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GUIDELINES

Recommendations on nuclear and multimodality imaging in IE and CIED infections

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Abstract

In the latest update of the European Society of Cardiology (ESC) guidelines for the management of infective endocarditis (IE), imaging is positioned at the centre of the diagnostic work-up so that an early and accurate diagnosis can be reached. Besides echocardiography, contrast-enhanced CT (ce-CT), radiolabelled leucocyte (white blood cell, WBC) SPECT/CT and [^{18}F]FDG PET/CT are included as diagnostic tools in the diagnostic flow chart for IE. Following the clinical guidelines that provided a straightforward message on the role of multimodality imaging, we believe that it is highly relevant to produce specific recommendations on nuclear multimodality imaging in IE and cardiac implantable electronic device infections. In these procedural recommendations we therefore describe in detail the technical and practical aspects of WBC SPECT/CT and [^{18}F]FDG PET/CT, including ce-CT acquisition

Preamble The European Association of Nuclear Medicine (EANM) is a professional nonprofit medical association that facilitates communication worldwide among individuals pursuing clinical and research excellence in nuclear medicine. The EANM was founded in 1985.

These recommendations are intended to assist practitioners in providing appropriate nuclear medicine care for patients. They are not inflexible rules or requirements of practice and are not intended, nor should they be used, to establish a legal standard of care.

The ultimate judgment regarding the propriety of any specific procedure or course of action must be made by medical professionals taking into account the unique circumstances of each case. Thus, there is no implication that an approach differing from the recommendations, standing alone, is below the standard of care. To the contrary, a conscientious practitioner may responsibly adopt a course of action different from that set out in the guidelines when, in the reasonable judgment of the practitioner, such course of action is indicated by the condition of the patient, the limitations of available resources or advances in knowledge or technology subsequent to publication of the recommendations.

The practice of medicine involves not only the science but also the art of dealing with the prevention, diagnosis, alleviation and treatment of disease. The variety and complexity of human conditions make it impossible to always reach the most appropriate diagnosis or to predict with certainty a particular response to treatment. Therefore, it should be recognized that adherence to these recommendations will not ensure an accurate diagnosis or a successful outcome. All that should be expected is that the practitioner will follow a reasonable course of action based on current knowledge, available resources and the needs of the patient to deliver effective and safe medical care. The sole purpose of these recommendations is to assist practitioners in achieving this objective.

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protocols. We also discuss the advantages and limitations of each procedure, specific pitfalls when interpreting images, and the most important results from the literature, and also provide recommendations on the appropriate use of multimodality imaging.

Keywords Infective endocarditis · Cardiac implantable electronic device · Infection · Radiolabelled WBC · ^{18}F PET/CT · Echocardiography · Cardiac CT

Introduction

Over the last decades, there have been a series of technology improvements that have significantly changed the role of clinical imaging in healthcare. Evolving technologies such as multimodality imaging have gained a central key role in the evaluation of several disease entities. Infectious endocarditis (IE), on both native valve (NVE) and prosthetic valve (PVE), and cardiovascular implantable electronic device (CIED) infections are examples of such diseases in which multimodality imaging is used effectively in decision-making.

Extensive clinical use of radiolabelled leucocyte (white blood cell, WBC) SPECT/CT and [^{18}F]FDG PET/CT in the imaging of IE has provided robust evidence of a major impact on patient management in terms of early diagnosis and the selection of optimal treatment strategies [1]. Therefore, in the latest update of the European Society of Cardiology (ESC) guidelines for the management of IE [2] both techniques are included as diagnostic tools in the diagnostic flow chart for PVE in particular. In these guidelines, imaging is a fundamental backbone of the diagnostic strategy, due to the concept that IE, rather than a single disease, may present with very different clinical patterns depending on the first organ involved, the underlying cardiac disease (if any), the microorganism involved, the presence or absence of complications, and the patient's characteristics. Therefore, imaging specialists with a high level of expertise need to participate in a multidisciplinary team together with practitioners from several other specialties, including cardiologists, microbiologists, clinicians and surgeons.

Following the clinical guidelines that provide a straightforward message on the role of multimodality imaging, we believe that it is highly relevant to produce specific recommendations on nuclear and multimodality imaging in IE and CIED infections. Therefore, in these procedural recommendations, we describe in detail the technical and practical aspects of WBC SPECT/CT and [^{18}F]FDG PET/CT, including contrast-enhanced CT (ce-CT) acquisition protocols. We also discuss the advantages and limitations of each procedure, specific pitfalls when interpreting images, the most important results from the literature and recommendations on the appropriate use of multimodality imaging.

Definition and clinical challenges in IE and CIED infections

IE is a life-threatening disease associated with a high mortality rate, difficult diagnosis and controversial management [3, 4]. The clinical history of IE is highly variable and depends on the causative microorganism, the presence or absence of preexisting cardiac disease, the presence or absence of prosthetic valves or cardiac devices, and the mode of presentation. IE may present as an acute, rapidly progressive infection, but also as a subacute or chronic disease, and should be suspected in a variety of very different clinical scenarios [2].

Echocardiography and blood cultures are the cornerstone of IE diagnosis. Three echocardiographic findings are considered as major criteria in the diagnosis of IE: vegetation, abscess or pseudoaneurysm, and new dehiscence of a prosthetic valve. However, the diagnostic accuracy of echocardiography may be challenging in PVE and intracardiac device infection, even with the use of transoesophageal echocardiography (TOE). Similarly, false diagnosis of IE may occur, and in some instances it may be difficult to differentiate vegetations from thrombi or other noninfective valvular lesions. Therefore, the results of the echocardiographic study must be interpreted with caution, taking into account the patient's clinical presentation and the likelihood of IE.

CIED infection is a dreadful complication of cardiac device implantation with a high mortality rate [5], and is increasingly observed in elderly patients [6]. The reported incidence of permanent pacemaker infection varies widely among studies [7]. A distinction should be made between local device infection and cardiac device-related IE (CDRIE). Local device infection is defined as an infection limited to the pocket of the cardiac device and/or extravascular lead infection, while CDRIE is defined as an infection extending to the intravascular and/or intracardiac lead, cardiac valve leaflets, or endocardial surface. Both diagnosis and therapeutic strategy are particularly challenging in these patients [2].

As in NVE, echocardiography plays a key role in CDRIE and is helpful in the diagnosis of lead vegetations and tricuspid involvement, quantification of tricuspid regurgitation, sizing of vegetations, and follow-up after lead extraction [2]. However, false-negative and false-positive echo studies are not rare, and the Duke criteria are difficult to apply in these

patients because of lower sensitivity [5], even when the modified Duke criteria are used.

Because of the frequently difficult diagnosis of the disease, and because of some limitations of echocardiography, particularly in patients with PVE and CDRIE, other imaging techniques have recently been applied, including nuclear techniques and ce-CT [8].

Summary of the 2015 ESC guidelines for the management of infective endocarditis

The recently published 2015 ESC guidelines on the management of IE [2] propose important new features, including the need for a collaborative approach (the 'Endocarditis Team'), the emergence of nuclear imaging techniques in the early diagnosis of IE, and the refinement of surgical indications.

The Endocarditis Team

An interdisciplinary approach is required for the successful treatment of patients with IE and CIED infection. This team approach involves specialists in imaging, cardiologists, cardiac surgeons, specialists in infectious disease, and others. This multidisciplinary approach has already shown significant advantages in the management of valvular heart disease (the 'Heart Valve Clinic'), particularly in the selection of patients for transcatheter aortic valve implantation procedures ('Heart Team' approach) [9]. Such a team approach has been recommended recently as class IB in the 2014 American Heart Association/American College of Cardiology (AHA/ACC) guidelines for the management of patients with valvular heart disease [10] as well as a class IIa, level B recommendation in the 2015 ESC guidelines [2]. In patients with IE, a team approach has been shown to significantly reduce 1-year mortality [11]. In the setting of the Endocarditis Team, a new entity, the 'imaging specialist', plays a fundamental role: specialists in echocardiography, but also experts in nuclear medicine imaging, cardiac CT, and magnetic resonance imaging (MRI) are increasingly included in the team. Decisions about how to diagnose, manage, treat and follow-up patients should be taken in reference centres based on consensus decisions by the Endocarditis Team (Table 1).

Cardiac imaging in the early diagnosis of IE

Early diagnosis of IE is a major challenge. In 2000, the modified Duke criteria were recommended for diagnostic classification, and are mainly based upon echocardiography and blood culture results [12]. This classification has a sensitivity of approximately 80% for the diagnosis of IE [13]. However, the modified Duke criteria have a lower diagnostic accuracy in clinical practice, especially in patients with PVE and CDRIE, in up to 30% of whom echocardiography is normal or inconclusive, and in patients with blood culture-negative IE. Recent advances in imaging techniques, including cardiac/whole-body CT, cerebral MRI, [^{18}F]FDG PET/CT and radiolabelled WBC SPECT/CT, have resulted in improved identification of endocardial involvement and extracardiac complications of IE [8]. Recent studies have demonstrated that the addition of a

Table 1 Characteristics of the Endocarditis Team

When to refer a patient with IE to an Endocarditis Team in a reference centre
Patients with complicated IE, i.e. endocarditis with HF, abscess, or embolic or neurological complication or CHD, should be referred early and managed in a reference centre with immediately available surgical facilities.
Patients with uncomplicated IE can be initially managed in a nonreference centre, but with regular communication with the reference centre, consultations with the multidisciplinary Endocarditis Team and, when needed, with external visits to the reference centre.
Characteristics of the reference centre
Immediate access to diagnostic procedures should be possible, including TTE, TOE, multislice CT, MRI, and nuclear imaging.
Immediate access to cardiac surgery should be possible during the early stage of the disease, particularly in patients with complicated IE (HF, abscess, large vegetation, or neurological and embolic complications).
Several specialists should be present on site (the Endocarditis Team), including at least cardiac surgeons, cardiologists, anaesthesiologists, infectious disease specialists and microbiologists, and when available specialists in valve diseases, CHD, pacemaker extraction, echocardiography and other cardiac imaging, and neurologists (together with facilities for neurosurgery and interventional neuroradiology).
Role of the Endocarditis Team
The Endocarditis Team should have meetings on a regular basis to discuss cases, take surgical decisions, and define the type of follow-up.
The Endocarditis Team chooses the type, duration, and mode of follow-up of antibiotic therapy, according to a standardized protocol, following current guidelines.
The Endocarditis Team should participate in national and international registries, publicly report the mortality and morbidity of their centre, and be involved in a quality improvement programme (certifications?), as well as in a patient education programme.
The follow-up should be organized on an outpatient visit basis at a frequency depending on the patient's clinical status (ideally at 1, 3, 6 and 12 months after hospital discharge, since the majority of events occur during this period).

