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IN DEPTH

Multimodality Imaging in Infective Endocarditis

An Imaging Team Within the Endocarditis Team

ABSTRACT: Infective endocarditis (IE) is a complex disease with cardiac involvement and multiorgan complications. Its prognosis depends on prompt diagnosis that leads to an aggressive therapeutic management combining antibiotic therapy and early cardiac surgery when indicated. However, IE diagnosis always poses a challenge, and echocardiography remains diagnostically imperfect in cases of prosthetic valve IE or cardiac implantable electronic device infection. In recent years, other imaging modalities (computed tomography, magnetic resonance imaging, nuclear imaging) have experienced significant technical improvements, and their application to the detection of cardiac and extracardiac IE-related lesions seems to be a strategic way forward in the management of patients with suspected IE. However, the scientific evidence in the literature remains limited; current guidelines address the use of the multimodality imaging in the field of IE with caution; the incremental value of each technique and their combinations is debated; and their use varies across countries. Despite these limitations, healthcare providers and surgeons should be aware of the possibilities offered by the multimodal imaging approach when appropriate. Here, we emphasize the value of a multidisciplinary heart valve team, the endocarditis team, underlining the importance of cardiac and extracardiac imaging experts in playing a key role in informing the diagnosis and management of patients with IE. Illustrative cases, critical appraisal of contemporary data, and conceptual and practical suggestions for clinicians that may help to improve the prognosis of patients with IE are provided in this review article.

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Infective endocarditis (IE) is a complex and deadly disease that is associated with cardiac-localized infection and multiorgan complications. Likewise, cardiac implantable electronic device (CIED) infection constitutes a complex scenario. In some cases, it is superimposable to valve endocarditis (when there is intravascular infection), whereas in other cases, it differentiates substantially from the classic concept of endocarditis (when there is only infection of the generator or the extravascular segment of the device). Diagnosis of IE remains challenging and includes identification of the infective pathogen and detection of cardiac lesions and noncardiac localization of the disease. Evidence of valve or intracardiac material involvement is a major diagnostic criterion, with echocardiography representing the first-line imaging method. However, it is well known that echocardiography has several limitations, and other imaging modalities (computed tomography [CT], magnetic resonance imaging, nuclear imaging) have progressively been shown to be useful to demonstrate or depict both valve involvement and the presence of IE-related peripheral complications (metastatic infection and infectious embolism), as well as occult predisposing lesions that may be the source of infection. Anatomic imaging such as multislice CT or hybrid modalities, which combine both anatomic and metabolic information such as positron emission tomography (PET)/CT and single photon emission tomography (SPECT), has been shown to be particularly useful in the presence of implantable/prosthetic material (valve prostheses, CIED, or other intracardiac implanted material).[1,2] Therefore, these techniques have gradually been included in the global assessment of patients with suspected IE, and the 2015 European Society of Cardiology (ESC) guidelines encouraged the multimodality imaging (MMI) approach by introducing image findings as new IE criteria.[3] However, the indication for each imaging modality remains unclear, and their recommendations for use are not organized or not well stated, included, or integrated into diagnostic workup algorithms. Hence, despite robust evidence supporting the value of MMI, the use of these imaging techniques has not yet been standardized and varies widely in clinical practice.[4,5]

The 2 main diagnostic challenges in patients with suspected IE or CIED infection are the confirmation of local involvement at the cardiac/device level and the detection of distant lesions related to the infectious process. Each technique has its diagnostic pros and cons in terms of these 2 issues (Table). In this sense, clinical discussion within the endocarditis team is, in our experience, the best way to overcome the limitations of the imaging techniques, thus optimizing imaging results for subsequent patient management. This review summarizes the current knowledge of the MMI approach in IE with the intent of providing evidence-based recommendations for each imaging technique and practical algorithms for the integrated use of MMI in different IE clinical scenarios.

SCENARIO 1: LEFT-SIDED IE

Value and Limitations of Echocardiography

Echocardiography is the first-line imaging modality to be performed in the context of IE. Echocardiography is of major importance for the diagnosis of IE and the assessment of disease severity, providing prognostic data such as embolic risk and patient follow-up assessments. The main echocardiographic criteria for IE are vegetations, perivalvular complications (abscess, pseudoaneurysm, new dehiscence of prosthetic valve), intracardiac fistula, and valve perforation or aneurysm.[3]

Both transthoracic (TTE) and transesophageal (TEE) echocardiography should be performed.[6] TEE allows better evaluation in several situations in which TTE has a limited sensitivity[4] such as prosthetic valve IE (PVE)[5] and small vegetations[7] and in the presence of perivalvular abscess.[8] Three-dimensional TEE allows better delineation of valvular vegetations and abscesses, perforations and paravalvular leaks, dehiscence, and localization of infection with regard to valve anatomy and its relationship with surrounding cardiac structures.

Echocardiography is also useful in predicting embolic events. Among several factors that have been associated with an increased risk of embolism[9] (age, diabetes mellitus, atrial fibrillation, embolism before antibiotics, vegetation size, and *Staphylococcus aureus* infection[10]), the size and mobility of vegetations are the most potent predictors of embolic events in patients with IE.[10–14] For example, the risk of neurological complications is particularly high in patients with large vegetations (>30 mm in the greatest dimension).[15] The 2015 ESC guidelines recommend urgent surgical therapy in the case of a large vegetation (>10 mm) after ≥1 embolic episodes, especially when the large vegetation is associated with other predictors of a complicated course.[3]

Value and Limitations of Cardiac CT Angiography and Extracardiac CT

ECG-gated cardiac CT with angiography (CTA) or without angiography is an imaging modality able to assess both valve and perivalvular IE lesions.[16] The 2015 ESC IE guidelines criteria included consideration for the use of cardiac CT in cases of possible IE or IE not confirmed by other criteria with high clinical suspicion in both native valve IE (NVE) and PVE, with special emphasis on the detection of perivalvular complications.[3]

Compared with surgical findings in left-sided valve IE, the sensitivity and specificity of CT to detect perivalvular lesions (abscesses and pseudoaneurysms) are very

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Table. Pros and Cons of Each Diagnostic Technique in IE and CIED Infections

