Imaging of Endocarditis and Cardiac Device-Related Infections

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Imaging of Endocarditis and Cardiac Device-Related Infections: An Update

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IE is a deadly disease requiring prompt diagnosis for adequate patient's management. The diagnosis requires the integration of clinical signs, microbiology data and imaging data and proper discussion within a multidisciplinary team, the endocarditis team. Since the introduction of ^{18}F-FDG-PET/CT and WBC SPECT/CT in the diagnostic algorithm of PVE the nuclear medicine imaging specialists is active part of the Endocarditis Team, requiring proper knowledge of dedicated imaging acquisition protocols, expertise for imaging reading and interpretations to select the best test or combination of tests for each specific clinical situation. In this manuscript, we will review the main technical aspects of each imaging procedure, the most recent literature with specific regards to special challenging populations and provide clinical examples.
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Infective Endocarditis

Infective endocarditis (IE) refers to the infection of the native structure of the heart, the heart valves native valve endocarditis (NVE) as well as of implanted devices such as all types of prosthetic valves prosthetic valve endocarditis (PVE), annuloplasty rings, intracardiac patches, shunts or cardiovascular implantable electronic devices (CIED, termed CIED infection or endoplastitis).

Endocarditis is sustained by a large spectrum of microrganisms, mostly bacteria which, adhere to damaged or inflamed valve surface or to the prosthesis, proliferate causing white blood cells and platelets recruitment and, possibly disseminate in the blood stream again resulting in distant infection foci.[1]

Even though it is still a relatively rare condition, with reported 3-10 cases/100,000/y in developed countries,[2] the incidence is increasing. Data from the most recent registry, the EURO-ENDO registry[3] clearly delineate the modified epidemiological profile of the disease which is nowadays increased with increasing age of the population, in the group of patients with prosthetic valve. The microbiological profile of the disease has also significantly changed over time with more IE currently sustained by staphylococcal and enterococcal spp as well as a number of culture-negative IE observed in EURO-ENDO (21%) higher than previously reported in other studies.[4,5]

Despite improvements in diagnostic and therapeutic strategies IE mortality is still unacceptable high. Overall, mortality rate is 20% at 30 days[6] and 40%-50% at late follow up,[7] due to local complications (valvular degradation and perivalvular abscesses) or distant embolization (notably to the brain)[2] which can occur in up to 40% of patients with IE (with a high burden of cerebral manifestations.[8]

Unexpectedly, prognosis is similar in NVE, PVE, and CDRIE, and is particularly severe in the group of patients in which surgery is not performed despite indicated.

Diagnosis of IE: From the Duke's Criteria to the ESC 2015 Criteria

Early diagnosis is crucial not only to promptly identify the disease, but also to prevent severe complications, thus

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reducing the mortality. However, diagnosis is still a challenging[9] and requires the integration of clinical signs, microbiology data and imaging findings through a multidisciplinary discussion. Traditionally the diagnosis of IE was based on the modified Duke's Criteria,[10] which classify patients in a probability system into 3 categories ("rejected," "possible" or "confirmed" endocarditis), combining major and minor criteria, based on microbiological[11,12] and echocardiographic (both transthoracic, TTE, and transoesophageal, TEE)[13] findings.

Three main echocardiographic findings were used as major Duke's Criteria of IE: vegetations, abscess and perivalvular complications, new dehiscence of prosthetic valve, with other findings such as prolapse, aneurysm or valve perforation considered helpful in the diagnosis process.[13]

Overall the Modified Duke's criteria had been widely used due to their accuracy and their easy translation in clinical practice. However, over time, it becomes clear that when echocardiography fails to identify valve or prosthetic abnormalities, the Duke's criteria decrease their diagnostic sensitivity. Indeed, echocardiography, especially TTE, remains diagnostically imperfect in the evaluation of PVEs and CDRIEs,[14] by failing to identify IE in about 30% of cases.[15,16] The most critical issues are identification of small size vegetations (sensitivity of TTE drops to 25% with vegetations smaller than 5 mm[17]), with better diagnostic accuracy for TEE,[18] accurate identification of perivalvular complications and the evaluation of the anterior structures and RVOT tract (the so-called right-sided IE). Increased sensitivity in the evaluation of valvular vegetations or perivalvular abscesses in patients with NVE from 28% to 63% using TTE to 87%-94% with TEE; no significant differences are described for specificity (superior to 90%).[19,20] It is worth mention that, despite accurate, TEE is a complex procedure with inherent intraoperative risks that not all patients can bear; there are factors that may increase the probability of esophageal perforation or prevent the probe from actually passing down (eg anatomic abnormalities, cancer, ulceration, and diverticulum).[21]