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CHD congenital heart disease, *HF* heart failure, *IE* infective endocarditis, *TOE* transoesophageal echocardiography, *TTE* transthoracic echocardiography

positive [^{18}F]FDG PET/CT scan to diagnostic criteria increases sensitivity without significantly decreasing specificity [14]. The value of cardiac CT was underlined in the AHA/ACC guidelines [10] and the ESC guidelines [2]. The ESC considers that the published data are sufficiently strong and convincing to propose new criteria (the 2015 ESC Modified Diagnostic Criteria) including these new imaging techniques as new criteria for the diagnosis of IE. Three items are added in the ESC diagnostic criteria (Table 2):

1. The identification of paravalvular lesions by cardiac CT should be considered as a major criterion.
2. In the setting of the suspicion of PVE, abnormal uptake of [^{18}F]FDG on PET/CT or WBC on SPECT/CT should be considered as a major criterion.
3. The identification by imaging of recent embolic events or infectious aneurysms (silent events) should be considered as a minor criterion.

Figure 1 presents the proposed ESC diagnostic algorithm including the 2015 ESC modified diagnostic criteria. The diagnosis of IE is still based upon the Duke criteria (blood cultures and echocardiography). However, when the diagnosis remains doubtful, other imaging techniques should be used, either for diagnosis of cardiac involvement or for imaging embolic events.

Cardiac imaging in treatment and follow-up of IE

Indications for surgery in IE may be subdivided into three categories: haemodynamic, infectious and embolic [2]. The decision to operate is frequently challenging and must be discussed on an individual basis using a multidisciplinary approach, i.e. by the Endocarditis Team. Imaging including echocardiography, cardiac CT and nuclear imaging, plays a central role in this decision, along with the clinical presentation.

Table 2 The 2015 ESC modified criteria for diagnosis of IE

Major criteria		
Blood cultures positive for IE	Typical microorganisms consistent with IE from two separate blood cultures	Viridans streptococci *Streptococcus gallolyticus* (formerly *S. bovis*) HACEK group *Staphylococcus aureus*
	or	
	Community-acquired enterococci, in the absence of a primary focus	
	or	
	Microorganisms consistent with IE from persistently positive blood cultures	Two or more positive blood cultures of blood samples drawn >12 h apart or All of three or a majority of four or more separate cultures of blood (with first and last samples drawn ≥1 h apart) or Single positive blood culture for *Coxiella burnetii* or phase I IgG antibody titre >1:800
Imaging positive for IE		
Echocardiogram positive for IE	Vegetation Abscess, pseudoaneurysm, intracardiac fistula Valvular perforation or aneurysm New partial dehiscence of prosthetic valve	
Abnormal activity around the site of prosthetic valve implantation detected by [^{18}F]FDG PET/CT (only if the prosthesis was implanted >3 months previously) or radiolabelled WBC SPECT/CT Abnormal activity around the site of prosthetic valve implantation detected by [18F]FDG PET/CT (only if the prosthesis was implanted for >3 months) or radiolabelled WBC SPECT/CT		
Definite paravalvular lesions on cardiac CT		
Minor criteria		
Predisposition such as predisposing heart condition, or injection drug use		
Fever defined as temperature >38 °C		
Vascular phenomena ***(including those detected only by imaging):*** major arterial emboli, septic pulmonary infarcts, infectious (mycotic) aneurysm, intracranial haemorrhage, conjunctival haemorrhages, and Janeway's lesions		
Immunological phenomena: glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor		
Microbiological evidence: positive blood culture but does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with IE		

The criteria in green boldface-italic-underlined are the new criteria included in the 2015 guidelines

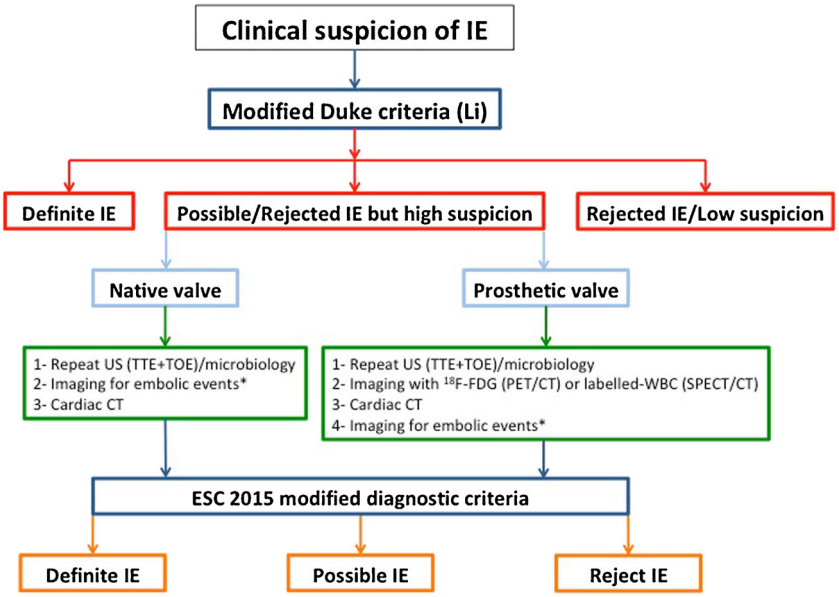

Fig. 1 Algorithm for the diagnosis of IE according to the 2015 ESC guidelines (reproduced from Habib et al. [2] with permission). *IE* infective endocarditis, *TTE* transthoracic echocardiography, *TOE* transoesophageal echocardiography, *US* ultrasonography; *asterisks* may include cerebral MRI and/or whole-body CT and/or FDG PET/CT or labelled WBC SPECT/CT

In summary, the 2015 ESC guidelines on the management of IE provide a novel approach in the diagnosis and management of this life-threatening disease. However, they are mainly based on expert opinion because of the low incidence of the disease, the few available randomized trials and the limited number of meta-analyses. The sensitivity of the Duke criteria can be improved by new imaging modalities (MRI, CT, PET/CT, SPECT/CT) that allow the diagnosis of embolic events and cardiac involvement when transthoracic echocardiography (TTE) or TOE are negative or doubtful. These criteria are useful, but they do not replace the clinical judgment reached and agreed by the Endocarditis Team.

Echocardiography for diagnosis of IE and CIED infections

Echocardiography is still the main diagnostic tool in the assessment of patients with IE [2]. It is essential for diagnosis, initial evaluation of the risk of complications and the need for surgery, assessment and monitoring of in-hospital complications, and morphological and functional assessment of the patient's heart condition before hospital discharge.

Diagnosis

TTE should be performed as soon as IE is suspected. TOE must be performed when TTE is negative and the clinical suspicion of left-sided IE is high [15]. In patients with an initially negative echocardiographic examination, TTE and TOE should be repeated 5–7 days later if the clinical suspicion of IE remains high [2]. Specific procedural recommendations for TTE and TOE have been addressed previously [16].

Vegetations are the hallmark lesions of IE, but other echocardiographic findings are also considered major criteria for the diagnosis of IE; for example, perivalvular abscesses, perivalvular pseudoaneurysms, intracardiac fistulas, valvular perforations, valvular aneurysms, and new dehiscence of a prosthetic valve [2]. The detection of these lesions in patients with prosthetic valves is more difficult than in patients with native valves. Currently, the sensitivity of TTE and TOE for the diagnosis of vegetations is 70% and 96%, respectively, in native valves and 50% and 92%, respectively, in prosthetic valves. Regarding abscesses, the sensitivity of TTE is about 50%, compared with 90% for TOE [2, 15]. The specificity for the detection of abscesses is higher than 90% with both echocardiographic modalities. Therefore, when IE is suspected in patients with prosthetic valves, both TTE and TOE must be done systematically.

It is worth emphasizing that the detection of a new large peri-prosthetic dehiscence should be considered a major criterion of IE even in the absence of other clinical signs or echocardiographic findings of IE [2].

TOE must always be performed when there is clinical suspicion of IE in prosthetic valve or CIED carriers [2]. In these patients, TOE is also clearly superior to TTE in the detection and sizing of vegetations [16]. TOE allows visualization of lead vegetations in the right atrium/superior vena cava area and in other regions less well visualized by TTE. Both echocardiographic modalities are complementary in the assessment of tricuspid valve involvement, and quantification of tricuspid valve regurgitation and pulmonary hypertension. Another echocardiographic technique, intracardiac echocardiography, may be considered in patients with suspected CIED infection, positive blood cultures, and negative TTE and TOE studies [2].

In patients with *Staphylococcus aureus* bacteraemia, the frequency of IE is high. Therefore, TTE or TOE should be performed according to the patient's clinical profile and risk factors for IE [17]. TOE is not mandatory in isolated right-sided NVE with good quality TTE and clear-cut echocardiographic findings [18]. Real-time three-dimensional (3D) TOE is useful for the assessment of vegetation morphology and size, and this may lead to a better prediction of the embolic risk in IE [19]. This echocardiographic technique is particularly useful in the assessment of perivalvular extension of the infection, prosthetic valve dehiscence, and leaflet perforation [20].

It is important to remember that a negative echocardiography study (TTE and TOE) does not rule out the diagnosis of IE. The negative predictive value (NPV) of a second TOE study in patients with the suspicion of NVE is extremely high. On the contrary, the NPV of TOE in patients with prosthetic valves is modest, and in many cases a second diagnostic imaging technique will be needed [21].

Initial evaluation of the risk of complications and need for surgery

The risk in patients with left-sided IE can be formally assessed according to clinical, microbiological and echocardiographic variables. Early TOE (during the first 48 h after admission) is advisable in most patients with left-sided IE in order to better assess vegetation size, degree of valvular regurgitation, and local perivalvular complications [22]. Patients with periannular complications, severe left-sided valve regurgitation, large vegetations, severe prosthetic valve dysfunction, low left ventricular ejection fraction, pulmonary hypertension or premature mitral valve closure are at highest risk of death, stroke, and the need for surgery in the active phase of the disease. All these parameters can be easily and rapidly obtained by echocardiography [23].

Assessment and monitoring of in-hospital complications

Local infection follow-up should be performed even when the clinical course of the patient with IE is good. Thus, in order to monitor vegetation size and to detect new silent complications, repeated TTE and TOE during in-hospital follow-up (7–10 days) of uncomplicated IE is recommended [2]. TTE and TOE must be repeated as soon as a new clinical complication appears during the patient's in-hospital clinical course (new murmur, heart failure, embolism, persisting fever, atrioventricular block).