	Imaging Technique	IE		CIED Infection	
		Pros	Cons	Pros	Cons
Cardiac assessment	Echocardiography	Good diagnostic ability in NVE (vegetations, leaks) Acceptable diagnostic ability in PVE (TEE>TTE) Valvular function assessment Evaluation of the hemodynamic consequences of the valve damage and PHT Prognostic value Prediction of embolic risk Useful for follow-up	Limited for evaluating anterior structures and RVOT tract (right-sided IE) Limited ability for perivalvular complications, especially in PVE Nondetection of peripheral complications Potential procedural complications for TEE	Acceptable diagnostic ability in CDIRE (TEE>TTE) Tricuspid valve function and PHT assessment Detection of potential residual material after device extraction	NA for generator / pocket and extracardiac or extravascular lead infection Frequent difficulties in differentiating lead vegetations from noninfected thrombi Nondetection of peripheral complications Potential procedural complications for TEE
	Cardiac CTA	Good ability to detect perivalvular complications in both NVE and PVE (abscess/pseudoaneurysm) Acceptable diagnostic ability for detecting vegetations, leaflet thickening and perforation, fistulas Coronary artery preoperative assessment	Limited in small vegetations Radiation exposure/risk of nephrotoxicity*	Detection of soft-tissue lesions and infected collections around the generator Assessment of venous accesses permeability (relevant for implantation of a new device)	Limited diagnostic ability for CDRIE (small vegetations and lead artifacts) Radiation exposure/risk of nephrotoxicity*
	WBC-SPECT	High specificity for infection Intermediate availability/low cost	Limited diagnostic sensitivity (lower spatial resolution) Longer acquisition time Radiation exposure	Good sensitivity and specificity for generator/pocket and extracardiac or extravascular lead infection	Limited diagnostic sensitivity for CDRIE Longer acquisition time Radiation exposure
	PET/CTA Cardiac	High sensitivity in PVE Hypermetabolism+anatomic lesions (vegetations, leaflet thickening and perforation, fistulas) Detection or clarification of perivalvular/periprosthetic complications Better definition of the locoregional extension of the infection Evaluation of other prosthetic materials beyond prosthetic valves (eg, in patients with congenital heart disease)	Low sensitivity in NVE Limited in small vegetations Possible false-positive studies resulting from inflammation (not recommended until > 3 mo after surgery) or FDG uptake of the prosthetic materials Possible false negative in patients with long antibiotic treatment Patient preparation (myocardial suppression) Radiation exposure/risk of nephrotoxicity*	Very high sensitivity and specificity for generator/pocket and extracardiac or extravascular lead infection Evaluation of other prosthetic materials beyond cardiac device (eg, coexisting prosthetic valve) Assessment of venous accesses permeability	Low sensitivity for CDRIE (small and mild hypermetabolism of vegetations and leads artifacts) Visual interpretation. Unstandardized quantification analysis Patient preparation (myocardial suppression) Radiation exposure/risk of nephrotoxicity*
Extracardiac assessment	Plus Whole body	Detection of distant lesions (embolic/ metastatic) Alternative diagnosis in rejected IE Detection of the infection source (especially in some IE-related microorganisms, sometimes unknown neoplastic lesions)		Detection of pulmonary embolic lesions Alternative diagnosis in rejected IE	
	Conventional CTA and MRI	Detection of distant lesions and systemic complications: intra-abdominal emboli, pulmonary embolic lesions, central nervous system, spondylodiscitis, mycotic arterial aneurysms	Radiation exposure/risk of nephrotoxicity*	Detection of pulmonary embolic lesions	Radiation exposure/risk of nephrotoxicity*

CDRIE indicates cardiac device–related infective endocarditis; CIED, cardiac implantable electronic device; CTA, cardiac tomographic angiography; FDG, fluorodeoxyglucose; IE, infective endocarditis; MRI, magnetic resonance imaging; NA, not applicable; NVE, native valve endocarditis; PET, positron emission tomography; PHT, pulmonary hypertension; PVE, prosthetic valve endocarditis; RVOT, right ventricular outflow tract; TEE, transesophageal echocardiography, TTE, transthoracic echocardiography; and WBC-SPECT, white blood cell single-photon emission computed tomography.

*In patients with renal impairment (CTA, iodinated contrast; MRI, gadolinium contrast).

high (>95%),[16] especially in the aortic position.[17] Detection of valve lesions as vegetations, leaflet thickening, valve perforation, or valve aneurysm is also feasible.[16] An excellent correlation with operative findings has been reported, with 96% sensitivity and 97% specificity of CT compared with surgery in a per-valve analysis,[17] as well as excellent reported interobserver agreement.[18] It should be recognized that data on the value of cardiac CTA in the diagnosis and treatment of IE are relatively scarce, are derived from a few patients in highly experienced centers, and may not be generalizable to all centers managing patients with IE. ECG-gated cardiac CTA also allows noninvasive assessment of coronary anatomy preoperatively in patients with surgical indication, in whom conventional invasive angiography could be contraindicated. The main relative limitations of CT are the radiation exposure and the risk of nephrotoxicity associated with iodinated contrast injection. However, the potential advantages of CT to provide relevant diagnostic information overcome these limitations.

Because of its capability to image the entire body, CT also allows detection of extracardiac IE-related lesions. Peripheral lesions include those that can be found in the systemic circulation in the case of left-sided endocarditis, mainly intra-abdominal lesions of infective origin (splenic, renal, and hepatic infarctions or abscesses; mesenteric ischemia),[18] central nervous system lesions, and other metastatic locations of the infection (spondylodiscitis, septic arthritis, vascular mycotic aneurysm, etc),[19] as well as those secondary to right-sided IE, mainly septic pulmonary emboli.

Value and Limitations of Nuclear Imaging Techniques

Abnormal activity around the site of prosthetic valve implantation detected by fluoro-18-fluorodeoxyglucose ([^{18}F]FDG) PET/CT or radiolabeled leukocytes SPECT/CT is considered a major criterion of the ESC 2015 IE criteria. PET technology delivers high-resolution images by the use of biologically active compounds labeled with positron emitters. Image acquisition starts ≈45 to 60 minutes after the injection of [^{18}F]FDG, a radiolabeled glycogen analog that accumulates into cells such as activated inflammatory cells in infection and inflammation processes (activated leukocytes,[20] monocyte macrophages,[21] and CD4$^+$ T lymphocytes[22]). Uptake of the radiopharmaceutical is based on the high expression of glucose transporters, which actively incorporate the tracer into the cells. Metabolic activity is evaluated both qualitatively and quantitatively.[23–26] To facilitate visualization of presumed sites of valve infection, suppression of [^{18}F]FDG uptake by normal myocardium in proper patient preparation is needed. There is a general consensus that a high-fat, low-carbohydrate diet for at least 2 meals with a fast of at least 4 hours is the minimum to obtain suppression of physiological myocardial glucose utilization.[25] Interpretation of [^{18}F]FDG PET/CT images requires proper knowledge of the potential confounding normal and pathological conditions that may resemble the uptake pattern typically observed in IE[27] (ie, persistent host reaction against the biomaterial coating the sewing ring of the pulmonary valve and chronic tension or friction exerted on these anchor points[28]), as well as of the factors affecting the intensity of [^{18}F]FDG uptake.[29–31] If PET/CT acquisition is combined with cardiac CT (PET/CTA), the metabolic findings provided by the [^{18}F]FDG uptake distribution and intensity might be added to the anatomic findings already described for cardiac CTA within a single imaging procedure.[32] The advantages of combining [^{18}F]FDG PET/CTA include the identification of a larger number of anatomic lesions, clinical clarification in the context of other indeterminate studies,[32,33] and its value in specific clinical situations such as in patients with aortic grafts and patients with congenital heart disease who have complex anatomy, because their surgical treatment often requires implantation of a large amount of prosthetic material.

The value of [^{18}F]FDG PET/CT is limited in NVE, when cardiac infection is the target of this imaging technique, in which the sensitivity is too poor to recommend its routine use.[34–36] However, in the case of NVE, the use of [^{18}F]FDG PET/CT is useful for the detection of distant embolic events, a condition currently considered a minor criterion in the 2015 ESC guidelines (see below).