Due to the limitations encountered in the application of the Dukes' Criteria in particular on the setting of PVE and CDRIE the guidelines for the management of IE by the European Society of Cardiology (ESC) published in 2015 introduced of other imaging findings based on cardiac computed tomography angiography (CTA) and computerized tomography (CT), 18-fluorine-fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET/CT), radiolabelled white blood cell (WBC) scintigraphy as major diagnostic criteria when an high suspicion of IE is present and echocardiography fail to provide a major diagnostic criteria.[22] The role of ^{18}F-FDG-PET/CT has also been emphasized by the American Heart Association (AHA), interestingly both in PVE and NVE.[23] Furthermore, the specific role of imaging in CDRIE has been addressed by the European Heart Rhythm Association.[24] Overall, a multimodality imaging approach is now recommended and should be always considered to solve the two main diagnostic challenges in IE diagnosis of confirming the local involvement at the cardiac/device level and the detection of distant lesions related to the infectious process. Since each technique has its diagnostic pros and cons[26] the clinical discussion within the endocarditis team is the way to provide to each imaging findings the proper clinical interpretation, thus optimizing imaging results in patients' management.

^{18}F-FDG-PET/CT and PET/CTA: Technical Consideration

The rational use of ^{18}F-FDG-PET/CT in infectious/inflammation processes is based on the tracer uptake in the site of disease reflecting the presence of activated leukocytes (macrophage and CD4-positive T cells).[26]

In the evaluation of IE, there are certain obstacles that require proper acknowledgment and intervention to optimize the scan results, the first is the physiological uptake in the myocardial cells which may hamper the overall accuracy of the scan.[27] Inflammatory cells and myocardial cells present different GLUT transporters among which GLUT 4, an insulin dependent glucose transporter, is expressed in the cell membrane of normal myocytes, but its expression depends on insulin levels and metabolic state. On the other hand, GLUT 1 and 3 are expressed on inflammatory cells and are completely independent by the metabolic status.[28]

Therefore, patient preparation is meant to reduce insulin levels and shift to a fatty acid metabolism rather than a glucose based metabolism, nulling ^{18}F-FDG uptake in the heart, thus resulting in an optimal target/background ratio. Different preparations have been proposed, Different preparations protocol have been proposed with a general agreement that low-carbo-high-fat diet (protein permitted) at for at least 24 hours followed by 6 hours fasting is the recommended method.[29] The procedure may be implemented with the administration of heparin 1 immediately before ^{18}F-FDG injection,[30,31] however, since many patients are already undergoing LMWH treatment with a similar effect, this latter can be avoid (REF) .

The administered dose is normally between 2, 5 and 5 MBq/kg e.v. ^{18}F-FDG and the standard uptake time is 60 minutes.[32] Some studies have suggested that a delayed acquisition may improve accuracy, but the results are still controversial.[33] In fact, it has been demonstrated that patients with suspected PVE may not benefit from a 150-180 minutes delayed acquisition, even though a higher target/background contrast was reported due to the reduction in activity in the blood pool: an increase rate of false positive findings without a definite improvement in the differentiation between infected and uninfected valves was observed.[33] On the contrary, in the evaluation of CDRIE, a delayed acquisition may be helpful in the detection of lead infection, improving sensitivity (61% vs 24%, $P = 0.062$) without affecting specificity (79% vs 79%) and is therefore a suitable option in patients with a negative 1-hour standard acquisition and a high pretest probability of pacing lead infection.[34]

The field of acquisition should extend to include the brain and lower limbs, to assess the presence of disseminated