Echocardiographic assessment before hospital discharge

TTE is recommended at completion of antibiotic therapy to assess left ventricular function, pulmonary pressure, and valvular morphology and function. For better comparison, TOE is needed during follow-up in some patients (PV carriers, patients with complex surgery) before hospital discharge. In patients with CIED infection, TTE before hospital discharge is also recommended to detect the presence of retained segments of the pacemaker lead, and to assess tricuspid valve function, right ventricular function, and pulmonary hypertension. In addition, TOE after percutaneous lead extraction should be considered to detect residual infected material and potential tricuspid valve complications [15].

Radiolabelled white blood cell imaging for diagnosis of IE and CIED infections

Radiopharmaceutical preparation and acquisition protocol

WBC can be radiolabelled either with ^{99m}Tc-hexamethylpropyleneamine oxime (^{99m}Tc-HMPAO, 370–555 MBq) or with ^{111}In-oxine (10–18.5 MBq), as detailed in the specific European Association of Nuclear Medicine (EANM) guidelines [24, 25]. Briefly, the procedure consists of isolation, radiolabelling and reinjection of autologous WBC obtained from the patient's blood (about 50 mL). Therefore, strict aseptic conditions are required for the labelling procedure. During labelling, care should be taken to avoid damage to leucocytes, as this would result in leakage of the radioactivity from the cell, adhesion of labelled leucocytes to the vascular endothelium and loss of motility. To avoid degradation of the radiopharmaceutical and radiation damage to labelled cells, radiolabelled WBC should be reinjected as soon as possible, and not later than 1 h after labelling. ^{99m}Tc-HMPAO is generally preferred, because of the better image quality (higher count statistics and spatial resolution), and lower radiation exposure (0.011 mSv/MBq of ^{99m}Tc-HMPAO versus 0.36 mSv/MBq ^{111}In-oxine). Patient preparation is equivalent to that for any other clinical indication. At least 2×10^8 leucocytes are required to achieve good labelling efficiency.

The image acquisition protocol includes planar acquisitions at 30 min (early images), 4–6 h (delayed images), and 20–24 h (late images) after reinjection of ^{99m}Tc-HMPAO/^{111}In-oxine WBC. A SPECT/CT acquisition is mandatory as part of the standard imaging protocol (as discussed in more detail in the section Technical issues) and it is usually acquired 4–6 h and/or 20–24 h after injection. Planar acquisitions will always include whole-body images (at least at 30 min) and anterior and posterior views of the thorax and any other region of interest (i.e. CNS, abdomen) when searching for septic emboli. In patients with CIED infection, care should be taken to ensure that the generator site is included in the field of view, considering all the possible generator positions (i.e.

abdomen). Late acquisitions are particularly relevant in cardiovascular infections since background activity related to blood pool spill-over strongly hampers the detectability of lesions. These should be acquired with a "time corrected for isotope decay" modality as described in the EANM guidelines. SPECT/CT performed at 4–6 h provides better image quality and might be repeated at 20–24 h if planar images (and SPECT images) at 4–6 h are negative.

A low-dose CT transmission scan is acquired while the patient continues tidal or shallow breathing, and is used for attenuation correction (CT-AC) and for colocalization (see below; on average 0.5–1.0 mSv radiation burden). Transmission data are reconstructed using filtered back-projection to produce cross-sectional images. With the availability of cutting-edge SPECT/CT systems, administration of contrast medium to perform ce-CT is also feasible, despite the fact that experience in this specific setting is very limited. Recently, a study including a small sample of patients compared the diagnostic performance of WBC SPECT acquired on a conventional (NaI) camera to a cardiac-dedicated high-sensitivity cadmium-zinctelluride (CZT) camera[26]. Using ^{111}In-oxine-labelled WBC, it has been shown that target-to-background contrast increases with the CZT camera. This approach has the advantages of overcoming the limitation of low count statistics with late acquisitions and reducing image noise due to better energy resolution. The field of acquisition of such cameras is limited to the cardiac area, but all-purpose CZT cameras are becoming commercially available and will be an attractive solution for late imaging in WBC SPECT.

Patient preparation

Preparation of patients with IE and CIED infection for WBC scintigraphy follow the general recommendations for any other nuclear medicine procedure and the general rules for WBC preparation. The major goals are to minimize tracer uptake in normal tissues, while maintaining uptake in target tissues. Because the effect of antibiotics on radiolabelled WBC uptake is unknown, it is important to be aware of ongoing antibiotic treatment, but no general recommendation on withdrawal can currently be made.

Image postprocessing and interpretation criteria

Both CT-AC and noncorrected SPECT images have to be evaluated in the coronal, transaxial and sagittal planes, as well as in 3D maximum intensity projection (MIP) cine mode. Misalignment between emission and transmission data may generate erroneous correction and thus data misinterpretation. Careful attention should be paid to quality control to avoid reconstruction artefacts. Noncorrected SPECT images become significantly important in the presence of prosthetic valves, generators and electrocatheters due to possible overcorrection artefacts on SPECT/CT images.

The interpretation of WBC scintigraphy should always begin with a visual quality control performed on whole-body images and chest planar acquisitions to check for: (1) the absence of high blood pool activity (suggesting the labelling of a substantial amount of erythrocytes) hampering interpretation even on delayed and late acquisitions, (2) liver uptake higher than spleen uptake, and (3) persistent pulmonary uptake (both 2 and 3 suggesting WBC damage prior to reinjection). The signal kinetics between the acquisitions at 4–6 h and 20–24 h are important features for interpretation: any stable or increased site of uptake (either intensity or size) over time, confirmed on SPECT/CT, is highly suggestive of infection. Overall pooled sensitivity and specificity have been reported to be 80–86% and 97–100%, respectively, with an AUC of 0.957 [27, 28]. Such a high specificity is also maintained in patients with very early IE [29–32], a clinical setting in which WBC should represent the imaging modality of choice. Semiquantitative evaluation of WBC is also feasible, despite the fact that it has been validated in musculoskeletal infections [33] and no data are currently available for IE/CIED infections. Figures 2 and 3 show examples of WBC SPECT/CT imaging in NVE and PVE.

In patients with suspected CIED infection and in patients implanted with a left-ventricular-assist device, WBC imaging revealed similar figures with a consistent high specificity [32–34]. In these studies, WBC SPECT/CT was found to be able to identify and define the precise anatomical location and extent of a suspected infection, improving patient management (Fig. 4). Additionally, WBC SPECT/CT allows the detection of additional unsuspected extracardiac sites of infection in up to 23% of patients with device-related sepsis [33, 35].

Abnormalities detected on WBC imaging should be localized as precisely as possible on SPECT/CT images since: (1) their colocalization with a structural abnormality considered as doubtful on echocardiography will support the hypothesis of infection, and (2) the localization and extent of the disease, on prosthetic material particularly, may help guide the surgical procedure. Localization of the sites of concomitant extracardiac infection from septic embolism is also possible on SPECT/CT images, influencing the Duke score and consequently the diagnostic certainty.

Pitfalls and differential diagnosis of IE/CIED infections with WBC imaging

False-positive WBC imaging findings in IE and CIED infections have been rarely described. On the other hand, false-negative scans have been observed in the presence of IE caused by some strains such as *Candida* spp. and *Enterococcus* spp. possibly due to the ability of these microorganisms (as well as others such as *Staphylococcus epidermidis*) to form a "biofilm" that results in resistance to

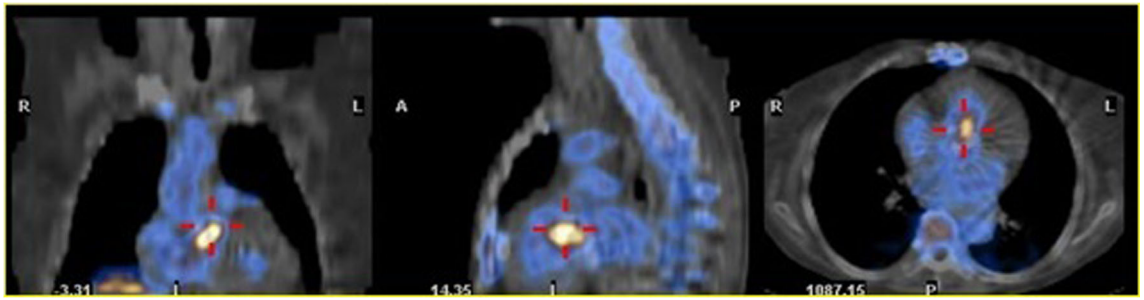

Fig. 2 ^{99m}Tc-HMPAO WBC SPECT/CT imaging in a patient with PVE. The emission image (*middle*) shows an area of increased radiopharmaceutical uptake which on the superimposed SPECT/CT image (*bottom*) corresponds to the prosthetic aortic valve. *Top* low-dose CT image

antimicrobial treatment and escape from the host defence mechanisms. Additionally, altered neutrophil recruitment at the primary site of IE by *Enterococcus faecalis* extracellular proteases constitutes a further mechanism of innate immune response impairment. Such mechanisms might reduce the sensitivity of scintigraphy with radiolabelled leucocytes in patients with IE. The same limitation has always to be considered in patients with CIED infection, in particular in the presence of very small vegetations along the electrocatheter.

Embolisms on WBC imaging might appear either as areas of increased uptake over time, for example in brain, lung and soft tissue embolism, or as cold spots, for example in spleen embolism and spondylodiscitis. This latter appearance has to be considered nonspecific for infectious embolism since it might be present in other benign or malignant conditions. Therefore, despite the fact that these findings in patients with IE are highly suggestive of septic embolism, they should be confirmed by additional diagnostic imaging tests. In addition, reduced sensitivity has been reported in patients with small embolisms [29].