Radiolabeled white blood cell (WBC) SPECT/CT imaging relies on the use of autologous radiolabeled leukocytes (^{111}In-oxine or ^{99m}Tc-hexamethylpropyleneamine oxime) that accumulate in infection foci in a time-dependent fashion (late versus earlier images).[37] However, the limited sensitivity of WBC SPECT/CT could affect its negative predictive value to exclude IE in all suspected cases. Disadvantages of WBC SPECT/CT are the requirement of blood handling for radiopharmaceutical preparation, the duration of the procedure, which is longer compared with PET/CT, and a slightly lower spatial resolution and photon detection efficiency compared with [^{18}F]FDG PET/CT.

Notable advantages of PET/CT and WBC SPECT/CT are their ability to perform the extracardiac workup within a single imaging procedure and to reveal the concomitant presence of extracardiac infection sites as the consequence of both septic embolism and primary infective processes (with the exception of the brain location because brain uptake is always high as a result of its specific metabolism).[34,38,39] Detection of metastatic infection by [^{18}F]FDG PET/CT led to a change in treatment in up to 35% of patients.[40] PET/CT has been demonstrated to be able to reveal the source of infection, including cases in which the sustaining portal of entry was a neoplasia (colonic cancer).[32]

Which Technique for Which Patient?

What the Guidelines Say

The 2015 ESC guidelines added as major imaging criteria "pseudoaneurysm, intracardiac fistula, and valve perforation or aneurysm" detected by echocardiography, but also "definite paravalvular lesion" detected by cardiac CTA,

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and in the case of prosthetic valves, "abnormal activity around the site of implantation" detected by [18F]FDG PET/CT.[3] The use of CT was also recommended in the 2014 American College of Cardiology Foundation/American Heart Association (Class IIa, Level of Evidence B) guidelines to evaluate morphology/anatomy in the setting of suspected paravalvular infections when the anatomy cannot be clearly delineated by echocardiography.[41] The 2015 American Heart Association scientific statement[18] does not assign recommendation class or level of evidence for the use of both CTA and nuclear imaging but highlights that the use of MMI in IE may increase in the future.

Figures 1 and 2 provide clinical cases that underline the value of a comprehensive MMI evaluation in a patient with NVE and PVE, respectively.

Proposed Clinical Algorithms for NVE and PVE

The following algorithm is for NVE (Figure 3):

- Echocardiography must be performed in all patients with suspected IE as the first imaging test. Both echocardiography modalities, TTE and TEE, should be performed in nearly all cases to evaluate anatomic involvement and hemodynamic consequences.
- When TTE is negative and the IE suspicion remains high, TEE is indicated to confirm or rule out the diagnosis because of its higher sensitivity to detect vegetations (90%–100% for TEE versus 40%–63% for TTE).[42]
- Beyond the diagnosis of IE, TEE should be performed for a better assessment of perivalvular complications. TEE sensitivity is higher than that of TTE to detect abscesses (sensitivity, 87%; specificity, 95%)[8] and overall perivalvular complications.[43]
- If both TTE and TEE are negative or inconclusive, especially when performed early in the clinical course,[44] they should be repeated within 1 week if high clinical probability of IE persists.
- Cardiac CTA might be used in the setting of suspected paravalvular infection extension when the anatomy cannot be clearly delineated by echocardiography because of suboptimal acoustic

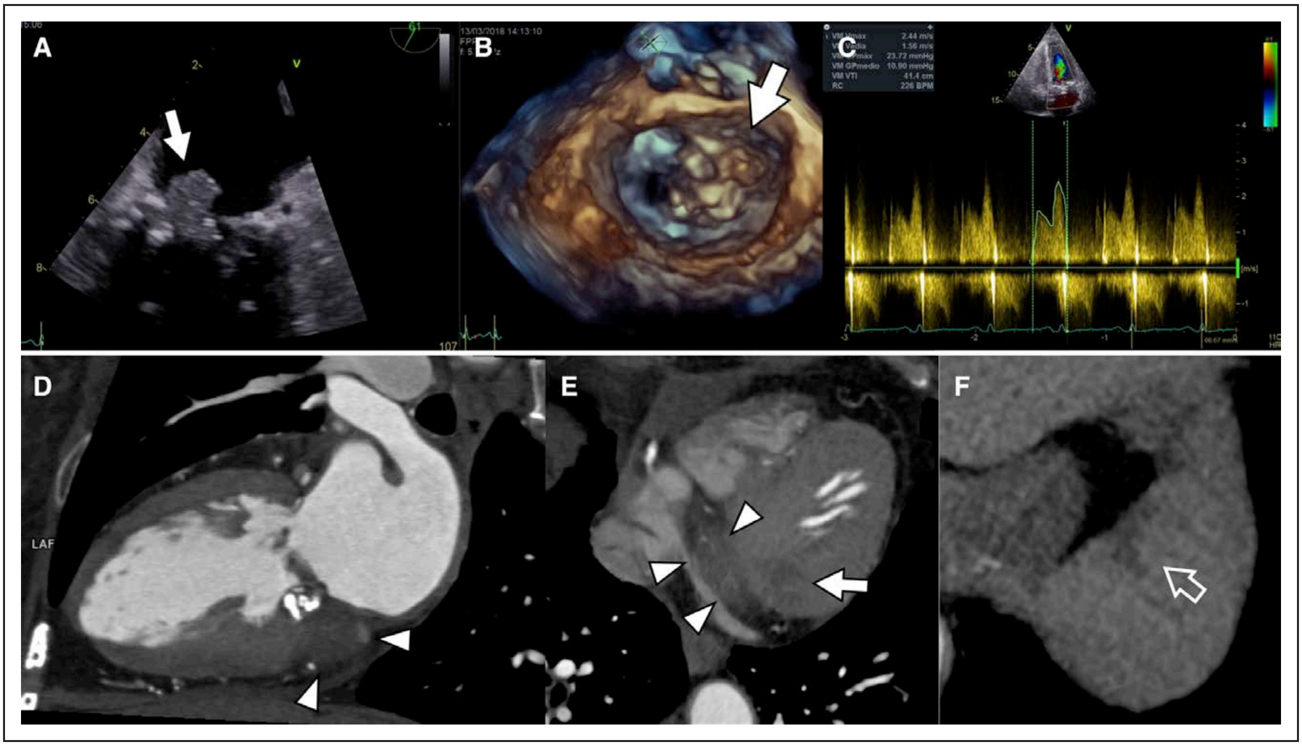

Figure 1. Mitral native valve infective endocarditis (NVE) complicated by perivalvular abscess and splenic embolism.
A 78-year-old patient was admitted with fever and had blood cultures positive for *Streptococcus agalactiae*. Echocardiography found several vegetations on the mitral valve (**A** and **B**, arrows). The diagnosis of mitral NVE was established, and antibiotic treatment was started. Because of respiratory conditions, transesophageal echocardiography was performed 7 days later and found vegetation growth (from 7–20 mm), causing significant mitral obstruction (**C**). Severe calcification of the mitral annulus did not allow perivalvular complications assessment. The patient had persistent fever and control blood cultures remained positive. Because of suspected perivalvular complications and uncontrolled infection, a cardiac computed tomography (CT) was performed and showed mitral valve leaflet thickening with multiple vegetations, severe calcification of the mitral annulus with destruction of its posterior aspect, and a poorly delimited soft-tissue lesion in the inferior atrioventricular sulcus consistent with a perivalvular abscess (**D**, arrowheads), causing compression of the coronary sinus (**E**, arrowheads). Hypodense intramyocardial areas suggested infectious involvement of the ventricular wall (**E**, arrow). Upper abdominal images also showed a small splenic embolism (**F**, arrow). On the basis of the cardiac CT angiography (CTA) findings, the multidisciplinary infective endocarditis team agreed on the indication to surgery followed by antibiotic treatment. All image findings were confirmed. Valve RNA polymerase chain reaction was positive for *S agalactiae*. The patient completed a total of 8 weeks of antibiotics and is doing well. This case illustrates the value of a comprehensive multimodality imaging evaluation in a patient with NVE when cardiac CTA completed a suboptimal echocardiographic study, adding information on perivalvular extension of the infection and thus reinforcing the surgical indication.