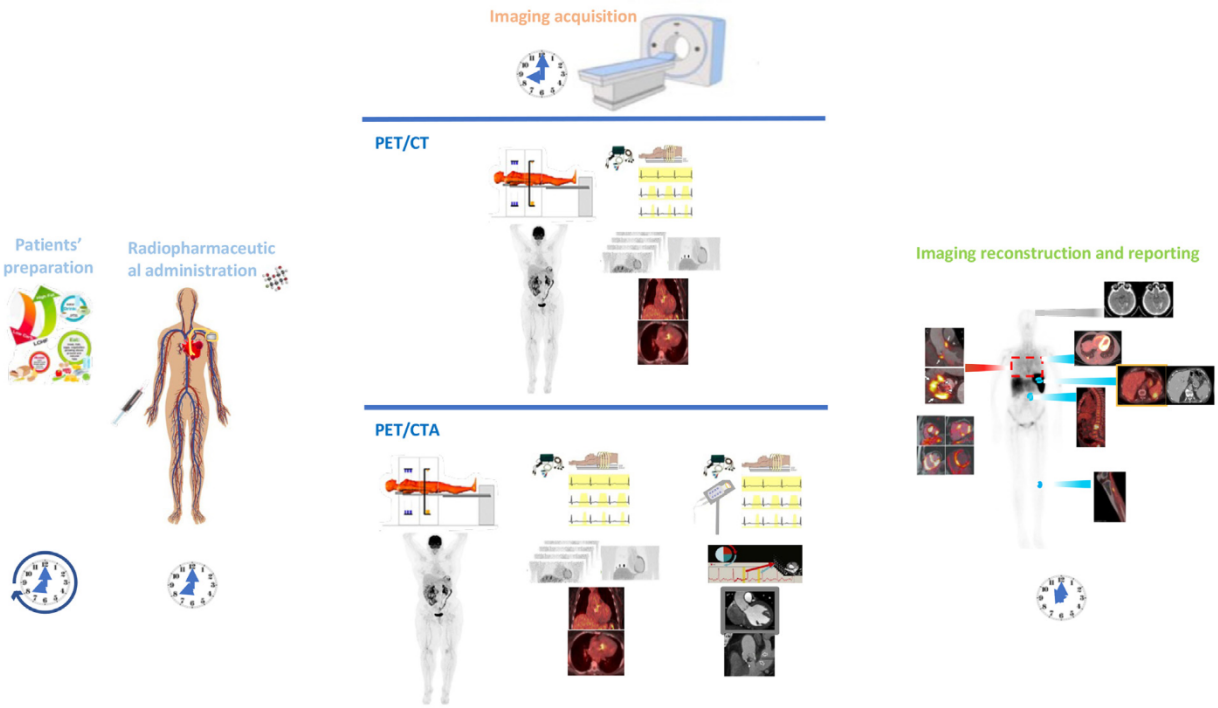

Figure 1 Schematic representation of the ^{18}F-FDG-PET/CT(A) imaging procedure in the context of IE and CIED infections. First in the right panel, the patient should be properly prepared high-fat-low-carb diet for 24hrs followed by 12 hours fasting before the radiopharmaceutical administration. After about 1 hour, the patient is imaged according to the specific protocol (middle panel, upper row PET/CT and lower panel PET/CT(A)). Finally, the images are reconstructed, reoriented, and assessed for the presence of uptake at the valve and extracardiac disease involvement, as in case of septic embolisms, metastatic sites of infection and the portal of entry or alternative source of infections (left panel).

septic emboli. To evaluate valves, perivalvular or lead involvement, a respiratory and/or cardiac-ECG gating during the whole body or by separate bed on the heart can be performed to improve sensitivity. Whenever feasible concomitant ECG-gated cardiac CT with angiography (CTA) should be performed with the advantages of identifying an increased number of anatomic lesions, clarifying indeterminate studies[35] and specific clinical situation such as in patients with composite aortic valve-aortic grafts and patients with congenital heart disease who have complex anatomy for the presence of a large amount of prosthetic implanted material.[36] Figure 1 provides a schematic representation of the ^{18}F-FDG-PET/CT imaging procedure.

In case of aortic valve prothesis, images should be reviewed and reconstructed in three different views: left sagittal oblique, left coronal oblique, and cross-sectional oblique view of the valve. For mitral valve prosthesis imaging, reconstruction of 4-chamber, 3-chamber, and 2-chamber views as well as short axis views of the mitral valve, is recommended. Imaging interpretation is based on visual assessment, a focal or multifocal uptake on the valvular plan exceeding the surrounding blood pool confirmed in both AC and NAC images is the typical PET features indicating IE. Figure 2 provides examples of the pattern of normal and pathological uptake in IE. 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. In particular, careful assessment of the presence of persistent host reaction against the biomaterial coating the sewing ring of the pulmonary valve,[37] chronic tension or friction exerted on anchor points as well as of all the factors affecting the intensity of [^{18}F]FDG uptake, thus SUV values (ie time elapse from surgery, surgical and postsurgical complications, ongoing antimicrobial treatment, and specific strains).[38]

