Cardiac device infections: definition, classification, differential diagnosis, and management

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Introduction The era of cardiac pacing began in the 1960s. Since then, the use of pacemakers (PMs) has increased rapidly and now includes traditional PMs, implantable cardioverter-defibrillators (ICDs), and cardiac resynchronization therapy devices (CRT-Ds). Unfortunately, the progress in pacing therapy is associated with the development of infections, which constitute an increasing clinical challenge and reduce positive effects of treatment. At present, the incidence of cardiac device infections (CDIs) in patients with implantable cardiac electronic devices (ICEDs) is estimated to range from 0.5\% to 2.2\%; however, the exact incidence is difficult to assess because different studies use different methodologies.\textsuperscript{1} Some investigators addressed the problem of CDIs in device-years, reporting an incidence of 1.8 to 1.9 per 1000 PM years and 3.1 to 10 per 1000 PM years for ICD and CRT-D, respectively.\textsuperscript{2,3} However, studies comparing the incidence of CDIs in patients with ICEDs have provided conflicting results.

Apart from the above data showing a significantly higher incidence of CDIs in patients with an ICD, and especially with a CRT-D, no such disproportions have been reported in other studies. The Dutch device registry including over 3000 patients with 1200 PMs, 1414 ICDs, and 795 CRT-Ds implanted between 2000 and 2007, did not show any differences in the development of CDIs between different pacing systems.\textsuperscript{6} Between 2006 and 2015, we conducted a single-center registry study including 1801 patients undergoing transvenous lead extraction (TLE) (1266 PMs, 385 ICDs, and 150 CRT-Ds). The registry showed a lower incidence of infectious complications in patients with ICDs than in those with PMs (35.8\% vs 42.2\%; $P = 0.009$), whereas the highest rate of infections was found in patients with CRT-D, namely, 51.3\% of patients with CDI-associated TLE (unpublished data).

Classification of cardiac device infections CDIs still pose a serious clinical problem. Varying terminology and different CDI classifications are one of the major diagnostic and therapeutic challenges that are encountered in routine clinical practice. The problem arises during an attempt to estimate...
Because there is no consensus regarding definitions of CDI infections, attempts are being made to systematize the knowledge of CDIs. According to the new British guidelines for the diagnosis and management of infection complications, CDIs are divided into generator pocket infections (PIs) and systemic infections. Clinical symptoms of a generator PI include mainly erythema, warmth, fluctuance, tenderness, dehiscence, purulent discharge, or erosion of generator or leads through the skin. According to the British guidelines, some patients with PI have early postimplantation inflammation defined as erythema occurring within 30 days of implantation, without other signs of localized infection. The term inflammation implies that there is no definite infection and routine antimicrobial therapy is not indicated, but patients should be observed closely for other signs, especially an allergic reaction. Additionally, a small area of erythema (<1 cm) or stitch abscess is included. In general, such patients should be observed for the extension of infection (blood cultures), but 1-week follow-up with possible empirical oral antimicrobial therapy for 7 to 10 days followed by clinical evaluation is recommended.3

According to the British guidelines, some patients with PI may also have complicated generator PI, that is, PI with signs of systemic infection and evidence of lead or endocardial involvement and positive blood cultures. It appears that the group of patients with generator PI is heterogeneous and requires different management strategies. The management of these patients according to the British guidelines depends on the extent of infection. Patients with concomitant presence of systemic symptoms (fever, chills) require careful clinical assessment including a series of 3 blood cultures and repeat echocardiography for direct visualization of possible vegetations. Patients with confirmed complicated PI should be managed as those with systemic infection.