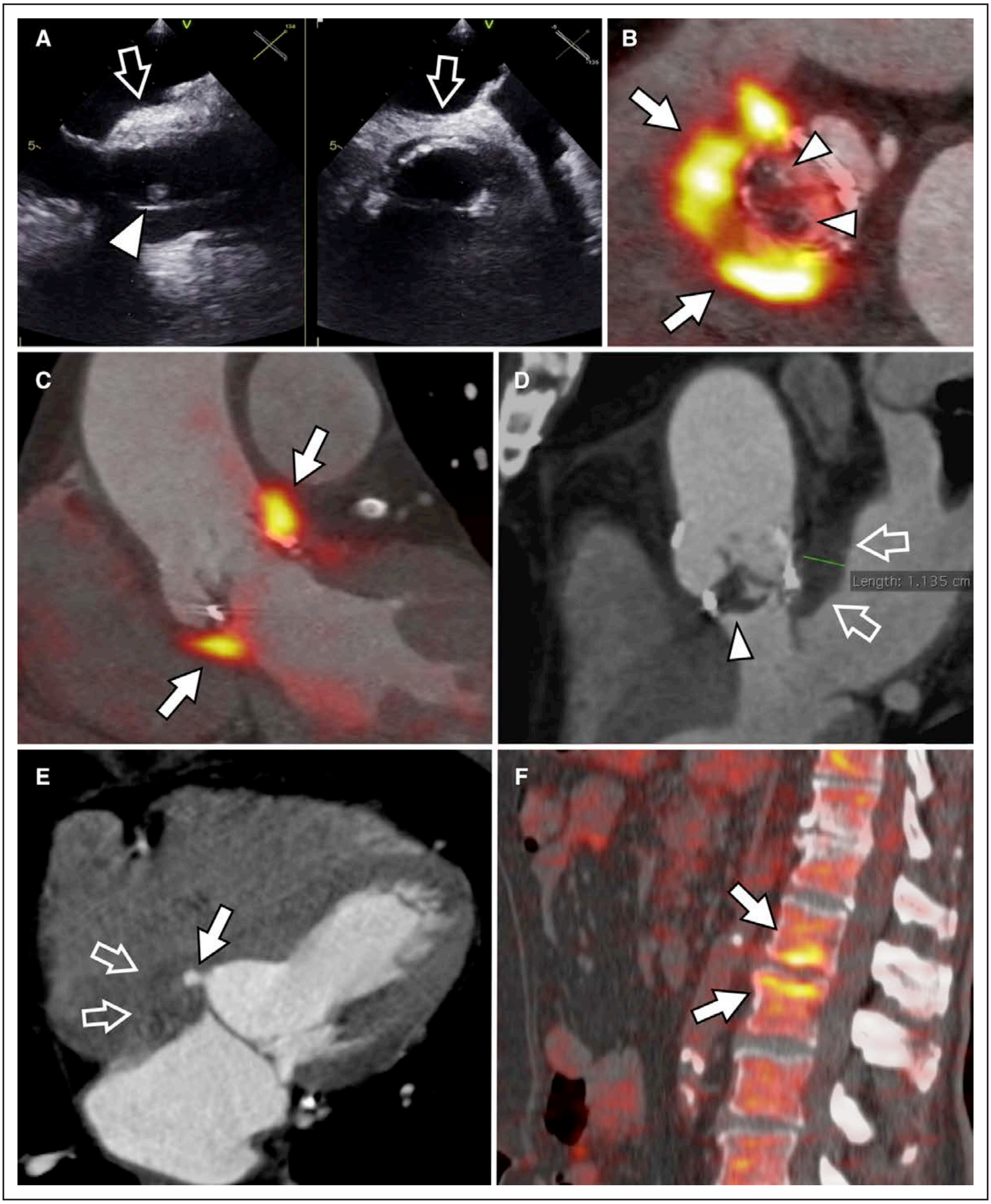

Figure 2. Aortic prosthetic valve infective endocarditis (PVE) complicated by periprosthesis abscess and spondylodiscitis.
A 73-year-old patient with an aortic bioprosthesis implanted 5 months previously was admitted for an ischemic stroke and suspected prosthetic thrombosis. A few days after admission, he developed fever and back pain. Blood cultures were positive for *Staphylococcus epidermidis*. Transesophageal echocardiography (TEE) showed an 8-mm aortic vegetation (**A**, arrowhead) and a possible periprosthetic thickening (**A**, arrows). In this case of *S epidermidis* early PVE, TEE revealed an inconclusive finding of periprosthetic thickening. Fluoro-18-fluorodeoxyglucose positron emission tomography ([^{18}F]FDG PET)/computed tomographic angiography (CTA) was then performed to clarify the periprosthetic extension of the infection and to rule out the presence of systemic embolism, which were suspected on the basis of the clinical history (ischemic stroke and occurrence of back pain). Images (**B** and **D**, arrowheads) show an intense hypermetabolic (maximum standard uptake value, 13.4), poorly delimited 11-mm-thick soft-tissue lesion around the valve (**B**, **C**, and **E**, arrows) consistent with a periprosthetic abscess and a small pseudoaneurysm from the left ventricular outflow tract (**E**, white arrow). The whole-body [^{18}F]FDG PET/CT also showed an L1-L2 spondylodiskitis (**F**, arrows). On the basis of the imaging findings, the multidisciplinary endocarditis team opted for surgery followed by antibiotics. This case illustrates the value of a multimodality imaging evaluation in a patient with PVE in whom [^{18}F]FDG PET/CTA identified both a periprosthetic involvement undiagnosed by echocardiography and the presence of infective endocarditis–related peripheral lesions, reinforcing the surgical indication. In this case, the choice of performing PET/CTA rather than cardiac CTA was based on the higher sensitivity of PET/CTA in the setting of PVE for both valvular involvement and extracardiac workup. Surgery confirmed all image findings, and the prosthetic valve culture was positive for the same microorganism. The patient was treated with antibiotics for a total of 8 weeks, and the course was uneventful.