The role of semiquantitative analysis is still controversial and so far, multiple studies have analysed the topic only in PVE and CDRIE. Currently, although there is no recognized cut-off value, evidence suggests that a higher SUV corresponds to a higher probability of infection.[39]

In case of PVE, the ratio SUV max valve/blood pool on the descending aorta $\geq$2.0 has been proposed as a cut off, yielding sensitivity and specificity of 100% and 91% respectively.[40] when all the main confounders affecting SUV values calculation are identified and excluded. Very scarce data are at the moment are available on the use of ^{18}F-FDG radiomics and machine learning-based algorithms in IE. However, preliminary data suggest the machine learning-based algorithms reached acceptable diagnostic performances in terms of sensitivity for a specificity equal to the one of visual assessment by very

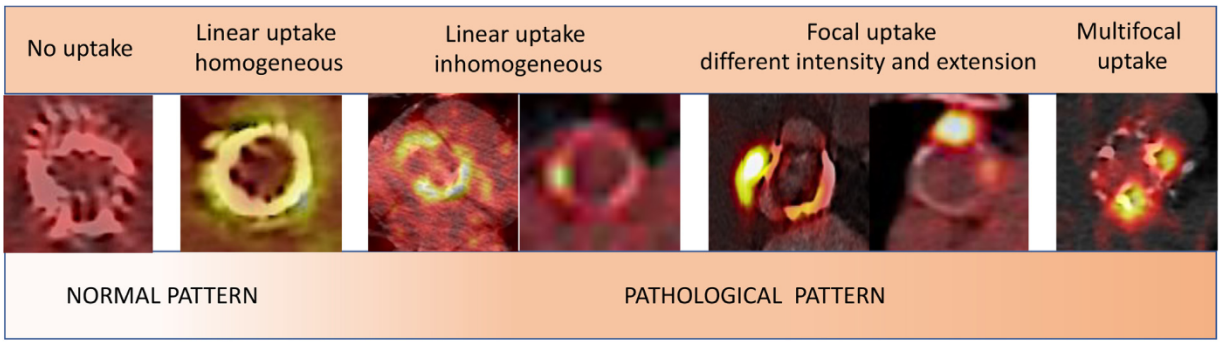

Figure 2 Examples of the pattern of normal and pathological ^{18}F-FDG uptake in IE (modified form Roque A, et al.[91])

