasc Electrophysiol 2023;34(1):7–13.
66. Fowler Jr VG, Durack DT, Selton-Suty C, et al. The 2023 Duke-International Society for Cardiovascular Infectious Diseases criteria for infective endocarditis: updating the modified Duke criteria. Clin Infect Dis 2023;77(4):518–26.

67. Wang TKM, Sanchez-Nadales A, Igbinomwanhia E, et al. Diagnosis of infective endocarditis by subtype using 18F-fluorodeoxyglucose positron emission tomography/computed tomography: a contemporary meta-analysis. Circulation: Cardiovascular Imaging 2020;13(6):e010600.
68. Pizzi MN, Dos-Subirà L, Roque A, et al. 18F-FDG-PET/CT angiography in the diagnosis of infective endocarditis and cardiac device infection in adult patients with congenital heart disease and prosthetic material. Int J Cardiol 2017;248:396–402.
69. Liang SY, Beekmann SE, Polgreen PM, et al. Current management of cardiac implantable electronic device infections by infectious disease specialists. Clin Infect Dis 2016;63(8):1072–5.
70. Margey R, McCann H, Blake G, et al. Contemporary management of and outcomes from cardiac device related infections. Europace 2010;12(1):64–70.
71. Lakkireddy DR, Segar DS, Sood A, et al. Early lead extraction for infected implanted cardiac electronic devices: JACC review topic of the week. J Am Coll Cardiol 2023;81(13):1283–95.
72. Sridhar ARM, Lavu M, Yarlagadda V, et al. Cardiac implantable electronic device-related infection and extraction trends in the US. Pacing Clin Electrophysiol 2017;40(3):286–93.
73. Arshad V, Baddour LM, Lahr BD, et al. Impact of delayed device re-implantation on outcomes of patients with cardiovascular implantable electronic device related infective endocarditis. Pacing Clin Electrophysiol 2021;44(8):1303–11.
74. Le KY, Sohail MR, Friedman PA, et al. Impact of timing of device removal on mortality in patients with cardiovascular implantable electronic device infections. Heart Rhythm 2011;8(11):1678–85.
75. Lin AY, Saul T, Aldaas OM, et al. Early versus delayed lead extraction in patients with infected cardiovascular implantable electronic devices. Clinical Electrophysiology 2021;7(6):755–63.
76. Tan EM, DeSimone DC, Sohail MR, et al. Outcomes in patients with cardiovascular implantable electronic device infection managed with chronic antibiotic suppression. Clin Infect Dis 2017;64(11):1516–21.
77. Tischer TS, Hollstein A, Voss W, et al. A historical perspective of pacemaker infections: 40-years single-centre experience. Europace 2014;16(2):235–40.
78. Klug D, Wallet F, Lacroix D, et al. Local symptoms at the site of pacemaker implantation indicate latent systemic infection. Heart 2004;90(8):882–6.
79. Gomes S, Cranney G, Bennett M, et al. Lead extraction for treatment of cardiac device infection: a 20-year single centre experience. Heart Lung Circ 2017;26(3):240–5.
80. Pappas PG, Kauffman CA, Andes DR, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis 2016;62(4):e1–50.
81. Blomström-Lundqvist C, Traykov V, Erba PA, et al. 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). Eur J Cardio Thorac Surg 2020;57(1):e1–31.

82. Nandyala R, Parsonnet V. One stage side-to-side replacement of infected pulse generators and leads. Pacing Clin Electrophysiol 2006;29(4):393–6.
83. Blomstrom-Lundqvist C, Ostrowska B. Prevention of cardiac implantable electronic device infections: guidelines and conventional prophylaxis. EP Europace 2021;23(Supplement_4):iv11–9.
84. Birnie DH, Healey JS, Wells GA, et al. Pacemaker or defibrillator surgery without interruption of anticoagulation. N Engl J Med 2013;368(22):2084–93.