According to the British guidelines, systemic CDIs are divided into ICED lead infections (ICED-LI) and ICED infective endocarditis (ICED-IE) (Figure 2).1 Diagnosis in patients with suspected systemic infection is based on clinical assessment, echocardiograms, blood cultures, and inspection of removed leads. Unfortunately, further diagnostic procedures are challenging: clinical symptoms are unspecific, echocardiographic imaging is of poor quality owing to artifacts related to lead reverberations, and vegetations may migrate to the pulmonary circulation, whereas microbial tests have low sensitivity. The problem with microbial tests is that blood cultures are most frequently collected after administration of antimicrobials. Contamination of blood cultures after ICED removal through the infected pocket is another challenge. The available evidence shows that blood cultures are positive in 20% to 67% of patients with systemic infection; in the Polish registry, the rate of positive blood cultures was 34% (unpublished data).10-13

A constant effort is made to improve sensitivity of microbial tests for detection of CDI. The British guidelines recommend the use of samples...
obtained proximally and distally to lead tips, from pocket site tissue and purulent matter. Novel methods of assessing microbial contamination of leads and tissue are now being developed. A vortexing-sonication technique used to disrupt the bacterial biofilm has been found to increase the sensitivity of culture results. The available studies in small patient groups show a sensitivity of 54% to 100% for sonication cultures.14

ICED infections are managed with TLE and antimicrobial therapy for a reasonably long period. The guidelines established by Sandoe et al1 recommend a thorough assessment to determine the duration of antimicrobial therapy. The longest, 6-week antimicrobial treatment is recommended for patients with an extracardiac focus of infection, whereas the diagnosis of ICED-IE is an indication for a 4-week therapy. It is noteworthy that in patients presenting with ICED-LI, antimicrobial therapy may be shortened to 2 weeks if there is no evidence of infection extending from leads into cardiac structures. Echocardiography, after TLE, is an important tool for detecting vegetations and lead remnants. It should be emphasized that the diagnosis of ICED-LI/ICED-IE should be established only after lead removal. Only if transthoracic and transesophageal echocardiography (TTE and TEE) does not reveal right-sided endocarditis, antimicrobial therapy may be shortened and the diagnosis of ICED-LI confirmed. However, evaluation of echocardiograms in patients after TLE is not easy as only an experienced sonographer is able to differentiate connective tissue remnants from true vegetations. Lead tip cultures should be taken in case of doubt.

The British guidelines recommend TLE in most patients presenting with CDI. Only early postimplantation inflammation is not an indication for urgent device removal. However, in some cases, TLE is associated with a high risk of complications or the patients do not consent to device removal. The available evidence shows that from 3% to 15% of patients presenting with CDI receive conservative treatment.14-18 In such cases, 6-week intravenous antimicrobial regimen and close clinical observation are mandatory, and if a relapse occurs, oral antimicrobial therapy should be continued for an indefinite time.1 There is still controversy regarding TLE in patients with large vegetations, some of whom are referred directly (perhaps too hastily) to cardiac surgeons for surgical removal.

It is difficult to define the cut-off point for large vegetations. It is commonly believed that a vegetation size over 2 cm should not be an indication for surgical intervention. There are single reports in the literature describing the efficacy of TLE in patients with larger vegetations (over 2 cm). The reported efficacy of TLE is high (93%–97%) despite frequent pulmonary embolism in the perioperative period (25%–55%), but according to most investigators, this does not have a positive effect on early mortality.19-21 Grammes et al22 described the outcomes of TLE in 100 patients with vegetations and reported that those with vegetations of up to 4 cm in size can safely undergo complete transvenous extraction. Such an approach seems reasonable in view of recent progress in TLE techniques with protection of the pulmonary bed against pulmonary embolism caused by large vegetations. According to a Polish TLE center with one of the largest databases in the world, transvenous device removal in patients with large vegetations is safe and effective. Between 2006 and 2014, a reference center in Lublin performed TLE in 54 patients with vegetations over 2 cm in size (maximum, 5.2 cm) (unpublished data). Procedural, radiological, and clinical success was achieved in 52 patients (96.3%). Pulmonary embolism in the perioperative period developed in 13 patients (25%), ending in perioperative death in 1 patient (1.85%). In patients with very large vegetations, TLE was performed using special baskets to prevent embolization from bacterial vegetations (figure 3).