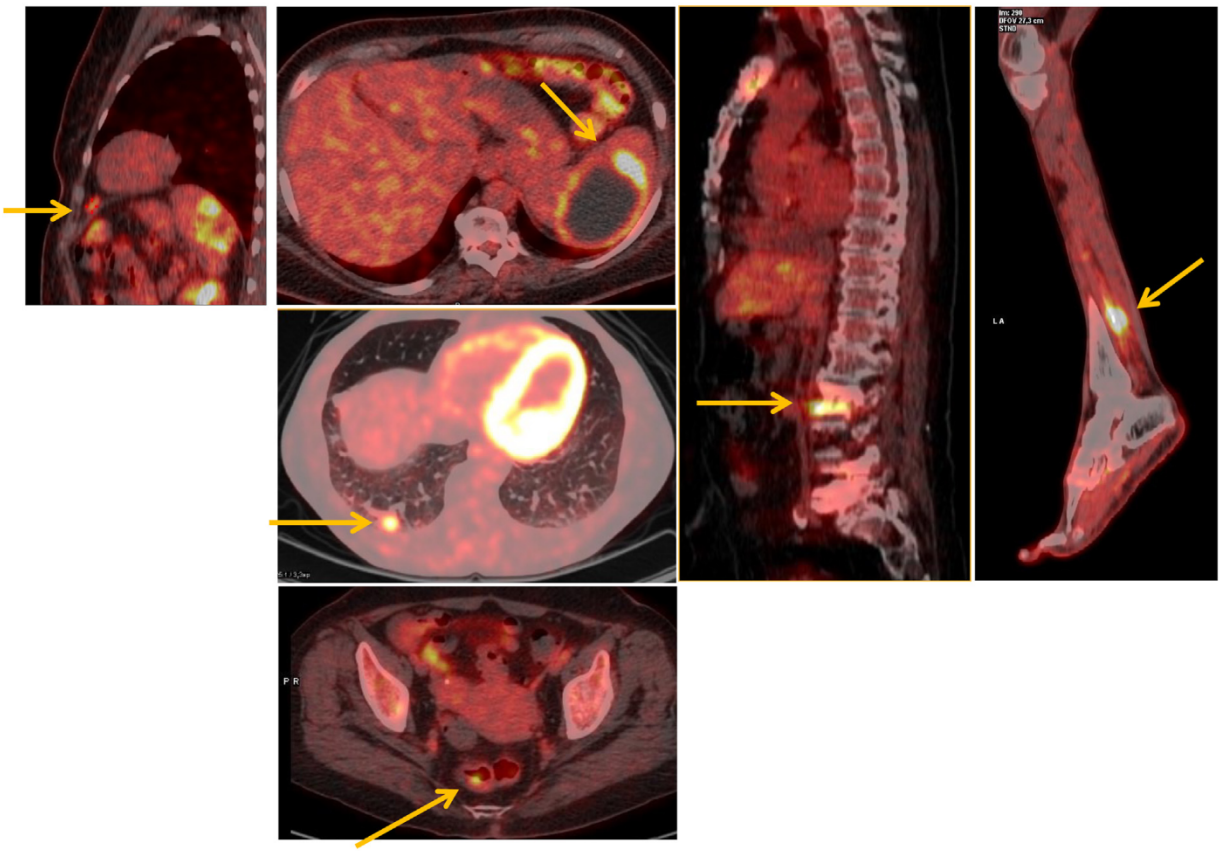

Figure 3 Examples of PET/CT findings in patients with embolism detection. From right to left superimposed PET/CT images ^{18}F-FDG-PET/CT (Discovery 710 PET/CT GE Healthcare) in mediastinal lymphnodes, in spleen embolism (upper panel) and lung embolism (middle panel), at the level of the rectal wall finally diagnosed as rectal cancer (lower panel), at the spine and at the level of the vascular wall in a mycotic aneurysm. In all cases, increased homogeneous FDG uptake is evident.

experienced readers[41,42] suggesting it's worth to explore this approach in when subjective visual assessment might be challenging.

A significant advantage of PET/CT is its ability to perform the extracardiac workup within a single imaging procedure as well to reveal the concomitant presence of extracardiac infection sites as the consequence of both septic embolism and primary infective processes. All these conditions are characterized by the presence of area of increased ^{18}F-FDG uptake of variable intensity with the exception of the brain location due to the specific ^{18}F-FDG biodistribution pattern.[43] Figure 3 provides examples of PET/CT findings in patients with embolism detection.

WBC Scintigraphy

WBC scintigraphy is based on the labelling of patients' autologous leucocytes, which are isolated, incubated with the tracer (either ^{111}In-oxine or ^{99m}Tc-hexamethylpropyleneamine oxime) and then reinjected. The procedure is relatively complex, despite well standardized and widely used and

involves blood handling, although in recent years new closed sterile devices have been developed, abridging the whole procedure. For detailed on the radiolabelling procedure, please refers to the specific guidelines from the European Association of Nuclear Medicine (EANM)[44] and the Society of Nuclear medicine and Molecular Imaging (SNMMI).[45] [^{99m}Tc]HMPAO radiolabeling is preferred since it allow to perform high quality SPECT/CT images which are fundamental for the imaging reading also at 24 hours, if needed. In patients with IE or or CIED infections the standard WBC imaging procedure in terms of patient preparation and WBC radiolabelling preparation are applied.

The distribution of the labelled cells from the blood stream to organs and infectious foci has several stages: after reinjection, the cells migrate to the lung, then to the liver, spleen, and bone marrow (endothelial system). After 1 hour, migration to infectious foci have begun and depends on several factors, such as the type of pathogen and the vascularisation of the tissue,[46] and is mediated by chemotactic attraction, thereby distinguishing infection from inflammatory processes, a feature that is particularly useful in those contexts where both can be ongoing, for example, postsurgery or in the presence of prostheses

The length of the migration process is reflected in the acquisition protocols which include early (1 hour), delayed (4 hours) and late (24 hours) acquisitions.[47]

SPECT/CT is necessary for a proper assessment of patients with IE in addition to confirm and localize findings consistent with infection visualized at planar images (ie signal kinetics between 4-6 hours and 20-24 hours acquisitions stable or increased in uptake intensity or size over time),[48] although imaging spatial resolution remains inferior to PET/CT. However, whole body images remain crucial to identify disseminated disease. Figure 4 provides a schematic representation of the WBC imaging procedure.