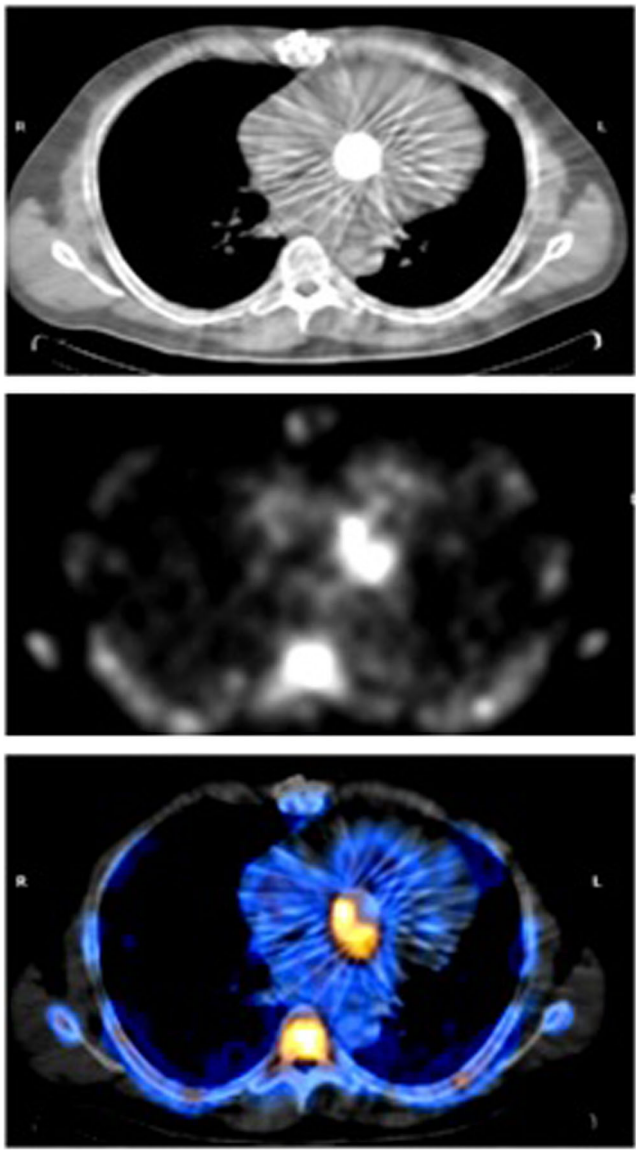

Fig. 3 ^{99m}Tc-HMPAO WBC SPECT/CT imaging in a patient with aortic NVE showing an increase in uptake of the radiopharmaceutical at the valve site (*from left to right* coronal, sagittal and transaxial superimposed (fused) SPECT/CT images)

[^{18}F]FDG PET/CT for diagnosis of IE and CIED infections

Patient preparation and acquisition protocol

When [^{18}F]FDG PET/CT is used to diagnose cardiac and pericardial infection, patient preparation is very important due to the possible presence of physiological uptake of [^{18}F]FDG in normal myocardium. Notably, these protocols differ fundamentally from cardiac viability imaging protocols in which myocardial glucose uptake is intentionally enhanced and homogenized by a combination of glucose loading and insulin. The current Society of Nuclear Medicine and Molecular Imaging (SNMMI)/American Society of Nuclear Cardiology (ASNC)/Society of Cardiovascular CT (SCCT) guidelines recommend preparation with a fat-enriched diet lacking carbohydrates for 12–24 h prior to the scan, a fast of 12–18 h, and/or the administration of intravenous heparin approximately 15 min prior to [^{18}F]FDG injection [36].

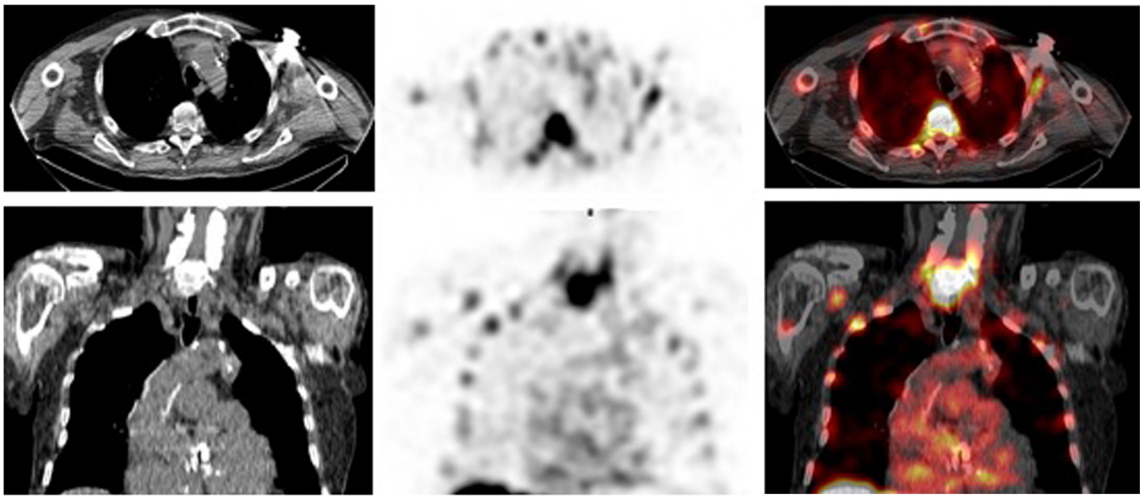

Fig. 4 ^{99m}Tc-HMPAO WBC SPECT/CT images in a patient with suspected CIED infection showing radiopharmaceutical uptake at the pocket site (*top* transaxial images, from *left to right* low-dose CT, emission and superimposed SPECT/CT images, respectively) and at the intracardiac portion of the leads (*bottom* coronal images, from *left to right* low-dose CT, emission and superimposed SPECT/CT images, respectively)

A recent review provides a unique overview of the available literature regarding preparation for cardiac [^{18}F]FDG PET imaging [37]. The data support the use of a high-fat, low-carbohydrate (HFLC) diet for at least two meals with a fast of at least 4 h for optimal suppression of physiological myocardial glucose utilization. Because there is no single superior patient preparation technique, in each institution image quality data should be continually evaluated to ensure that adequate suppression of [^{18}F]FDG is achieved in more than 80% of the scans (Table 3). Finally, following [^{18}F]FDG injection and before the images are obtained, the patient should continue to fast and should not be physically active, as either of these will enhance myocardial glucose uptake.

Although antimicrobial treatment is considered to decrease the intensity of [^{18}F]FDG accumulation [38], there is no evidence at this stage to routinely recommend treatment discontinuation before performing PET/CT. On the contrary, steroid treatment should be discontinued or at least reduced to the lowest possible dose in the 24 h preceding the examination [39].

Blood glucose levels should always be checked and recorded, keeping in mind that, in contrast to tumour imaging, neither diabetes nor hyperglycaemia at the time of the study has been demonstrated to increase the false-negative rate in patients with infection or inflammation [40]. Therefore, although efforts should be made to decrease blood glucose to the lowest possible level, hyperglycaemia should not represent an absolute contraindication to performing the study [41]. [^{18}F]FDG imaging can be performed in patients with kidney failure, although the image quality may be suboptimal and prone to interpretation pitfalls [42].

The administered activity does not crucially affect the results of the examination within a certain range and also depends on the type of PET scanner. The EANM guidelines on [^{18}F]FDG PET imaging in inflammation/infection suggest a dose of 2.5–5.0 MBq/kg, that is 175–350 MBq or 4.7–9.5 mCi in a 70-kg standard adult. In the US, the [^{18}F]FDG administered activity should be 370–740 MBq (10–20 mCi) in adults and 3.7–5.2 MBq/kg (0.10–0.14 mCi/kg) in children [43].

Technical issues

The acquisition is usually performed according to routine protocols, 45–60 min after intravenous injection of [^{18}F]FDG, with an emission time/bed position depending on the sensitivity of the scanner. One report suggests that delayed imaging acquired 3 h after injection (while maintaining the count

Table 3 Recommendations for patient preparation for cardiac [^{18}F]FDG PET/CT imaging for IE/CIED infections

Recommendation	Intervention
High evidence	High-fat no-carbohydrate diet for at least two meals
	Fast for at least 4 h prior to examination
	Avoid carbohydrate consumption
	Optimize fat intake
	Avoid vigorous exercise during the 24 h before the examination
Intermediate evidence	Heparin given intravenously 15 min before [^{18}F]FDG with dietary preparation/fasting
Low evidence	Any food or drink during the 4 h before the examination
	Unrestricted diet
	Isolated fasting (<12 h)
	Calcium channel blockers

Adapted from Osborne et al. [37]

statistic by doubling the time per bed position) is associated with greater contrast and improves the accuracy in diagnosing pacing lead infections in comparison with the standard protocol [44]. However, recently and in a small series of patients images acquired at late time-points (150 min) after injection in patients with PVE have been found to be more prone to false-positive interpretation in both visual and semi-quantitative analyses [45].

The field of acquisition is usually derived from oncology studies from the skull base to the mid-thighs. Cerebral complications are frequent in left-sided IE and MRI studies have shown that early brain imaging can affect the diagnosis and management of patients [46]. Due to the low sensitivity of [^{18}F]FDG PET in the detection of brain lesions, inclusion of the brain in the field of acquisition is not recommended. A series of case reports suggest that the extension of the field of acquisition to the lower limbs allows the detection of complications of IE such as mycotic aneurysms that may require specific treatment by embolization to prevent rupture [47]. All these data are preliminary, based on small population samples, and require further validation.

The majority of PET/CT studies involve the use of a protocol comprising a scanogram/scout scan/topogram and CT-AC. Overall, the CT scan parameters should be such that patient exposure is the minimum necessary to provide diagnostic information. The simultaneous acquisition of a standard diagnostic CT scan with intravenous contrast agent is possible and should be preferred when appropriate in order to maximize the diagnostic information provided by the examination. Different imaging protocols might be suggested for a PET/ce-CT scan (Tables 4 and 5 and Addendum 1).

In a series of patients with suspected PVE or CIED infection, Pizzi et al. showed that the addition of ce-CT to the standard [^{18}F]FDG PET/CT protocol results in a high rate of patients reclassified from "possible" IE to "definite" IE, thus improving the overall diagnostic accuracy as compared with PET/CT without contrast enhancement combined or not with the Duke score [49]. The main additional information provided by ce-CT was: better discrimination of the origin of FDG uptake between prosthetic valves or incomplete myocardial suppression; better coregistration between PET and ECG-gated CT angiography; identification of a greater number of anatomical lesions in the valve area and of periannular complications; and the preoperative evaluation of coronary artery disease. Though not recommended for routine use, ce-CT combined with PET may prove useful in selected patients, particularly when echocardiography is of poor quality or did not allow precise evaluation of the periannular area. Limiting the wider use of ce-CT is the deleterious impact of contrast agents on kidney function. Patients with IE or CIED infection are likely to receive high doses of antibiotics, some of them nephrotoxic, over long periods of time. It is therefore crucial to avoid any unnecessary exposure to additional nephrotoxic agents.