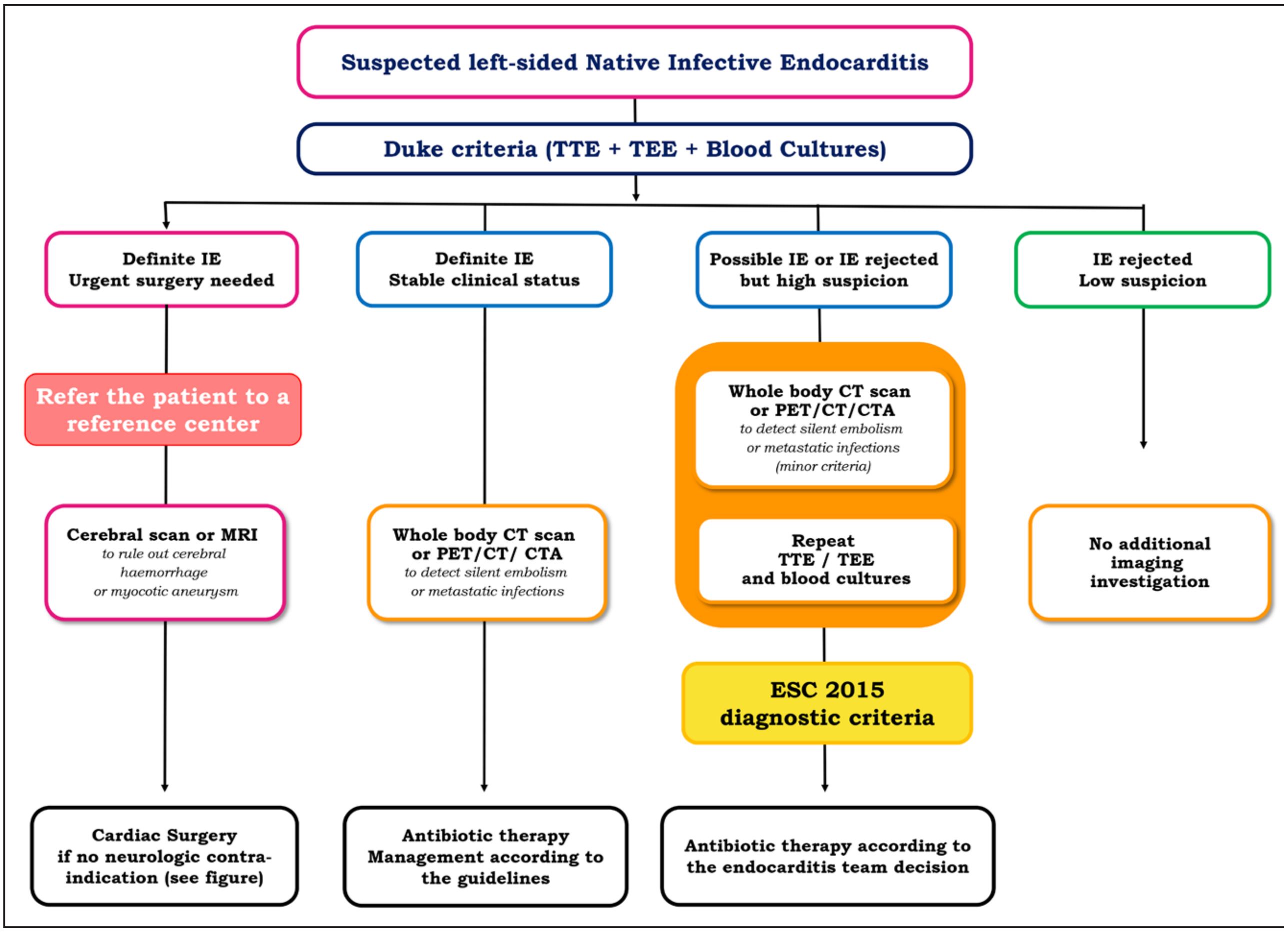

Figure 3. Diagnosis algorithm for suspected native valve infective endocarditis (IE).
CT indicates computed tomography; CTA, computed tomographic angiography; ESC, European Society of Cardiology; MRI, magnetic resonance imaging; PET, positron emission tomography; TEE, transesophageal echocardiography; and TTE, transthoracic echocardiography.

windows or artifacts caused by, for example, severe calcifications. In addition, cardiac CTA allows pre-operative risk stratification, accurately assessing the IE-related perivalvular lesions for a better procedure planning,[17,45] and allows the evaluation of coronary artery disease.

- [^{18}F]FDG PET/CTA, if available, can be used as alternative or complementary technique to cardiac CTA. Although there is no consistent scientific evidence, the addition of metabolic activity information could increase diagnostic accuracy.

For PVE (Figure 4), the following algorithm apples:

- TTE and TEE must be performed systematically in patients with PVE.[3,41,46] The sensitivity of TTE and TEE in PVE is 50% and 92%, respectively.
- If TTE and TEE are negative, especially when performed early in the clinical course,[44] they might be repeated within 1 week if high clinical probability of IE persists.
- Patients with possible or even ruled-out IE by Duke criteria but with high clinical suspicion should be sent to a reference center, where the most appropriate technique to be performed can be chosen (CTA, PET/CTA, WBC imaging) to confirm or rule out IE.

SCENARIO 2: RIGHT-SIDED IE

Value and Limitations of Echocardiography

Right-sided heart involvement is usually easy to detect with TTE because of the anterior location of this valve and usual large vegetations,[47,48] although the right side of the heart has many echocardiographically anatomic facets that may be difficult to distinguish from vegetations.[49] Eustachian and pulmonary valves should always be assessed. TEE is more sensitive in the detection of pulmonary vegetations[50] and associated left-sided involvement and in the evaluation of central intravenous catheters and devices, prosthetic valve, foreign bodies, unusual locations of right-sided IE, and complications (eg, perivalvular abscesses) after failure to respond to therapy.[51]

TTE and TEE have complementary roles and are recommended in cases of suspected CIED infections. TTE defines better the presence of prognostic features such