The interpretation of WBC scintigraphy begins with a visual quality control of images to check; (1) 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 superior to spleen uptake or; (3) persistent pulmonary uptake, both suggestive of WBC damage prior to re-injection.

SPECT/CT images are interpreted visually to localized sites of increased WBC uptake, taking into consideration the pattern (focal, linear, and diffuse), the intensity, and the relationship to areas of physiologic distribution. Multiplanar reformations (MPR) of the cardiac SPECT/CT images are necessary for proper valve assessment with the same reconstruction views described for PET/CT.

Both CT-attenuation corrected and non-corrected SPECT images have to be evaluated to check for misalignment between emission and transmission data which can results in

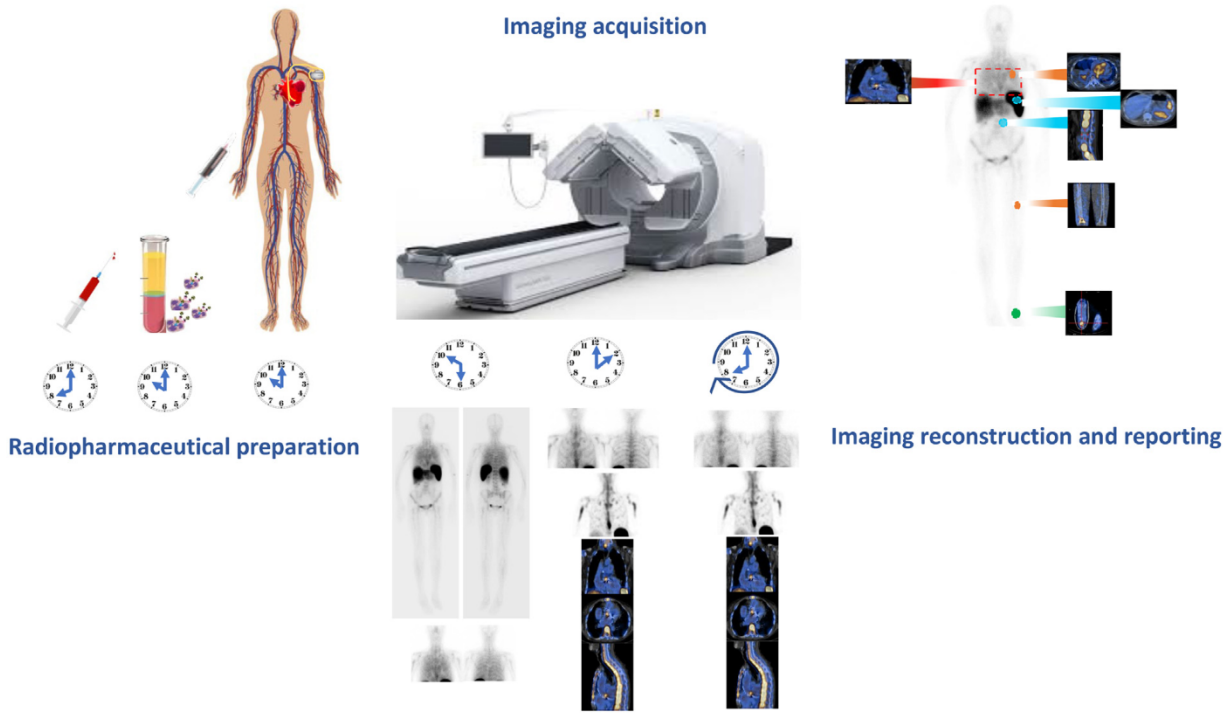

Figure 4 Schematic representation of the flow in radiolabelled WBC scintigraphy. First in the left panel, the radiopharmaceutical preparation starting with blood sampling and the WBC isolation. After the administration of the radiolabelled cells, the patient is scanned at different time-points (middle panel, orange). Early images (30 minutes) consists of total-body and spot of the thorax. Late images (4-6 hours) and delayed images (20 hours) includes spot images and SPECT/CT of the thorax, eventually followed by additional SPECT/CT based on the specific clinical condition. Finally the images are reconstructed, reoriented and assessed for the presence of uptake at valve/devices and extracardiac disease involvement as in case of septic embolisms, metastatic sites of infection and the portal of entry or alternative source of infections (right panel).