Clinical aspects of the new classification of cardiac device infections Therapeutic decisions in...
patients presenting with a CDI are directly related to the type of infection. The new classification of CDIs proposed by Sandoe et al. is precise and appears to include all possible clinical scenarios. However, it is controversial that LRIE is not regarded as a separate entity. According to the new classification, LRIE should be regarded as one of the subtypes of CDI: complicated PI, ICED-IE, or ICED-LI (definite or possible diagnosis). This is a novel approach to classification because LRIE may be diagnosed in patients without vegetations (rarely addressed in the available literature) or on the basis of a documented infection with extension to the leads (the diagnostic criterion not considered so far). However, the term “lead-related infective endocarditis” should be advocated for use in clinical analysis in order to emphasize a systemic nature of infection. It appears that the above term most adequately defines the mechanism involved in the development of CDI. To better understand the phenomenon, it should replace the former term “lead-dependent infective endocarditis”, which was used in the Polish literature. Therefore, adapting the guidelines described above for use in clinical practice, we propose a simplified classification of CDIs into “pocket infection” and “lead-related infective endocarditis”, with the latter term including the formerly defined disease entities (FIGURE 4).

In our opinion, the diagnosis of LRIE should be based on the current Duke criteria taking into account the new British strategy (positive cultures from leads removed through the noninfected pocket) and the new 2015 European Society of Cardiology (ESC) guidelines. In routine clinical practice, there are examples showing that the Duke criteria are not perfect for the diagnosis of LRIE. Therefore, the current ESC recommendations on the prevention, diagnosis, and treatment of infective endocarditis include 2 additional major criteria related to $^{18}$F-fluorodeoxyglucose positron emission tomography / computed tomography ($^{18}$F-FDG PET/CT or radiolabeled white blood cell (WBC) single-photon emission...
computed tomography (SPECT/CT) or cardiac computed tomography (CT) for visualization of vegetations/perivalvular lesions. According to the modified ESC 2015 guidelines, an additional minor criterion is silent peripheral embolism or the presence of infective aneurysms confirmed by brain magnetic resonance imaging or whole-body CT/PET.

The definite diagnosis is made with a combination of 2 major or 1 major and 3 minor or 5 minor criteria, whereas 1 major and 1 minor criterion or 3 minor criteria should be fulfilled to make a possible diagnosis of LRIE. In the case of LRIE, similarly to patients with artificial valves, the use of 2 new major criteria should improve the diagnosis; however, the specificity of LRIE requires that we take into account generator PIs and pulmonary embolism as major criteria. The current 2015 ESC guidelines still do not contain clear recommendations, leaving the problem of decision making to clinicians. Another problem is the interpretation of the results of blood cultures in the diagnosis of LRIE. Obviously, the most common pathogens cultured in LRIE are coagulase-negative staphylococci (CNS) and Staphylococcus aureus. However, CNS are not considered as typical isolates for LRIE by the 2015 ESC guidelines. Therefore, detection of CNS requires the confirmation by major number of the cultures or positive cultures within a longer period of time (>12 hours), or, as mentioned before, using novel, more sensitive microbiological tests.

Another problem with the diagnosis of LRIE is the low usefulness of minor criteria, which are not adapted to evaluate right-sided endocarditis. In the modified 2015 ESC guidelines, the minor Duke criteria include fever (>38°C), predisposing heart disease or injection drug use, vascular signs (including the clinically silent signs that are detected by new imaging techniques), immune response, or microbiological evidence (positive cultures not fulfilling major criteria or positive serological tests typical of active microbial infection consistent with endocarditis). An in-depth analysis of the above criteria shows that only the presence of fever and microbiological evidence is helpful in diagnosing LRIE. The remaining signs (vascular and immunological) may possibly be associated with systemic manifestations of left-sided endocarditis coexistent with LRIE. However, such coincidence is very rare. In the Polish registry of 1856 patients undergoing TLE between 2006 and 2015, the concomitant presence of left-sided infective endocarditis was found in 4.6% of 513 patients with the final diagnosis of LRIE (unpublished data). In turn, the term “predisposing heart disease” in the case of LRIE may be interpreted in many ways and refers to all patients with PM/ICD/CRTD, or, what seems more logical, to patients with heart defects, most frequently left heart valve defects. The new minor criterion according the 2015 ESC guidelines, namely, confirmed peripheral embolism, is also characteristic of left-sided infective endocarditis.