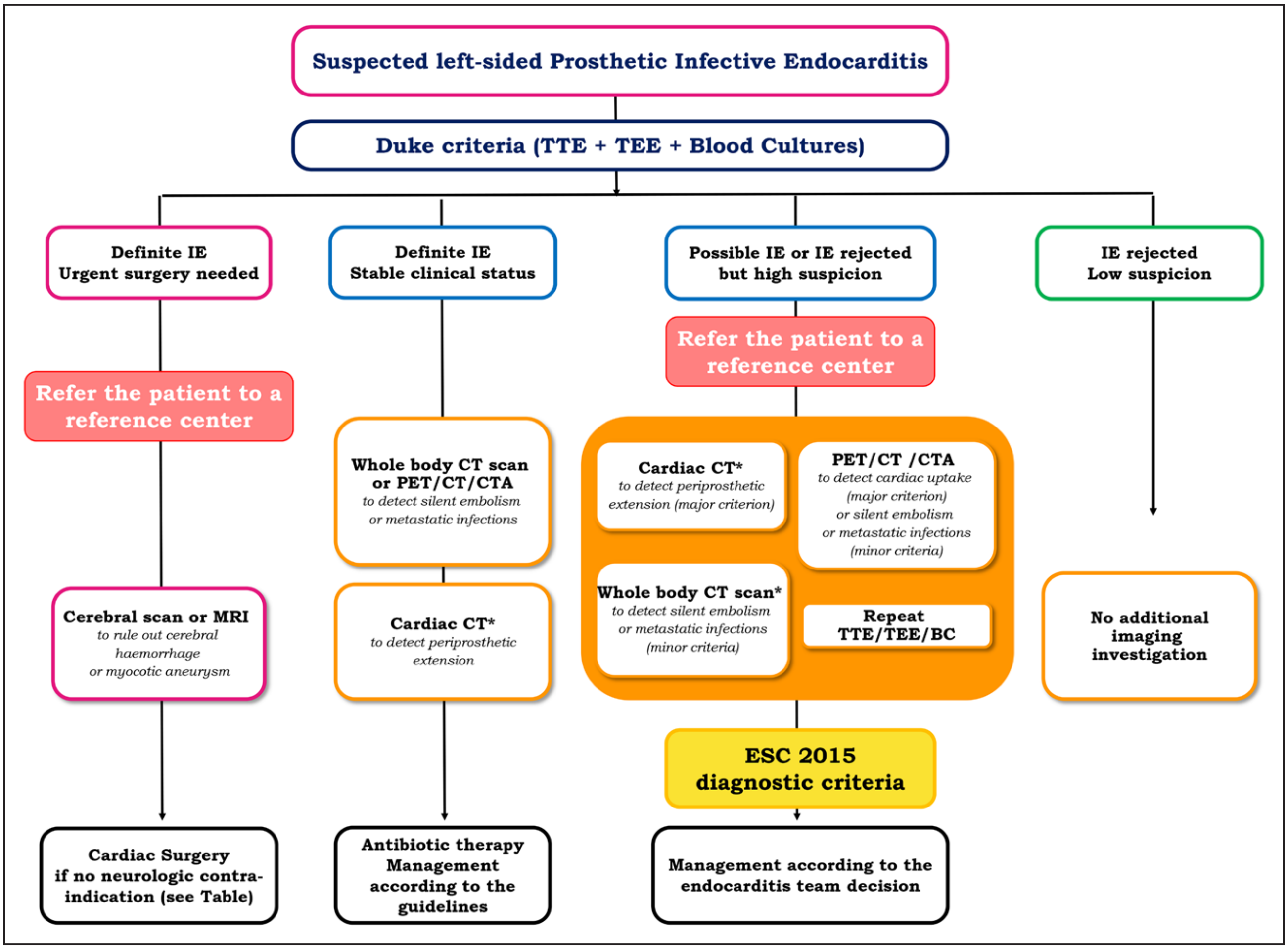

Figure 4. Diagnosis algorithm for suspected prosthetic valve infective endocarditis (IE).
BC indicates blood culture; CT computed tomography; CTA, computed tomographic angiography; ESC, European Society of Cardiology; MRI, magnetic resonance imaging; PET, positron emission tomography; TEE, transesophageal echocardiography; and TTE, transthoracic echocardiography. *If contrast agent injection is not contraindicated.

as pericardial effusion, ventricular dysfunction, and pulmonary arterial pressure. TEE is superior to TTE in the detection and sizing of vegetations[52] and allows visualization of lead vegetations in the right atrium–superior vena cava area and in other regions less well visualized by TTE. Diagnosis of CIED infection is frequently difficult by both TTE and TEE, particularly the differentiation between noninfected thrombus and infected vegetation. In addition, a negative result cannot exclude infection of the extracardiac portion of the device, the assessment of which is beyond the reach of echocardiography.

In patients with CIED infections, a TTE before hospital discharge is also recommended to detect the presence of retained segments of pacemaker leads and to assess tricuspid valve function, right ventricular function, and pulmonary hypertension. In addition, a TEE after percutaneous lead extraction should be considered to detect residual infected material and potential tricuspid valve complications.

Intracardiac echocardiography has been found to be feasible and effective in patients with a cardiac device with high sensitivity for detecting vegetations in cardiac devices.[53]

Value and Limitations of Other Imaging Techniques

CTA, [^{18}F]FDG PET/CTA, and WBC SPECT/CT might be used in all cases when right-sided IE (particularly PVE) or CIED involvement is suspected. Contrast-enhanced CT may reveal pulmonary emboli, infarcts, and abscesses. Ventilation-perfusion scintigraphy may be an alternative to CT to screen for septic pulmonary embolism.[54] [^{18}F]FDG PET/CTA and WBC SPECT/CT have largely replaced ventilation-perfusion scintigraphy, allowing the contemporary assessment of right- and left-sided valves and sites of distant embolisms and portal of entry.[1]

[^{18}F]FDG PET/CTA is useful in patients with evidence of pocket infection (local signs of inflammation at the generator pocket, including erythema, warmth, fluctuance, wound dehiscence, erosion, tenderness, or purulent drainage[3]) and negative microbiological and echocardiographic examination and in patients with positive

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blood cultures but negative echocardiographic examination. [18F]FDG PET/CTA provides added diagnostic value to the Duke criteria, particularly in the subset of patients with possible CIED infection,[55–60] and it has the capability to explore the whole device. Its diagnostic accuracy is very high in pocket/generator infection, in which mild inflammatory changes after device implantation usually do not extend beyond 6 weeks and are easily differentiated from infection after this period. Studies have shown almost 100% accuracy for diagnosing infection of the generator pocket and the extracardiac portion of the lead[55–57,60] (sensitivity, specificity, and accuracy for the diagnosis of pocket infection were 93%, 98%, and 98%, respectively). In cases of lead-related IE, [18F]FDG PET/CTA is very specific when tracer uptake is visualized. However, its sensitivity is low, and a negative result does not completely exclude the presence of small vegetations with low metabolic activity.[57]

Which Technique for Which Patient?

What the Guidelines Say

TTE should be performed in all patients with suspected right-sided heart endocarditis, complemented by TEE in case of inconclusive TTE results and in the presence of an intracardiac prosthesis or device, even if only pocket infection is suspected.[3] Radiolabeled leucocyte scintigraphy and [18F]FDG PET/CTA scanning may be considered additive tools in patients with suspected CIED infection, positive blood cultures, and negative echocardiography.

Figures 5 and 6 provide clinical cases that underline the value of a comprehensive MMI evaluation in a patient with right-sided NVE and CIED infection, respectively.

Proposed Clinical Algorithm in CDRIE

Figure 7 provides an algorithm for suspected cardiac device-related IE.