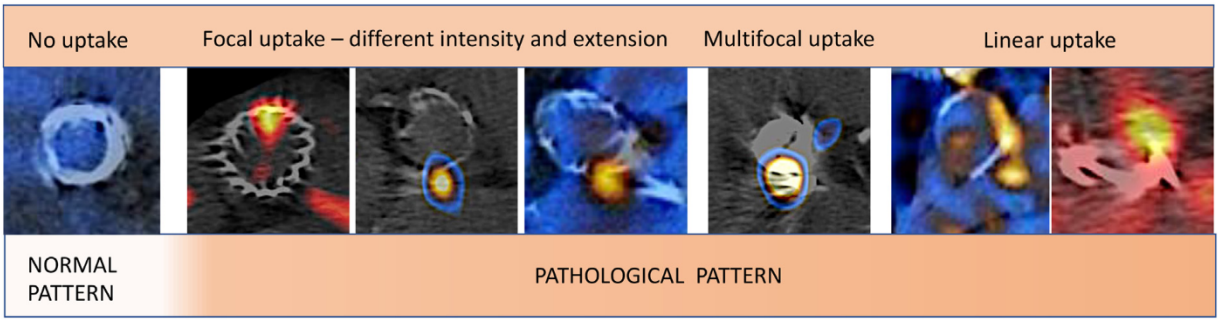

Figure 5 provides examples of the pattern of normal and pathological WBC uptake in IE.

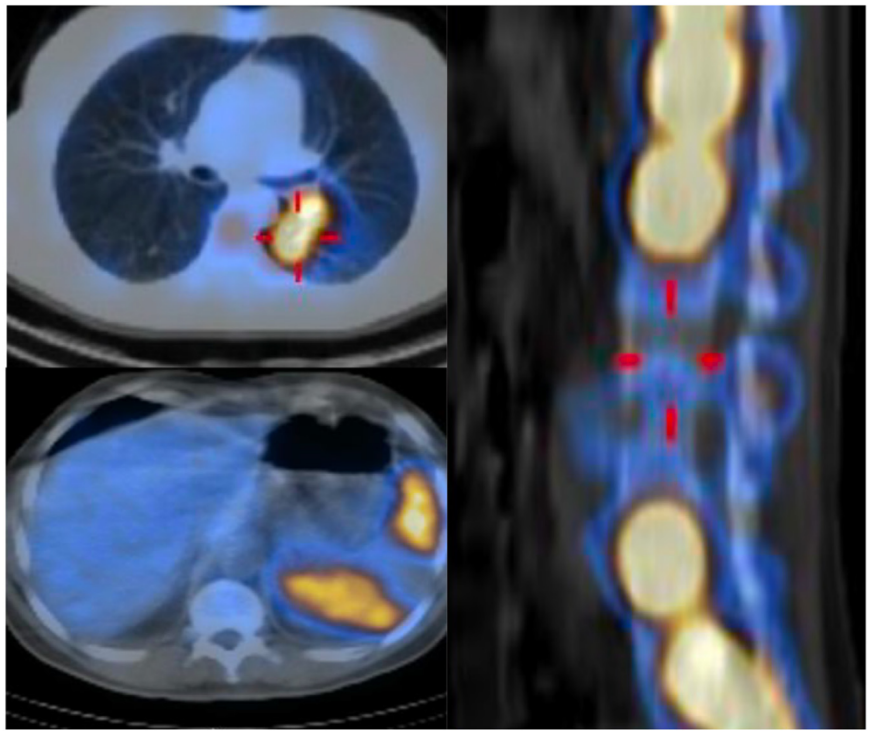

Figure 6 Examples of WBC findings (^{99m}Tc-HMPAO WBC) in patients with lung embolism (upper right panel) a finding typically presenting with increased radiolabelled WBC uptake, spleen embolism (lower right panel) and spondilodiscytis (left panel) both lesions appearing as "cold spots."

erroneous correction, thus data misinterpretation. Careful attention should be paid to quality control to avoid reconstruction artefacts in particular when PVs, generators and electro catheters are present due to possible overcorrection artefacts on SPECT/CT images.