In view of the above shortcomings of the minor criteria, it is fully justified to consider septic pulmonary embolism and generator PI as major criteria as suggested by the ESC guidelines of 2009 and 2015. Relapsing pulmonary infections as a marker of septic pulmonary embolism have been found in 25.2% of patients presenting with LRIE in the single-center Polish TLE registry (unpublished data). According to single studies taking into account this important diagnostic factor, the rate of diagnosed pulmonary embolism in patients with LRIE was 33%, with a high specificity of recurrent pulmonary infections as a symptom associated with transient migration of vegetations into the pulmonary circulation. Unfortunately, the British guidelines, despite emphasis on its diagnostic impact, do not recommend septic pulmonary embolism as a major criterion for the detection of LRIE. It is also reasonable to consider generator PI as a major diagnostic criterion because of the high rate of PIs coexisting with LRIE (in the literature, LRIE with accompanying PI was found in 46% to 70% of patients versus 72.4% in the Polish registry [unpublished data]). Additionally, an in-depth assessment in all patients with PI in order to evaluate the extension of infection is needed because of high rates of late mortality in patients with uncomplicated PI. According to the Polish TLE registry, 5-year mortality in patients with uncomplicated PI was 28% as compared with nearly 48% in patients with LRIE and 18% in patients undergoing TLE for noninfectious causes (unpublished data). This is probably a result of underestimating LRIE in patients with seemingly uncomplicated PI. Therefore, the inclusion of PI as a major criterion should improve diagnosis in such patients, and favor reasonably prolonged antimicrobial therapy. Unfortunately, similarly to pulmonary embolism, the British guidelines do not explicitly recommend PI as a major criterion, although they recommend close observation of patients with PI (even with early postimplantation inflammation) for possible development of LRIE. Bearing in mind the possibility of including additional major criteria in the current schema in order to simplify the terminology, we propose to use the already known term “Modified Duke Lead Criteria” (MDLC) for diagnosing LRIE.

Another important diagnostic criterion is positive culture from transvenously explanted leads. The 2009 ESC guidelines recommended cautious interpretation of such results owing to risk of lead contamination through the infected pocket; in 1 study, positive lead cultures were taken in 72% of 50 patients with the symptoms limited only to the generator pocket. The current ESC guidelines recommend taking cultures from transvenously explanted leads (class IC); however, they do not comment on the interpretation of results in diagnosing LRIE. The available studies in large patient populations suggest a greater role of positive cultures, even in the concomitant presence of PI. In one study, 18% of patients...
had positive cultures from leads explanted transvenously through the infected pocket, although pocket cultures were negative, and vice versa, there were negative cultures from leads extracted transvenously through the pocket which was culture-positive (15%). The Polish TLE registry provided similar data (1801 patients, including 746 with CDI): 11% of positive lead cultures were obtained from patients with the symptoms of PI, although pocket cultures were negative; 16.7% of negative lead cultures were concomitant with positive pocket cultures (unpublished data). In view of the low rate of discordance, positive lead cultures should be regarded as very helpful in the diagnosis of LRIE. At the present stage, the British guidelines should be officially updated to include positive cultures from leads extracted through the noninfected pocket as a significant diagnostic criterion of ICED-LI. It appears that this criterion should be included in the schema as a minor MDLC criterion.

A more problematic issue is the interpretation of laboratory tests in the diagnosis of LRIE. The 2015 ESC guidelines recommend a cautious interpretation of the most common inflammatory parameters, underlining the worth of the biomarkers in facilitating risk stratification but contesting the use as a diagnostic criterion because of their poor specificity. Of note, the 2015 ESC guidelines cite our findings relating to the specific constellation of laboratory tests in patients with LRIE that encompasses significantly elevated C-reactive protein levels and erythrocyte sedimentation rate, with normal white blood cell count and procalcitonin levels. If future studies on larger populations of patients confirm these findings, it will be possible to use the parameters as an additional minor diagnostic criterion.