- Blood cultures and echocardiographic examinations (TTE and TEE) should be performed in all patients with suspected CIED infection, even if only pocket infection is suspected.
- When echocardiography and blood cultures remain negative and in patients without evidence of pocket infection, no additional imaging is needed.
- However, a normal echocardiography does not rule out CIED infection. The Duke criteria are difficult to

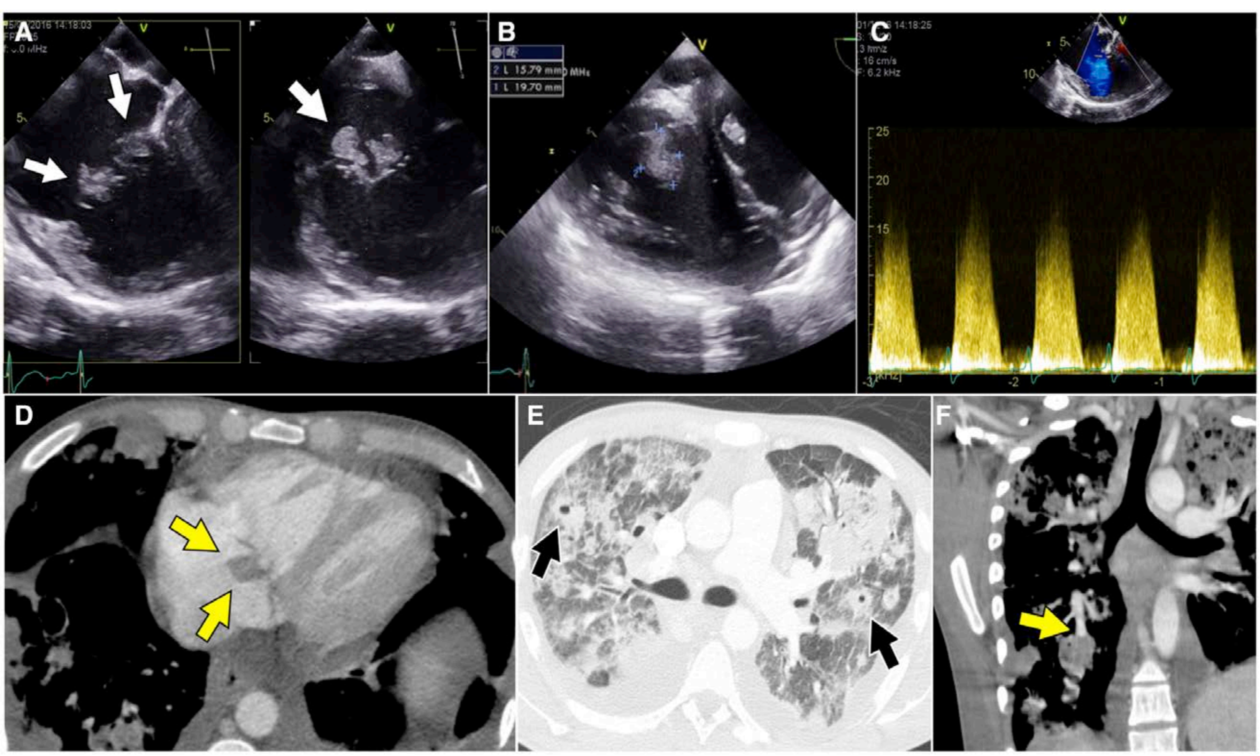

Figure 5. Tricuspid native valve infective endocarditis (NVE) complicated by pulmonary embolism.
A 29-year-old man, an intravenous drug abuser, was admitted with fever and blood cultures positive for *Staphylococcus aureus*. Transesophageal echocardiography (TTE) showed a 14×11–mm tricuspid vegetation (**A**, arrows). This case of *S aureus* tricuspid NVE was promptly diagnosed by TTE. Despite adequate antibiotic treatment (cloxaciline), the patient developed septic shock, right-sided heart failure, and respiratory insufficiency with severe hypoxemia and massive hemoptysis. A repeat TEE revealed vegetation growth (19×15 mm; **B**), right ventricular dilatation with severe tricuspid insufficiency (**C**), and severe pulmonary hypertension. A thoracic non-ECG-gated computed tomography (CT) was performed and showed a large tricuspid vegetation (**D**, arrows); multiple bilateral pulmonary nodules, some of them cavitated (**E**, arrow); congestive signs; and pulmonary emboli (**F**, arrow). The multidisciplinary endocarditis team chose a conservative approach in this patient. This case illustrates the role of a multimodality imaging evaluation in a patient with right-sided NVE in whom CT was useful for an adequate assessment of septic pulmonary embolism lesions.