85. Birnie DH, Healey JS, Wells GA, et al. Continued vs. interrupted direct oral anticoagulants at the time of device surgery, in patients with moderate to high risk of arterial thrombo-embolic events (BRUISE CONTROL-2). Eur Heart J 2018; 39(44):3973–9.
86. Essebag V, Healey JS, Joza J, et al. Effect of direct oral anticoagulants, warfarin, and antiplatelet agents on risk of device pocket hematoma: combined analysis of BRUISE CONTROL 1 and 2. Circulation: Arrhythmia and Electrophysiology 2019;12(10):e007545.
87. de Oliveira JC, Martinelli M, Nishioka SADO, et al. Efficacy of antibiotic prophylaxis before the implantation of pacemakers and cardioverter-defibrillators: results of a large, prospective, randomized, double-blinded, placebo-controlled trial. Circulation: Arrhythmia and Electrophysiology 2009;2(1):29–34.
88. Da Costa A, Kirkorian G, Cucherat M, et al. Antibiotic prophylaxis for permanent pacemaker implantation: a meta-analysis. Circulation 1998;97(18):1796–801.
89. Kusumoto FM, Schoenfeld MH, Wilkoff BL, et al. 2017 HRS expert consensus statement on cardiovascular implantable electronic device lead management and extraction. Heart Rhythm 2017;14(12):e503–51.
90. Olde Nordkamp LR, Dabiri Abkenari L, Boersma LV, et al. The entirely subcutaneous implantable cardioverter-defibrillator: initial clinical experience in a large Dutch cohort. J Am Coll Cardiol 2012;60(19):1933–9.
91. Krahn AD, Longtin Y, Philippon F, et al. Prevention of arrhythmia device infection trial: the PADIT trial. J Am Coll Cardiol 2018;72(24):3098–109.
92. Kolek MJ, Patel NJ, Clair WK, et al. Efficacy of a bio-absorbable antibacterial envelope to prevent cardiac implantable electronic device infections in high-risk subjects. J Cardiovasc Electrophysiol 2015;26(10):1111–6.
93. Callahan TD, Tarakji KG, Wilkoff BL. Antibiotic eluting envelopes: evidence, technology, and defining high-risk populations. EP Europace 2021;23(Supplement_4): iv28–32.
94. Tarakji KG, Mittal S, Kennergren C, et al. Antibacterial envelope to prevent cardiac implantable device infection. N Engl J Med 2019;380(20):1895–905.
95. Koerber SM, Turagam MK, Winterfield J, et al. Use of antibiotic envelopes to prevent cardiac implantable electronic device infections: a meta-analysis. J Cardiovasc Electrophysiol 2018;29(4):609–15.
96. Ullah W, Nadeem N, Haq S, et al. Efficacy of antibacterial envelope in prevention of cardiovascular implantable electronic device infections in high-risk patients: a systematic review and meta-analysis. Int J Cardiol 2020;315:51–6.
97. Mittal S, Wilkoff BL, Kennergren C, et al. The world-wide randomized antibiotic envelope infection prevention (WRAP-IT) trial: long-term follow-up. Heart Rhythm 2020;17(7):1115–22.
98. Malagù M, Donazzan L, Capanni A, et al. Risk scores for cardiac implantable electronic device infection: which one to believe in? J Clin Med 2022;11(21): 6556.

99. Boriani G, Proietti M, Bertini M, et al. Incidence and predictors of infections and all-cause death in patients with cardiac implantable electronic devices: the Italian nationwide RI-AIAC registry. J Personalized Med 2022;12(1):91.
100. Dias Ferreira Reis J, Valente B, Ferreira V, et al. Performance of the padit score in patients undergoing transvenous lead extraction. Eur Heart J 2020; 41(Supplement_2). ehaa946. 0830.
101. Sławek-Szmyt S, Araszkiewicz A, Grygier M, et al. Predictors of Long-Term Infections After Cardiac Implantable Electronic Device Surgery—Utility of Novel PADIT and PACE DRAP Scores. Circ J 2020;84(10):1754–63.