Taking all the above into account, we propose to modify the Duke criteria for the diagnosis of LRIE. According to the diagnostic schema described in the present paper, the major criteria for the diagnosis of LRIE include: 1) positive blood cultures (typical of LRIE microbes, minimum 2×); 2) presence of vegetations on the leads or right heart structures visualized by TTE, TEE, or new techniques: [18F]-FDG PET/CT or radiolabeled WBC SPECT, and also visualization of vegetations that migrated to the pulmonary circulation in CT angiography; 3) septic pulmonary embolism (also recurrent pulmonary infections in patients with ICED); and 4) PI. The minor criteria include: 1) fever over 38°C, chills; 2) positive blood cultures not fulfilling the Duke criteria or serological evidence of active infection with organisms consistent with IE; 3) culture, histology, or molecular evidence of infection on explanted leads (FIGURE 5).

The diagnosis of definite LRIE should be based on the presence of minimum 2 major criteria, or 1 major and 3 minor (non-fulfillment of 5 minor criteria eliminates this diagnostic variant). Patients with 1 major and 1 minor or 3 minor criteria should be considered as having possible LRIE.

It should be emphasized that in case of possible LRIE, we have a range of options, including patients presenting with PI with fever and PI with positive lead cultures or relatively asymptomatic patients with suspected vegetations on the leads and positive cultures from the explanted leads. Such cases are frequently encountered in clinical practice. It is especially important to monitor patients with PIs, also after TLE, because long-term follow-up shows exceptionally high mortality in this group of patients. If additional structures on the leads are detected, further diagnostic procedures using novel imaging techniques are mandatory. It is extremely important to confirm LRIE in order to initiate adequate therapy, as in patients with this insidious entity, long-term...
mortality rates remain very high despite a widespread use of TLE.

**Antimicrobial therapy in cardiac device infections**

There are no randomized controlled trials to guide therapy in patients with CDIs, so recommendations are based on small reports, the spectrum of antimicrobial activity, and consideration of potential adverse effects. Before initiation of the use of antibiotics, the 3 sets of blood cultures should be drawn at 30-minute intervals. According to the British guidelines in the clinical evidence of generator PI, empirical antimicrobial therapy should be started. Because of the high probability of spreading the infectious process along the leads to the endocardium, initial intravenous antibiotic therapy is advised: vancomycin, 1 g every 12 hours; daptomycin, 4 mg/kg every 24 hours; or teicoplanin, 6 mg/kg to a maximum of 1 g given at 0, 12, and 24 hours and then every 24 hours. Patients suspected of having LRIE should also be empirically treated after taking 3 blood samples at 30-minute intervals, although according to the British guidelines, the need for empirical antimicrobial treatment with ICED-LI or ICED-IE is a clinical decision based on the severity of infection. The antimicrobial regimen for empirical treatment in these patients needs to have activity against both Gram-positive and Gram-negative bacilli; therefore, the combined therapy with either vancomycin (1 g every 12 hours) and meropenem (1 g every 8 hours) or daptomycin (8–10 mg every 24 hours) and meropenem (1 g every 8 hours) is recommended. Importantly, empirical treatment is often less clinically effective than targeted antimicrobial regimens; therefore, the identification of the pathogen is very important. The optimal time of antibiotic therapy is determined by the type of CDIs. Patients with PI should be treated within 10 to 14 days, and patients with LRIE, within 4 to 6 weeks.

In general, the duration of antimicrobial therapy after system removal should depend on the involvement of native or prosthetic heart valves, the initial clinical response to antimicrobials and the presence of extracardiac foci of infection. It is believed that a total of 4 weeks of therapy is usually sufficient. Six weeks of therapy are advised for prosthetic valve endocarditis and for attempted salvage of ICED. As mentioned before, treatment may be shortened to 2 weeks if there is no evidence of the infection spreading. Nevertheless, considering the high long-term mortality of patients treated with LRIE, careful clinical observation is required to determine success after the course of antimicrobial therapy.