Table 4 Protocol for WBC SPECT/CT

Acquisition time	Acquisition
30 min (early)	Whole-body and/or planar thorax/upper abdomen
followed by	
4–6 h (delayed images)	Planar images of the thorax followed by Planar images of any additional FOV followed by SPECT/CT acquisitions of the thorax with patient continuing tidal or shallow breathing followed by SPECT/CT acquisitions of any additional FOV
followed by	
20–24 h (late images)	Planar images of the thorax followed by Planar images of any additional FOV followed by SPECT/CT if needed

FOV field of view

Table 5 Protocols for [^{18}F]FDG PET/CT and for [^{18}F]FDG PET with ce-CT

Protocol	Acquisitions
1. [^{18}F]FDG PET/CT when CT is used for attenuation correction and localization only (not intended as a clinically diagnostic CT scan)	CT topogram followed by Low-dose CT scan (continuous tidal or shallow breathing)[a] followed by PET acquisition
2. [^{18}F]FDG PET/CT with diagnostic CT scan [45]	CT topogram followed by Whole-body CT-AC followed by Whole-body PET followed by Gated cardiac PET followed by ECG-gated cardiac CT angiography
3. [^{18}F]FDG PET/CT with diagnostic CT scan [48]	CT topogram followed by Thoracic CT in deep inspiration to acquire images of the arterial phase followed by Whole-body CT in portal phase followed by Whole-body PET

[a] In the case of CT systems with up to six rings, a protocol using breath-hold in normal expiration is preferred

Imaging postprocessing and interpretation criteria

It is recommended that reconstructions be performed with and without attenuation correction to identify potential reconstruction artefacts. Such artefacts have been well investigated in CIEDs, including pacing lead artefacts [50, 51]. Metal artefact reduction techniques are useful for minimizing overcorrection artefacts, despite not always being successful in annulling their impact on PET image quality. The CT data acquired during the PET/CT study are usually reconstructed using filtered back projection. Recently introduced iterative reconstruction methods for CT data may be applied, if available on the PET/CT system. Depending on the CT protocol and the clinical case, separate CT reconstructions may be performed for diagnostic purposes.

PET images have to be visually evaluated for increased [^{18}F]FDG uptake, taking into consideration the pattern (focal, linear, diffuse), intensity and relationship to areas of physiological distribution. PET information is compared with morphological information obtained by CT (Figs. 5 and 6). Several recent meta-analyses have indicated that the overall pooled sensitivity of [^{18}F]FDG PET/CT in IE is 61% [1], increasing to 73% when only PVE are considered and to 76% [27] or 81% with good overall accuracy (AUC 0.897) [28] when including only studies reporting adequate cardiac preparation. Thus, even if the PET results are negative (including whole-body evaluation for embolism detection), thorough interpretation of the echocardiography and CT scan is essential.

The pooled specificity of [^{18}F]FDG PET/CT in patients with adequate cardiac preparation has been reported to be between 85% and 90% [27, 28]. Indeed. in the absence of infection, [^{18}F]FDG uptake around the prosthetic valve might be visible particularly early after surgery, and has different causes. Faint and homogeneous [^{18}F]FDG uptake strictly limited to the

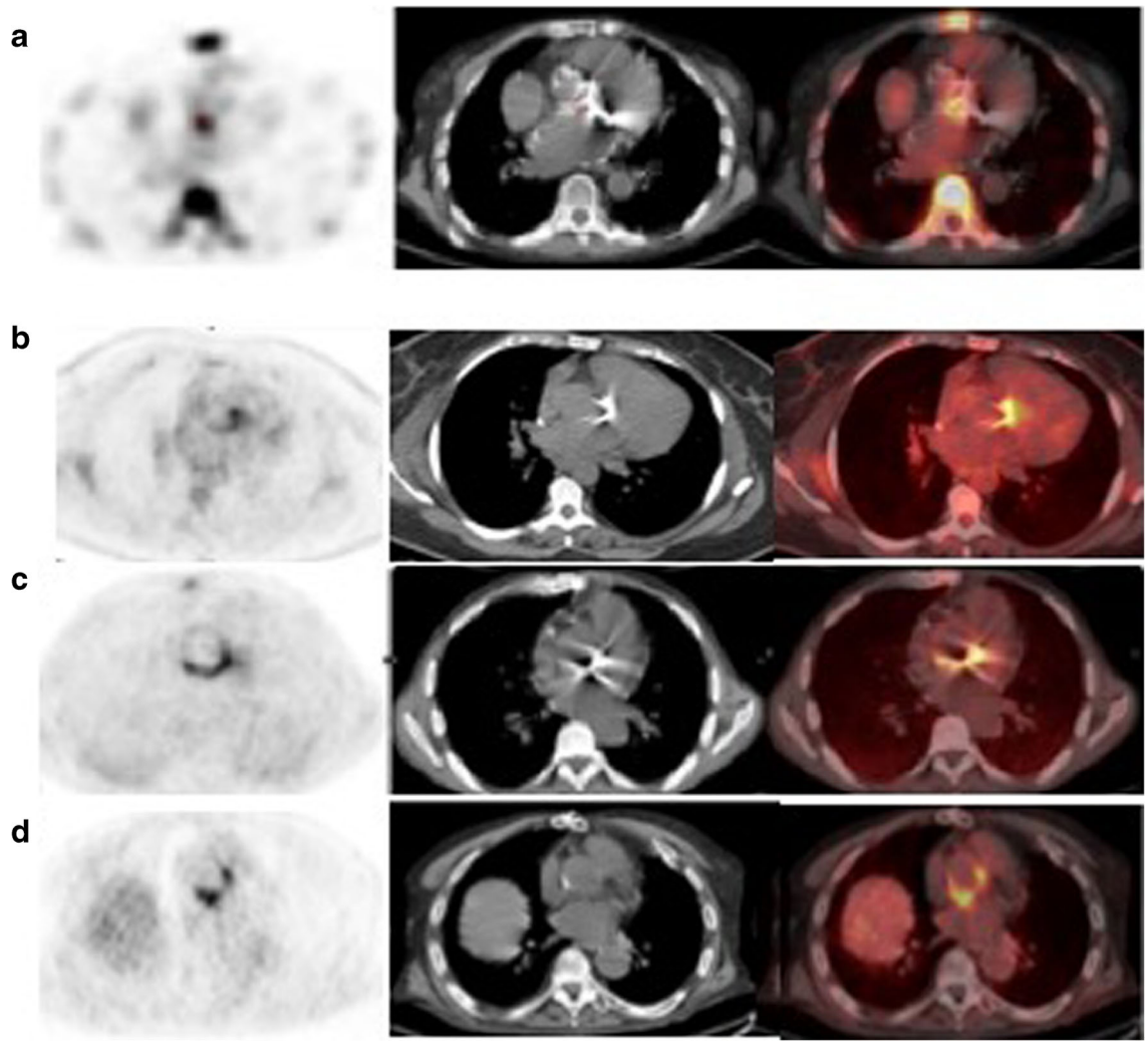

Fig. 5 Examples of different patterns of ^{99m}Tc-HMPAO WBC and [^{18}F]FDG uptake in patients with confirmed PVE: **a** typical focal pattern at ^{99m}Tc-HMPAO WBC imaging; **b** focal pattern of [^{18}F]FDG; **c** diffuse [^{18}F]FDG uptake of; **d** focal uptake over an area of diffuse [^{18}F]FDG uptake. *From left to right* transaxial emission, low-dose CT and superimposed SPECT/CT or PET/CT images

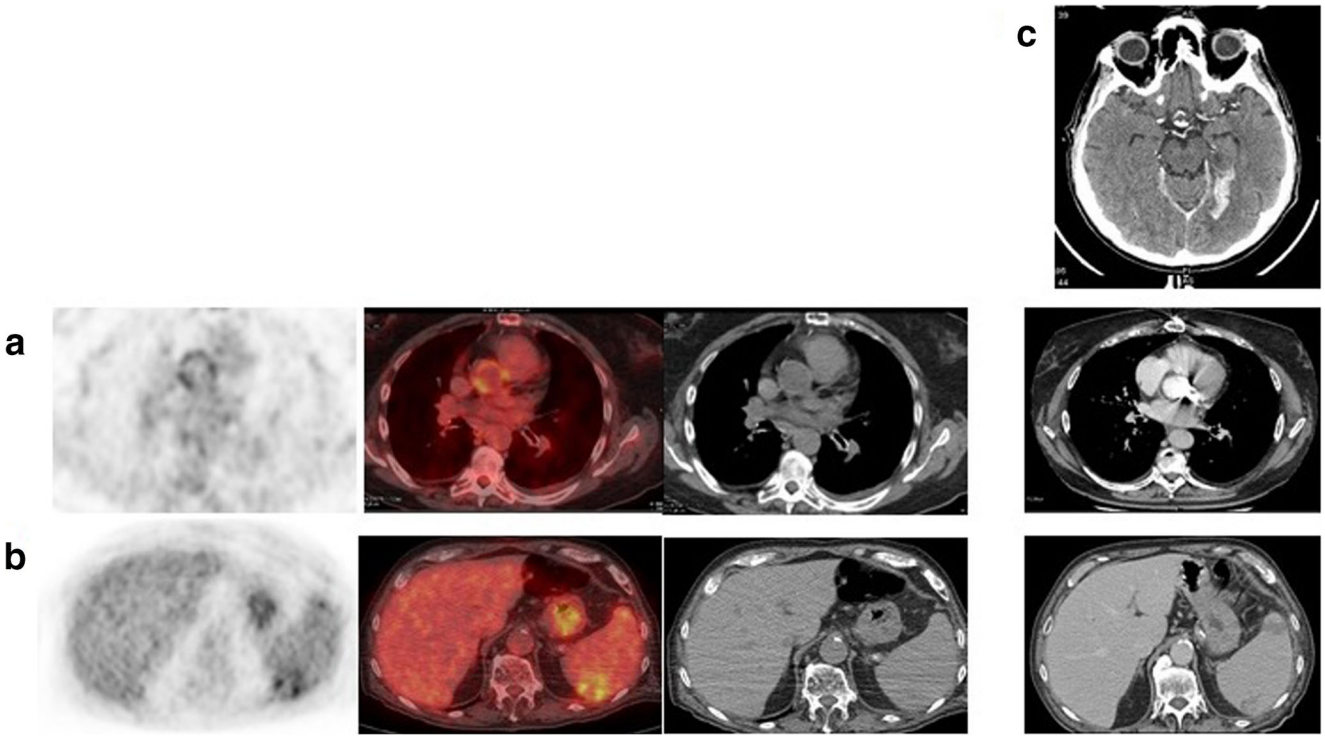

Fig. 6 Same patient as in Fig. 5c. In addition to the diffuse uptake of mild intensity at the valve prosthesis (**a** *from left to right* transaxial emission, superimposed PET/CT, low-dose CT and ce-CT images), combined [^{18}F]FDG PET/CT with ce-CT allows the identification of spleen embolism as shown on both the PET/CT and ce-CT images (**b** *from left to right* transaxial emission, superimposed PET/CT, low-dose CT and ce-CT images), and brain embolism as shown only on the ce-CT images (**c**, ce-CT transaxial image)

valve annulus or around the struts of a bioprosthetic valve, very similar to the pattern observed in prosthetic vascular grafts [52], is most likely to have resulted from a persistent host reaction against the biomaterial coating the sewing ring of the prosthetic valve and chronic tension or friction exerted on these anchor points [53, 54]. Such [^{18}F]FDG uptake seems to be slightly greater in mechanical than in biological prostheses and in patients with vasculitis [55]. To prevent misinterpretation of a positive scan due to imaging too early after valve implantation, the ESC guidelines recommend that [^{18}F]FDG PET results should not be considered in the 3-month period following prosthetic valve implantation [2]. However, if surgery was uncomplicated, imaging before the recommended 3 months might be considered in an individual patient with awareness of this possible limitation [55].