102. Maclean E, Mahtani K, Honarbakhsh S, et al. The BLISTER Score: A Novel, Externally Validated Tool for Predicting Cardiac Implantable Electronic Device Infections, and Its Cost-Utility Implications for Antimicrobial Envelope Use. Circulation: Arrhythmia and Electrophysiology 2024;17(3):e012446.
103. El-Chami MF, Bonner M, Holbrook R, et al. Leadless pacemakers reduce risk of device-related infection: review of the potential mechanisms. Heart Rhythm 2020;17(8):1393–7.
104. Phillips P, Krahn AD, Andrade JG, et al. Treatment and prevention of cardiovascular implantable electronic device (CIED) infections. CJC open 2022;4(11): 946–58.
105. Steinwender C, Lercher P, Schukro C, et al. State of the art: leadless ventricular pacing: a national expert consensus of the Austrian Society of Cardiology. J Intervent Card Electrophysiol 2020;57:27–37.
106. Reddy VY, Exner DV, Cantillon DJ, et al. Percutaneous implantation of an entirely intracardiac leadless pacemaker. N Engl J Med 2015;373(12):1125–35.
107. Reddy VY, Exner DV, Doshi R, et al. Primary results on safety and efficacy from the LEADLESS II–phase 2 worldwide clinical trial. Clinical Electrophysiology 2022;8(1):115–7.
108. Reddy VY, Exner DV, Doshi R, et al. 1-Year Outcomes of a Leadless Ventricular Pacemaker: The LEADLESS II (Phase 2) Trial. Clinical Electrophysiology 2023; 9(7_Part_2):1187–9.
109. Beurskens NE, Tjong FV, Dasselaar KJ, et al. Leadless pacemaker implantation after explantation of infected conventional pacemaker systems: a viable solution? Heart Rhythm 2019;16(1):66–71.
110. Lambiase PD, Barr C, Theuns DA, et al. Worldwide experience with a totally subcutaneous implantable defibrillator: early results from the EFFORTLESS S-ICD Registry. Eur Heart J 2014;35(25):1657–65.
111. Weiss R, Knight BP, Gold MR, et al. Safety and efficacy of a totally subcutaneous implantable-cardioverter defibrillator. Circulation 2013;128(9):944–53.
112. Kaya E, Rassaf T, Wakili R. Subcutaneous ICD: Current standards and future perspective. IJC Heart & Vasculature 2019;24:100409.
113. Knops RE, Olde Nordkamp LRA, Delnoy PHM, et al. Subcutaneous or transvenous defibrillator therapy. N Engl J Med 2020;383(6):526–36.
114. Brouwer TF, Yilmaz D, Lindeboom R, et al. Long-term clinical outcomes of subcutaneous versus transvenous implantable defibrillator therapy. J Am Coll Cardiol 2016;68(19):2047–55.
115. Honarbakhsh S, Providencia R, Srinivasan N, et al. A propensity matched case–control study comparing efficacy, safety and costs of the subcutaneous vs. transvenous implantable cardioverter defibrillator. Int J Cardiol 2017;228:280–5.
116. Knops RE, Van Der Stuijt W, Delnoy PPH, et al. Efficacy and safety of appropriate shocks and antitachycardia pacing in transvenous and subcutaneous

implantable defibrillators: analysis of all appropriate therapy in the PRAETORIAN trial. Circulation 2022;145(5):321–9.
117. Aktaa S, Tzeis S, Gale CP, et al. European Society of Cardiology quality indicators for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: developed in collaboration with the European heart rhythm association of the European society of cardiology. Europace 2023;25(1):199–210.
118. Al-Khatib SM, Stevenson WG, Ackerman MJ, et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2018;72(14):e91–220.
119. Nieves J, Laslett DB, Basil A, et al. Simultaneous leadless pacemaker and subcutaneous ICD implantation with intraoperative screening: workflow in two patients. Case Reports 2022;4(23):101535.