**Reimplantation of implantable cardiac electronic devices after cardiac device infections**

There are no strict recommendations regarding ICED reimplantation times after CDI. The first step before reimplantation is repeat evaluation of the necessity of ICED implantation, because the initial indications were often borderline and the clinical circumstances might have changed over years. It has been reported that about 30% of patients did not require new ICED placement. When implantation of a new device is necessary, optimal timing of the procedure is dependent on factors such as the type of CDI, persistent bacteremia, persistent vegetations, and pacing dependency. European guidelines do not specify the time of reimplantation in patients with PI. According to American recommendations, repeat implantation is possible after 72 hours of TLE if the blood cultures are negative. In patients with LRIE, implantation should be delayed for at least 14 days (theoretically, in urgent cases, the minimum 72 hours after negative blood cultures), but all guidelines strongly emphasize that the maximum delay of reimplantation reduces the risk of reinfection. In clinical practice, both antibiotic therapy and the timing of reimplantation are prolonged in patients in which the implantation of a more complicated system (ICD, CRT) is necessary and also when the infection is caused by *Staphylococcus aureus*.

**Summary**

Diagnosis and treatment of CDI remain challenging; therefore, it is important to aim for the alignment of terminology and diagnostic–therapeutic pathways. Certainly, the new guidelines proposed by the British microbiological and cardiovascular societies and the modified 2015 ESC criteria are important steps towards facilitating diagnosis, as well as preventing and managing CDIs in this clinically challenging group of patients. The new classification of CDIs appears to consider all variants; however, in routine clinical practice, it is first of all important to differentiate the local process from a systemic one. For this reason, we should aim at establishing the definite diagnosis of PI or LRIE (with or without concomitant PI). LRIE should be diagnosed on the basis of MDLC, taking into account the diagnostic variants of the infection. Each patient with PI should be evaluated thoroughly for a possible development of LRIE because mortality in this group of patients remains high, probably due to underestimation of the incidence of systemic infection. Similarly, good clinical judgment is required for each patient with fever of unclear origin and ICED.

TLE remains the preferred management strategy in patients with PI and LRIE. It should be remembered that contraindications to TLE are very rare and are becoming less frequently related to large vegetations, as today lead extraction with distal embolization protection is a safe procedure. It is very important to use adequate antimicrobial therapy, carefully assess the indications for reimplantation of ICED and, if necessary, delay the time of repeat procedure as long as possible. In case of doubt regarding the spread of infection, the diagnostic workup should include additional novel imaging techniques and thorough evaluation of echocardiograms after TLE to establish optimal duration of therapy.
REFERENCES


Infekcje urządzeń stymulujących serce – definicje, podziały, różnicowanie i postępowanie

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infekcje układów stymulujących serce, odelektrodowe zapalenie wsięrszdu, przeżywane usuwanie elektrod wewnątrzsercowych, zmodyfikowane kryteria Duke

STRESZCZENIE

Infekcje urządzeń stymulujących serce (cardiac device infections – CDI) to wciąż olbrzymi problem kliniczny, a także – ze względu na niejednolitą terminologię i różnorodność klasyfikacji – jedno z większych wyzwań diagnostyczno-terapeutycznych w codziennej praktyce klinicznej. Trudności wiążą się z próbą oszacowania rozległości procesu infekcyjnego, co determinuje wybór strategii leczenia (czas trwania antybiotykoterapii). Najgroźniejszą postacią CDI jest odelektrodowe zapalenie wsięrszdu (lead-related infective endocarditis – LRIE). Dotychczas nie dysponujemy precyzyjnymi kryteriami diagnostycznymi LRIE; kryteria Duke University są trudne do zastosowania u pacjentów z podejrzeniem LRIE z powodu niskiej czułości. Ponieważ terapia LRIE jest kosztowna i kłopotliwa, w praktyce klinicznej występuje tendencja do zbyt niskiej rozpoznawalności tej choroby oraz do poszukiwania form pośrednich między miejscową infekcją loży stymulatora a pewnym LRIE. Niniejszy artykuł zawiera propozycje usystematyzowania CDI wraz ze ścisłym wyodrębnieniem LRIE jako ich najgroźniejszej postaci.