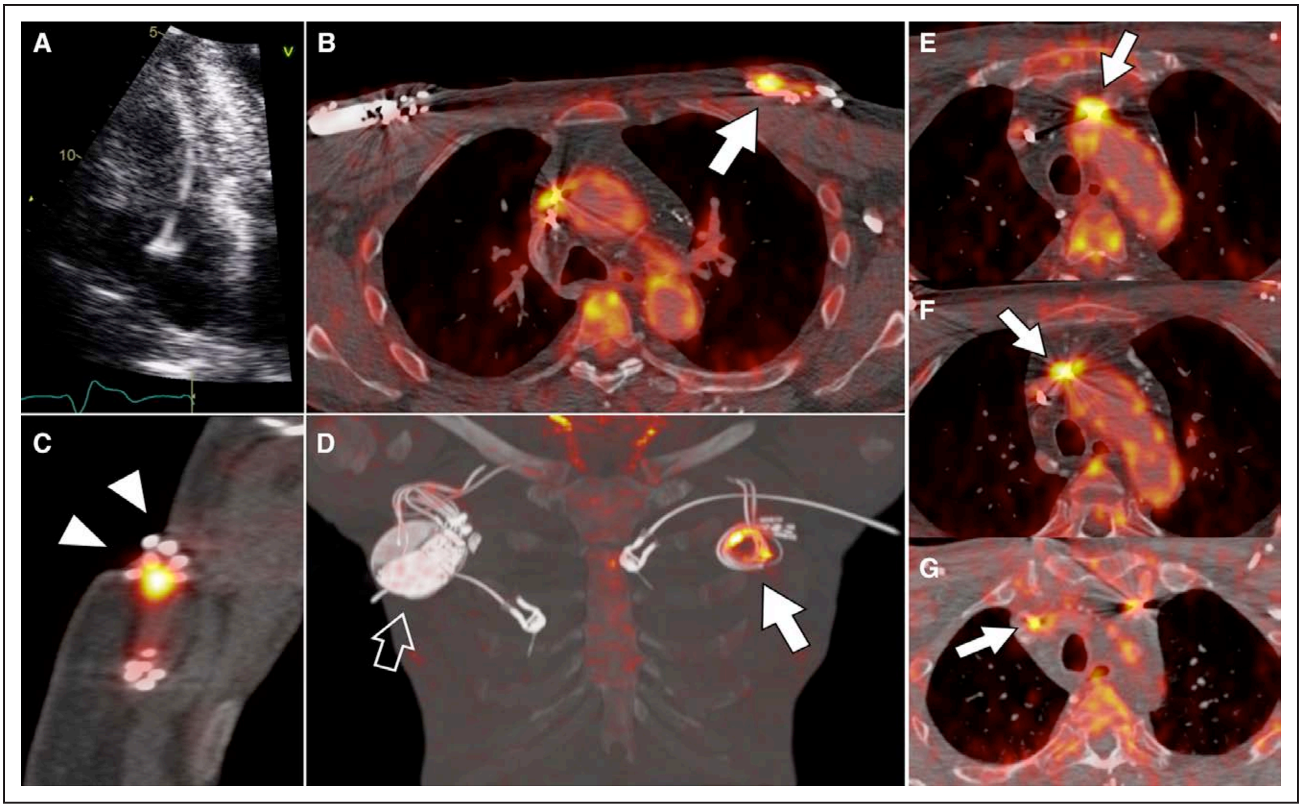

Figure 6. Cardiac implantable electronic device (CIED)–related infective endocarditis.
A 66-year-old patient had an implantable cardioverter defibrillator (ICD) with a generator placed in the left side of the chest and leads in the right atrium and ventricle. During a generator replacement, a lead was damaged, and a complete contralateral right-sided chest device had to be implanted. As a result of left subclavian vein occlusion, the old left leads could not be removed and were entirely abandoned. He was evaluated for pain, swelling, and erythema of the left-sided old pocket. Blood cultures were negative, but local purulent material culture was positive for *Staphylococcus epidermidis*. Local infection at the site of the previous ICD was diagnosed. Echocardiography was performed (**A**) and was negative. A fluoro-18-fluorodeoxyglucose positron emission tomography ([^{18}F]FDG PET)/computed tomography (CT) was performed to assess the involvement of the abandoned left-sided leads and the status of the new CIED. A [^{18}F]FDG PET/CT showed focal [^{18}F]FDG uptake on the abandoned leads at the old left-sided pocket (**B** and **D**, arrow) and on their intravascular segment (**E** and **F**, arrows). Old pocket–associated anatomic findings were fat stranding and skin retraction (**C**, arrowheads). There were no signs of infection of the new ICD generator pocket (**D**, open arrow), but focal [^{18}F]FDG uptake was visualized on the intravascular segment of the new device leads (**G**, arrow). On the basis of the results of PET/CT, extraction of both the old and new ICD systems was performed followed by treatment with daptomycin. Device cultures confirmed *S epidermidis* infection. A new right-sided ICD was implanted after 5 weeks of antibiotic treatment. The use of multimodality imaging in this high-risk patient with local CIED infection significantly affected the therapeutic decision.

apply in these patients because of lower sensitivity,[61] even when the modified Duke criteria are used.

- Because of the frequently difficult diagnosis of the disease and some limitations of echocardiography, MMI has been successfully applied in patients with CIED infections.
- [^{18}F]FDG PET/CTA is useful in patients with evidence of pocket infection and negative microbiological and echocardiographic examination and in patients with positive blood cultures but negative echocardiographic examination.
- Its diagnostic accuracy is very high in pocket/generator infection but is lower when the infection is limited to the lead of the device.
- When [^{18}F]FDG PET/CTA is not available, chest CTA may be performed to detect pulmonary embolism, infarct, or abscess. A venous-phase CT can be performed to assess permeability of venous access when a new device has to be implanted.

CONCLUSIONS

MMI is of utmost value in the diagnosis and management of IE. Echocardiography, cardiac and extracardiac CT, cerebral magnetic resonance imaging, and nuclear techniques have been shown to be useful in suspected and definite IE, but their indications may depend on the type of endocarditis (prosthetic versus native versus cardiac device related), the clinical status of the patient, and the possible limitations in using contrast agents. Although promising, this new approach needs further validation in prospective cohorts to define the optimal indications and timing of each of these techniques.

The next challenges are listed below:

- The determination of the MMI prognostic value;
- The demonstration that MMI can help in the choice of the best therapeutic option;
- The cost-efficiency of using MMI in IE, especially what is the least costly with highest efficiency in each individual patient; and

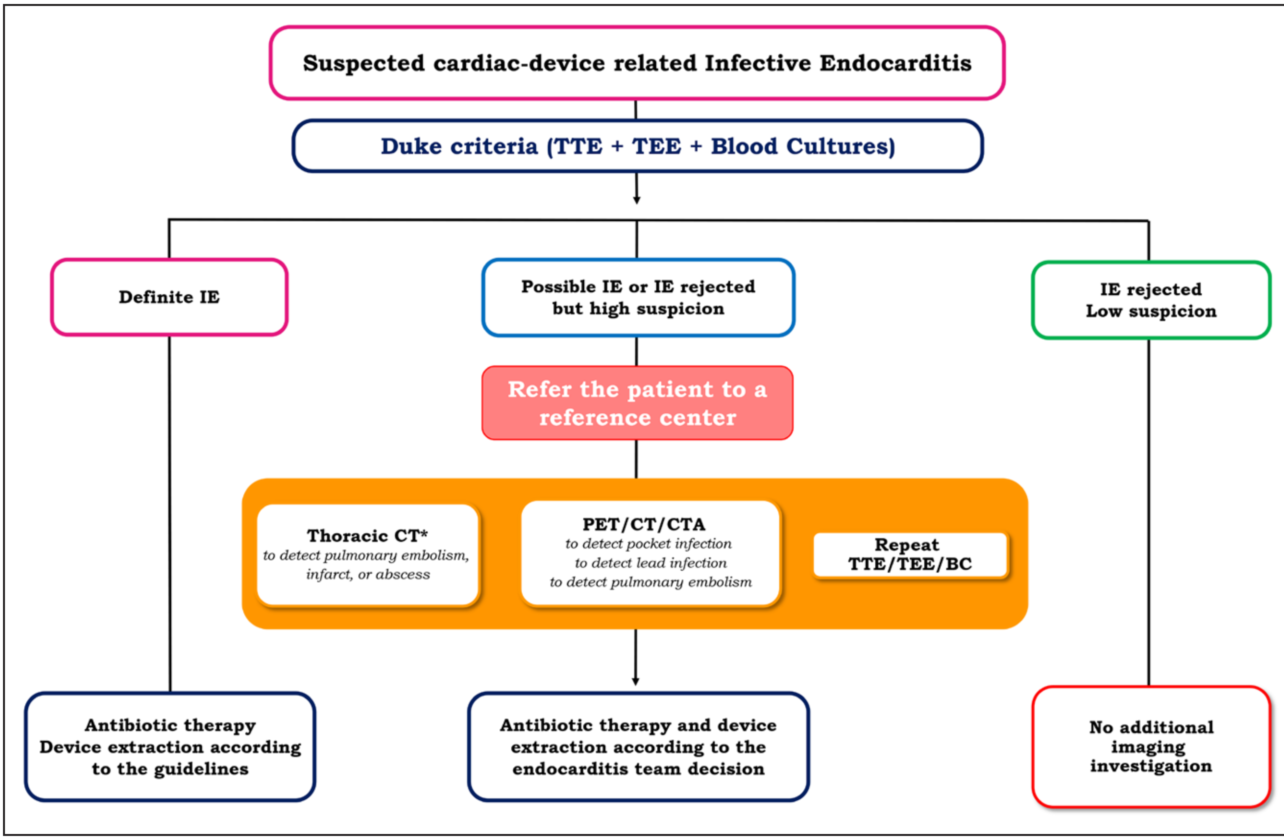

Figure 7. Diagnosis algorithm in suspected cardiac device-related infective endocarditis.
BC indicates blood culture; CT computed tomography; CTA, computed tomographic angiography; MRI, magnetic resonance imaging; PET, positron emission tomography; TEE, transesophageal echocardiography; and TTE, transthoracic echocardiography. *If contrast-agent injection is not contraindicated.

– The assessment of the feasibility of using this MMI strategy in different countries with different access to imaging techniques.

The decision to use MMI should ideally be made in reference centers complemented by the use of an endocarditis team. The MMI approach also requires cardiac imaging experts to be involved in the evaluation of patients with suspected or proven IE, ideally as an imaging team within the endocarditis team.

ARTICLE INFORMATION

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Disclosures

None.

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