In patients with NVE, interpretation of [^{18}F]FDG uptake when the HFLC diet has been successfully adhered to is more straightforward than in those with PVE since any focal [^{18}F]FDG uptake should be considered as abnormal. However, the diagnostic value of [^{18}F]FDG PET in patients with NVE has not been well determined, due to higher rates of patients with prosthetic valves or mixed patients with native and prosthetic valves included in most studies. Recently, Granados et al. found that [^{18}F]FDG PET was negative in six of six patients diagnosed with definite NVE [56]. In a recent meta-analysis pooled sensitivity for NVE was 71% [27]. The lack of sensitivity of [^{18}F]FDG PET in NVE is probably related to: (1) the size of the lesion (NVE is generally limited to the presence of a vegetation, whereas in PVE generally spreads along the sewing ring or leads to abscess formation), and (2) the fact that blurring artefacts due to motion are more important at the tip of a valve leaflet than at the annulus. In this regard, ECG-gated acquisitions could help. This further emphasizes the need for a multimodality approach in which each imaging modality overcomes the other's possible limitations in this clinical setting.

Semiquantitative analysis using the standardized uptake value (SUV) is also possible. However, in contrast to its application in oncology, SUV has not been validated in inflammation and infection. The additional value of quantitative parameters (SUVmax normalized or not to the blood pool activity, referred to as the target-to-background ratio) in differentiating between infected and non-infected material is a matter of debate. Whereas some literature tentatively provides values likely to identify infection with high specificity, it seems that the overlap of SUV between infected and non-infected prosthetic valves precludes determination of a threshold. In this regard, all the factors influencing SUV quantification should be carefully considered, including those related to patient preparation (glycaemia, concurrent treatment, etc), time of uptake and the use of positive contrast.

The value of [^{18}F]FDG PET in the diagnosis of CIED infection is substantiated by a large body of literature. After some

case reports and the seminal work of Ploux et al. [57], a larger scale study compared three groups of patients implanted with CIEDs: patients with suspicion of device infection, patients with a recently implanted device, and a control group of patients without infection [58]. Images without attenuation correction were used for final interpretation and to determine a parameter referred to as the semiquantitative ratio (SQR; the maximum count rate of the pocket device divided by the mean count rate of the lung parenchyma). The study showed the presence of mild postoperative residual inflammation up to 2 months after device implantation, whereas infected devices showed a significantly greater SQR. Both the sensitivity and specificity were >85% in a population with a high prevalence of infection. Finally, those patients with suspicion of infection but without [^{18}F]FDG uptake had a favourable outcome under antibiotic therapy, suggesting the absence of bacterial colonization of the CIEDs. It is noteworthy that no abnormal uptake was detected in the control group. A prospective study further supported the value of SQR for diagnosing CIED infection, and suggested that this parameter could help identify patients requiring device extraction [59]. More recently, normalization of SUVmax around the CIED to the mean hepatic blood pool activity has been shown to be an accurate and consistent quantitative parameter for discriminating infected from asymptomatic and symptomatic non-infected devices. In the same study, however, no significant differences were found between several different SQRs with the exception of the contralateral reference region that showed the lowest values. Metabolic uptake was increased at later acquisition time-points (90 and 180 min), suggesting potential usefulness of delayed imaging in terms of visual assessment and increasing reporter confidence [60].

Recent meta-analyses have shown a pooled sensitivity of [^{18}F]FDG PET/CT of 83–87% and a pooled specificity of 89–94%. These values were higher for generator/pocket infections (93–96% and 97–98%, respectively) than for infections at the side of electrocatheters, where they were 65–76% and 83–88%, respectively [27, 61, 62], as a consequence of the very small size of the vegetations along the leads, which are often smaller than the spatial resolution of the system [57]. Therefore, [^{18}F]FDG PET/CT has been suggested to be of value in guiding the clinician in choosing the most suitable treatment, i.e. conservative treatment (antimicrobial agents alone, or removal of just the generator) versus device removal. This is especially relevant considering the ongoing debate concerning the observation that novel antimicrobial agents can penetrate the bacteria-produced biofilm [63], thus potentially decreasing the need of hardware removal in CIED infection [64]. However, considering that the differential diagnosis between an infection limited to the skin/pocket and more severe infection that involves the device over the pocket is the clue to choosing medical or surgical treatment in CIED infection, further investigation is needed before [^{18}F]FDG PET/CT can be introduced into the routine diagnostic work-up to guide such a clinical decision. Figure 7 shows an example of [^{18}F]FDG PET/CT in a patient with CIED infection.

One of the main features of [^{18}F]FDG PET/CT is the ability to perform whole-body evaluation for abnormal focal uptake of [^{18}F]FDG in a single scan with very high sensitivity [65]. In the setting of IE/CIED infection, the detection of septic emboli affects the Duke score and consequently the diagnostic certainty [44, 56, 65–69]. This comprehensive evaluation of the disease extent will affect therapeutic management and lead to a reduction in the risk of relapse [59, 70]. This has been shown to be particularly useful in the identification of embolisms in unexpected locations, such as mycotic aneurysms [47], a potential life-threatening complication requiring specific treatment. Similarly, in right-sided IE or CIED infection the detection of lung embolisms, considered as a major criterion of the Duke score, increases the diagnostic sensitivity [71]. In addition, identification of the infection portal of entry on [^{18}F]FDG PET/CT is critical to prevent IE relapse. This primary infectious site may be orientated by the common biotope of the bacteria strain (digestive, skin, catheter) and should be part of the report.

Finally, an additional promising role of [^{18}F]FDG PET/CT is in patients with established IE, in whom it can be used to monitor response to antimicrobial treatment. Indeed, considering the difficulties in the choice of type, dose and duration of antimicrobial treatment, the possibility of using PET/CT imaging to distinguish between patients who respond favourably to treatment from those who require intensified administration or alternative treatment options is extremely attractive. However, significant data in this regard are scarce and the use of PET/CT in this clinical scenario can be suggested only as part of a case-based discussion within the Endocarditis Team.

Pitfalls and differential diagnosis of IE/CIED infections with [^{18}F]FDG PET/CT

As discussed in detail, the diagnostic performance of [^{18}F]FDG PET in IE and CIED infections is highly dependent on the background activity from physiological [^{18}F]FDG myocardial uptake, and accordingly on the correct adherence to the HFLC diet followed by a fast of >12 h as discussed above in more detail. This is critical for the optimal analysis of valvular regions. Another potential confounding factor for [^{18}F]FDG PET/CT is increased metabolic activity along the posterior part of the heart, where lipomatous hypertrophy of the interatrial septum may appear as a fat-containing mass with increased [^{18}F]FDG uptake [72]. Early PET/CT scanning following valve implantation is not recommended since persistent reaction of the host against the synthetic component of the sewing ring might cause false-positive results. The persistent host reaction against the biomaterial coating of the sewing ring of the prosthetic valve may persist for years after valve implantation and should always be considered as a source of misinterpretation.

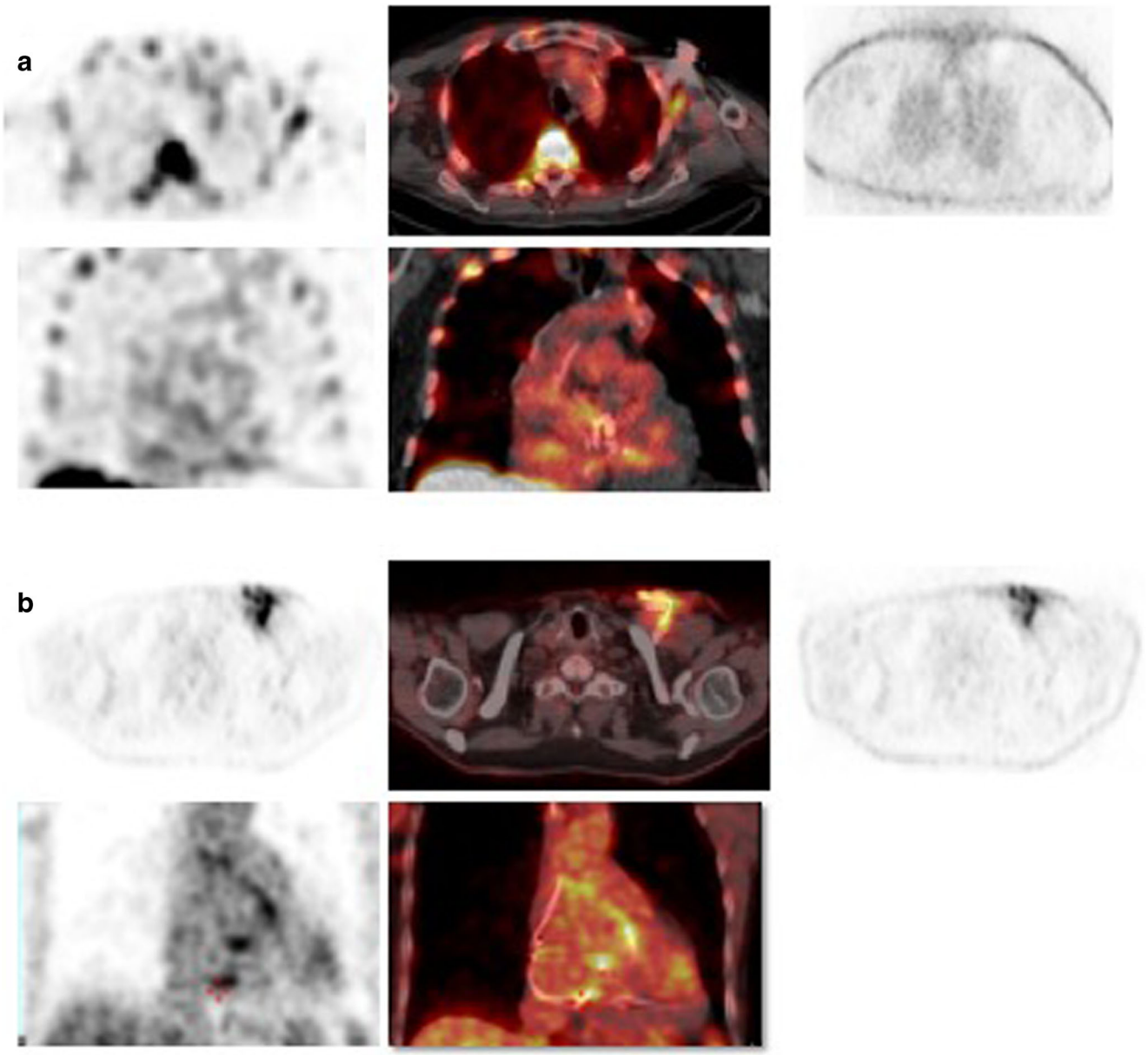

Fig. 7 ^{99m}Tc-HMPAO WBC (a) and [^{18}F]FDG PET/CT (b) in patients with CIED infection. Faint WBC uptake is prentent at the pocket site which is an artifact due to attenuation correction as demonstrated by the disappearnce of the uptake at the non-attenuated corrected images(a *upper panel from left to right transaxial emission, superimposed SPECT/CT and non-attenuated corrected*), whereas the uptake at the intracardiac portion of the leads, is consistent with infection (*lower panel, coronal view emision and fused SPECT/CT*). In b increased [18F]FDG uptake at both the pocket site and at the intravascular portion of the leads, persisten at the non-attenuated corrected images (upper, from left to right transaxial emission, superimposed PET/CT and non-attenuated corrected) and at the intracardiac portion of the leads (lower panel from left to right coronal emissiona nd fused PET/CT) confirming the presence of device infection. *From left to right* transaxial images and coronal images emission, low-dose CT, superimposed PET/CT and non-attenuated emission images, respectively

A wide range of pathological conditions can mimic the pattern of focally increased [^{18}F]FDG uptake. The following conditions might present with focal [^{18}F]FDG uptake: active thrombi [73], soft atherosclerotic plaques [74], vasculitis [75], primary cardiac tumours [76] and cardiac metastasis [77], postsurgical inflammation [78] and foreign body reactions (such as a reaction to BioGlue, a surgical adhesive used to repair the aortic root) [79], and stitches [80]. Recently intense [^{18}F]FDG uptake has also been found in a patient with Libman-Sacks endocarditis [81]. Therefore, to maintain the high specificity of [^{18}F]FDG for IE, it is essential that patient selection and inclusion criteria, as well as image reading, are accurate. In this regard, the CT component of PET/CT plays a crucial role by accurately localizing vascular wall uptake and intracardiac lesions.

As already discussed, antimicrobial therapy and/or vegetation size can account for false-negative [^{18}F]FDG PET/CT results.

Cardiac CT for diagnosis of IE and CIED infections

Since the introduction of the first 64-slice CT devices in 2005, cardiac CT has evolved to be one of the most important structural imaging techniques of the heart. Its strengths lie in the high isotropic (i.e. in all three axes of 3D space) spatial resolution in the range of 0.2 to 0.3 mm with the most recent devices, and its ease of use and wide availability. The drawbacks of cardiac CT are the need for iodinated contrast agent administration and ionizing radiation. The latter, however, can be limited with appropriate imaging protocols and newer devices to a radiation dose in the low single-digit millisievert range (depending on the field of view). Temporal resolution has also been improved considerably (from 250 ms with the first generation four-slice CT scanners down to 66 ms with the most recent dual-source devices), allowing high-quality images to be obtained in patients with faster heart rates or even in selected patients with rate-controlled atrial fibrillation [82].

In the context of IE and CIED infections, cardiac CT may serve two different purposes. First, cardiac CT almost invariably complements every radionuclide imaging study (e.g. [^{18}F]FDG PET or WBC scintigraphy) to provide an anatomical map for coregistration with radionuclide signals. This allows identification of the particular anatomical structures with pathological uptake and improves the diagnostic accuracy of the technique. Most often, this objective is achieved with a native low-dose CT scan, although some have suggested that performing ECG-gated ce-CT angiography may improve the diagnostic accuracy of the combined hybrid study (as mentioned before) [83]. Second, the anatomical information provided by CT may itself allow the diagnosis of IE or CIED infection, particularly in the presence of vegetations and complications such as abscesses, pseudoaneurysms, fistulas or septic embolization. Moreover, cardiac CT, if performed on a high-end CT device, allows the assessment of coronary arteries prior to any surgical procedure. This avoids preoperative invasive coronary angiography, which (in the case of aortic valve endocarditis) carries a certain risk of vegetation embolization due to manipulation of the catheter in the aortic root [84].

Patient preparation

Only minor patient preparation is required prior to cardiac CT. In fact, cardiac CT offers the advantage of also being available for urgent indications or in critically ill patients. The level of patient preparation depends solely on the type of scan envisaged, and the latter in turn depends on the clinical situation and the question of interest. In the simplest case, where only a native (noncontrast) nongated CT scan is required (e.g. for simple coregistration with radionuclide imaging according to a standard PET/CT protocol), no particular patient preparation is needed. The scan is usually performed immediately before or after the acquisition of PET emission data. Occasionally, however, if indicated for IE and/of CIED infection, a high-resolution contrast-enhanced ECG-gated scan will be preferred to resolve anatomical details of moving heart structures. In this case, it is generally recommended that the patient should fast for 3–4 h prior to the scan [85]. A careful history with regard to potential pregnancy, allergy to contrast agents, and impaired renal function should be taken.

Despite the high temporal resolution of current CT devices, image quality still depends considerably on heart rate. In patients with heart rates >65 bpm, pretreatment with a beta-receptor antagonist (either intravenously or orally depending on the clinical setting) is recommended to lower the heart rate as much as possible, preferably below 60 bpm, providing there is no contraindication to the use of these agents [85]. Although achieving diagnostic quality for the assessment of coronary arteries may not be the primary goal of the scan, it may still be advisable to lower the heart rate and administer nitrates prior to image acquisition. Special care should be taken in patients with severe aortic regurgitation, in whom lowering the heart rate may have detrimental haemodynamic effects.

Imaging protocols and technical issues

As mentioned above, different image acquisition protocols may be used depending on the scanner platform and the type of scan ordered. To obtain high-quality images in regions affected by cardiac motion, ECG gating by either retrospective or prospective triggering is indispensable. Retrospective gating offers the advantage of allowing reconstruction of CT images over all phases of the cardiac cycle. This allows the demonstration of the oscillation of masses, visualization of native or prosthetic valvular function, and identification of rocking motion in prosthetic dysfunction. However, the radiation dose is considerably higher with retrospective ECG triggering (depending on scan parameters and the use or not of dose-modulation algorithms, up to 20 mSv). On the other hand, prospective ECG gating triggers image acquisition during a predefined interval of the RR cycle and therefore is obtained with a fraction of the exposure radiation of retrospective helical scans. Radiation dose also depends on the longitudinal field of view of the scanner and is higher for partial-body CT angiography than for cardiac CT angiography. High-end CT devices with 64 slices or more are generally preferred due to their higher spatial resolution, larger axial coverage and shorter scan time. Good quality images are difficult to obtain in patients with atrial fibrillation or

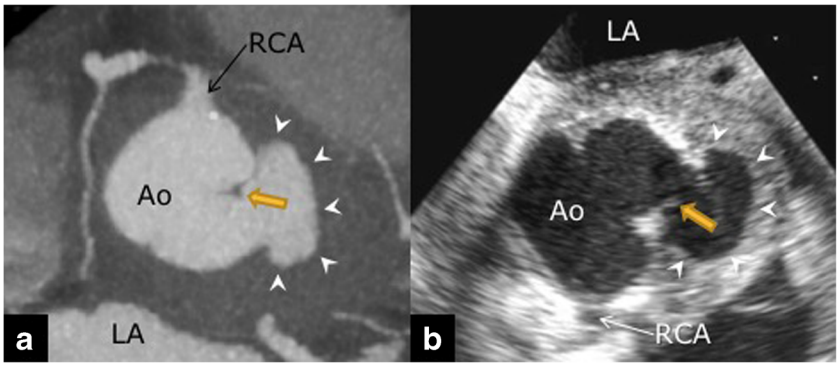

Fig. 8 A 52-year-old man with prosthetic aortic valve endocarditis (coagulase-negative staphylococci) 4 years after aortic root replacement with a 25-mm Freestyle biological valve, replacement of the ascending aorta with a 28-mm Dacron graft and reconstruction of the posterior sinus with xenopericardium. **a** ECG-gated contrast-enhanced cardiac CT image (GE VCT 64-slice CT scanner) of the aortic root (*Ao*) shows a pseudoaneurysm of the left coronary sinus (*arrowheads*) with a small 3–4 mm vegetation (*yellow arrow*) attached to the anterior aspect of the neck of the pseudoaneurysm. **b** Transoesophageal echocardiography (TOE) image confirms the CT findings. Note that the CT and TOE images have opposite anteroposterior orientation (*LA* left atrium, *RCA* right coronary artery)

tachycardia due to the deleterious effect on image quality of motion artefacts. In these patients, it is recommended that the heart rate is lowered as much as possible using oral or intravenous beta-blockers (if clinically feasible) and that devices with the highest temporal resolution are used (e.g. dual-source scanners, if available).

Imaging postprocessing and interpretation criteria

Images are generally reconstructed as transaxial images, multiplanar reformations, maximum intensity projections, and 3D volume renderings. For fusion with radionuclide images, axial and coronal source images are usually the preferred mode

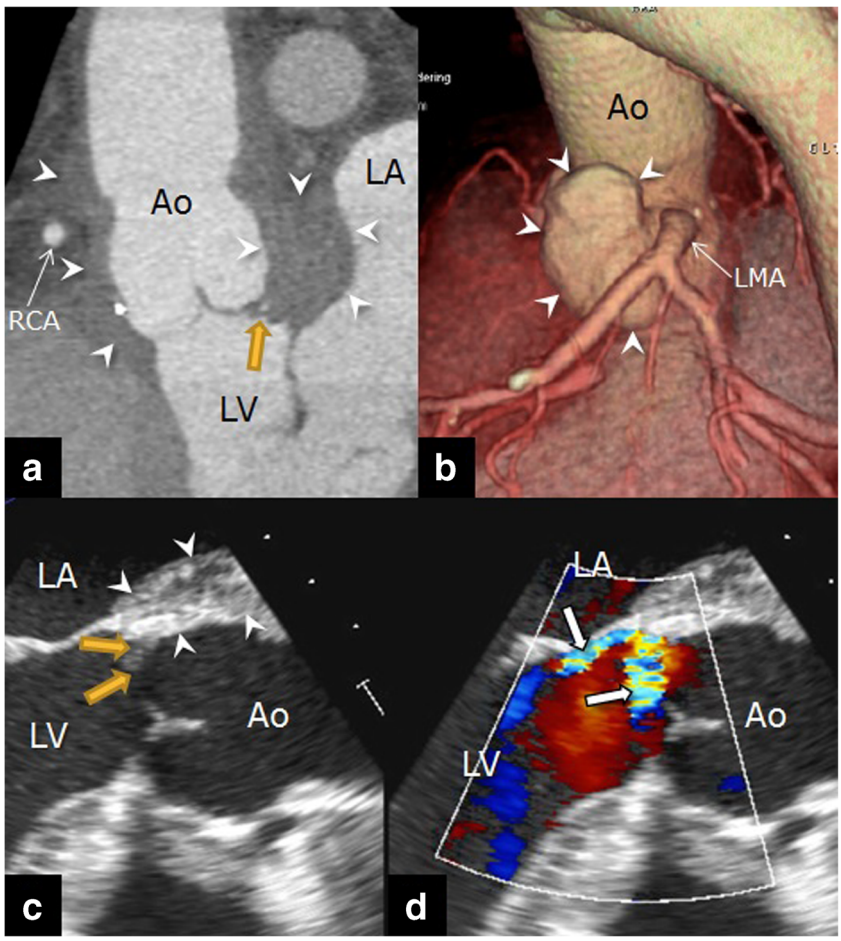

Fig. 9 Same patient as in Fig. 8. **a** Double-oblique multiplanar reformatted cardiac CT image shows a perivalvular abscess (*arrowheads*) surrounding the entire aortic root (*Ao*) with the largest collection between the left atrium (*LA*) and the left coronary cusp. **b** 3D volume-rendered CT image shows the relationship between the pseudoaneurysm (*arrowheads*) and the other anatomical structures: The pseudoaneurysm is located just anterior of the left main coronary artery (*LMA*) but does not compromise the vessel. **c** Transoesophageal echocardiography (TOE) image shows a hypoechogenic abscess between the aortic root and the left atrium. **d** The colour Doppler image confirms the presence of at least two small perforations of the left coronary cusps (*white arrows*, *yellow arrows* in **c**) which are not clearly visible on the CT image (*yellow arrow* in **a**)

of display. Multiplanar reformations of ce-CT images allow reconstruction of the structure of interest in every possible plane, and thereby allow assessment of its structure, size and extent. Vegetations appear as irregularly shaped, hypodense, oscillating structures adherent to the endocardium (Fig. 8). Abscesses are defined as irregularly shaped, inhomogeneous masses within the paravalvular myocardium or pericardium, while a pseudoaneurysm is defined as space filled with contrast medium with connection to any of the cardiac chambers (Fig. 9). CT has shown very high sensitivity in comparison with TOE or surgery in detecting the presence and extent of paravalvular complications such as abscesses and pseudoaneurysms [86, 87]. TOE, on the other hand, is probably superior to CT for the diagnosis of small vegetations and for detecting leaflet perforations, particularly if they are smaller than 2 mm (Fig. 9).

However, in the setting of PVE, the diagnostic yield of TOE is lower than in NVE as previously mentioned. In PVE, the onset of infection may be more insidious, extension of infection into the perivalvular tissue more common, and acoustic shadowing from metallic prostheses interferes with TOE imaging (particularly in the detection of paravalvular complications located in or close to the right coronary cusp). In this setting, CT may even be superior to TOE in detecting vegetations, abscesses, and pseudoaneurysms [88]. TOE remains more sensitive than CT for valvular dehiscence, although using retrospective ECG triggering and image reconstruction at different time intervals during the RR cycle after a full helical CT scan, even rocking motion from a severely detached prosthesis can be visualized. However, large comparisons between CT and TOE are lacking, therefore CT and TOE are considered complementary techniques, but it is recommended that TOE remain the first-line test in suspected PVE. Moreover, CT allows the assessment of systemic complications from IE including septic embolization (e.g. lung, spleen, brain), mycotic aneurysms, and intracranial bleeding, which may all have important implications for patient prognosis and management and may add to the diagnostic criteria for IE.

In recognition of the increasing role of cardiac CT, the 2015 ESC guidelines for the management of IE have been modified by adding to the traditional Duke criteria "definite para valvular lesions by cardiac CT" as a *major* criterion, and "vascular phenomena detected by CT including arterial emboli, septic pulmonary infarcts, infectious (mycotic) aneurysm, intracranial haemorrhage, conjunctival haemorrhages, and Janeway's lesions" as a *minor* criterion for endocarditis [2].

In CIED infections, cardiac CT probably has a more limited role than radionuclide imaging, except for providing anatomical maps to coregister signal from radionuclide imaging with anatomical structures (e.g. device pocket or leads). In the majority of cases, nongated native CT scans are considered sufficient for this purpose. Small vegetations on pacemaker leads may be difficult to detect on ce-CT angiography and the generator often causes significant blooming and beam hardening artefacts in the pacemaker pocket. However, as mentioned before in the field of IE, CT angiography may add important remote information on vascular complications such as mycotic aneurysms, arterial emboli, and septic pulmonary infarcts, which adds to the diagnostic criteria and affect the overall treatment strategy.

Pitfalls, differential diagnosis of IE/CIED infections with CT

Even though CT has been demonstrated to be more accurate in the presence of metallic prostheses, it is not devoid of artefacts. Some tilting-disc metallic prostheses, such as the Björk-Shiley valve, have been associated with severe beam-hardening artefacts, which affect the correct evaluation of the perivalvular region [89]. Increased wall thickness of the aorta has been proposed as a sign of early aortic root infection after surgery. However, there is no consensus about the upper limits of the normal aortic root thickness after aortic valve surgery. In addition, in the early postoperative period, the aortic wall may be thickened from haematoma or oedema, which may resolve within 3 to 6 months, requiring close imaging follow-up and integration of clinical findings. The differential diagnosis of valvular vegetations includes mobile strands or free sutures arising from sewing rings or prosthetic valves, and cardiac (mostly benign) masses such as thrombus, fibroelastoma and myxoma.

The "imaging specialist" in the Endocarditis Team: role, challenges and education

The new ESC guidelines for the management of IE introduce the Endocarditis Team as the basis for maximizing the likelihood of success in managing patients with IE and CIED infections. They delineate the wide scope and complexity of the Endocarditis Team and provide a general framework for its functioning, including recommending the professionals who should be involved in the decision making process. Given the complexity of the topic, a team approach provides the most logical solution to delivering interdisciplinary competence. The benefits of teamwork are obvious. The team approach leads professionals to evaluate IE as a whole complex, multisite disease that should be addressed with an integrated diagnostic-therapeutic strategy rather than a single isolated medical action. The diverse range of professionals working together, bringing together diverse knowledge and skills, results in higher levels of innovation in patient care and faster decision making. From the patients' (and also the families') perspective, teamwork affects compliance since it is easier to communicate with a cohesive team than with practitioners who work in isolation.

Efficient team functioning is challenging. Building well-functioning teams requires time, education and support. With time, team members get to know each other and learn about each other's professional work and attitudes to change and

innovation. More time is necessary to allow team meetings to discuss patient and programme issues. Yet time for education, a complex issue that requires a shared team vision to improve specific medical knowledge and skills to accomplish team development, has to be planned. The "Imagers" are called to play a more and more active role in the team programme and in the global educational planning. With evolving technologies, the choice of investigation and the interpretation of results have become more complex. Therefore teamwork serves as an important opportunity to update professional knowledge and for continuing professional development. With this changed way of thinking, the team can effectively collaborate and ultimately provide the best care to the patients so that they receive the proper diagnosis and treatments [90]. Locally available resources might be critical and it may seem impossible to fit more time for working with the team into the competing priorities of healthcare and educational professionals. But the time spent working on more effective approaches may actually save time in the long run. A quotation from Henry Ford seems apt: "coming together is (just) the beginning of the process". For this issue, strong joint educational initiatives are needed to set a European standard for competency in the practice of imaging.

Conclusions

The Endocarditis Team is a rapidly emerging concept that aims to provide the most appropriate management of patients with IE or CIED infections. The team should include cardiologists, cardiovascular surgeons, specialists in infective diseases or clinical microbiologists, imagers such as echocardiographists, radiologists and nuclear medicine physicians. Accordingly, the ESC has recently published new guidelines on IE in collaboration with representatives of other disciplines. Imaging is included In these new guidelines as central in the diagnostic algorithm. Therefore, imaging procedures have moved from an extemporaneous procedure used in selected patients and in selected centres to a widely available method with specific clinical indications. In these guidelines we aim to provide detailed information on standardized imaging acquisitions and reporting in patients with suspected IE or CIED infections, based on consensus agreement among a wide panel of experts from several disciplines. This document will help professionals in the management of patients with IE and CIED infections, strengthen multidisciplinary collaboration to provide better healthcare and reduce costs by helping to avoid unnecessary or wrongly executed diagnostic examinations. Even if multimodality imaging is changing the face of endocarditis diagnosis and management, and is now included in the ESC guidelines, it is important to re-emphasize:

- The need for specific expertise in reference centres
- The existence of a long and specific learning curve for each technique
- The need for interpreting imaging data taking into account the clinical presentation and the advice of the Endocarditis Team
- The need for additional future registries and studies to prospectively validate the use of multimodality imaging in IE

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These recommendations, that represent a policy statement, have undergone a thorough consensus process in which they were subjected to extensive review. The EANM recognizes that the safe and effective use of diagnostic imaging requires specific training, skills, and techniques, as described in each document.

The recommendations were brought to the attention of all other EANM committees and of the National Societies of Nuclear Medicine. The comments and suggestions from the Translational Molecular Imaging Committee, Oncology Committee, Radiation Protection Committee and the Physics Committee and National Society are highly appreciated and were considered during the preparation of these recommendations.

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Compliance with ethical standards

Conflicts of interest None.

Ethical approval This article does not describe any studies with human participants or animals performed by any of the authors.

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The facilities in a specialized practice setting may be different from those in a more general setting. Resources available to care for patients, legislation and local regulations may vary greatly from one European country or one medical facility to another. For these reasons, these recommendations cannot be rigidly applied.

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