Abnormalities detected on WBC imaging should be localized as precisely as possible since at SPECT/CT images: (1) their co-localization 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 contribute to guide surgical procedure. Figure 5 provides examples of the pattern of normal and pathological WBC uptake in IE. Rarely, false positive findings have been described for WBC imaging in IE and CIED infections, even in case of very early infections. As expected, nonpyogenic microrganisms as well ongoing antibiotic therapy may affect diagnostic accuracy, increasing the rate of false negatives scans, particularly if the treatment is administered intravenously, definite or if it is combined with other antibiotics.[49] As for PET/CT, also WBC imaging can identify sites of embolisms as well as possible sites of uptake which might represent the portal of entry of the infection or alternative source of infections.[48] However, the pattern of embolism at WBC imaging can be either an area of increased uptake (ie brain, lung, and soft tissue) or a cold spot if affecting organs with intense background activity as for normal biodistribution (ie, spleen and the bone marrow, Fig. 6), thus requiring proper differential diagnosis by additional imaging tests.

NVE

The role of nuclear medicine techniques is limited in the evaluation of NVE, with low sensitivity for ^{18}F-FDG-PET/CT and WBC in the detection of intracardiac lesions due to the

small size of the vegetations and composition, consisting of limited white blood cell response and a high level of fibrosis.[50] Nevertheless, a valid indication to perform ^{18}F-FDG-PET/CT can be the differentiation of patients with limited disease from patients with local complication and/or disseminated disease, as shown by a recent study in which by ^{18}F-FDG-PET/CT extracardiac sites of disease were identified in 55% of patients with NVE and related to a more complicated infection with involvement of perivalvular structure.[51]

Overall ^{18}F-FDG-PET/CT has been reported to change the therapeutic management (antibiotic or surgical strategy) in 1/3 of patients belonging to a large cohort of patient with NVE.[52] The role of WBC scintigraphy in this field is limited, and focus mainly on the evaluation of disseminated disease.

Recommended Diagnostic Strategy in NVE

The general consensus on the use of imaging modalities in NVE recommend the use of echocardiography, both TTE and TEE (mainly for a better assessment of perivalvular complications for his higher sensitivity), in all patients with suspected IE as the first imaging test, to evaluate anatomic involvement and hemodynamic consequences. If both TTE and TEE are negative or inconclusive, especially if performed early in the clinical course, a repetition within 1 week if high clinical probability of IE persists is suggested. Alternatively, Cardiac CTA or ^{18}F-FDG-PET/CTA might be used in the setting of suspected paravalvular infection extension in case of suboptimal acoustic window at echocardiography or artifacts. Cardiac CTA also allows preoperative risk stratification, accurately assessing the IE-related perivalvular lesions for a better procedure planning[53,54] and the evaluation of CAD.

PVE

From the EUROENDO registry we know that ^{18}F-FDG-PET/CT is currently the second most used imaging modality for the diagnosis of IE and it was performed in 16.6% of the patients (WBC in only 1.2%) more frequently used in PVIE (25.0%) and CDRIE (26.0%) than in NVE (9.5%) at a mean of 8 days (IQR, 4.0-15.0) after enrolment, including 46.7% during the first week. In the registry. ^{18}F-FDG-PET/CT resulted positive in 69.7% of the patients, 74.9% in PVIE, 62.5% in NVE, 77.5% in CDRIE.

^{18}F-FDG-PET/CT is a major player in PVE to identify local valvular and perivalvular involvement as well as distant foci of disease. In the cluster of patients in whom echocardiography presented significant limitations pool sensitivity and specificity in the most recent meta-analysis was reported 86% and 84%, respectively.[44] When the proper protocol for patients' preparation and imaging acquisition, including contemporary CTA are followed and proper specific imaging interpretation criteria are used sensitivity and specificity can reach 91%.[55] Furthermore, a prognostic significance of ^{18}F-FDG uptake has been recently demonstrated: positive ^{18}F-FDG-PET/CT was significantly associated with a higher rate of primary endpoint such as death, recurrence of IE, acute cardiac failure, non-scheduled hospitalization for cardiovascular indication. In addition, moderate to intense ^{18}F-FDG valvular uptake was also associated with worse outcome and to new embolic events in both PVE and in NVE.[56]

The 2015 ESC guidelines emphasized the role of WBC scintigraphy in the evaluation of PVEs, in identifying both disseminated disease and intracardiac lesions, reducing the number of patients classified as "possible" IE by the modified Duke criteria.

The 2015 ESC guidelines emphasized the role of WBC scintigraphy in the evaluation of PVEs, in identifying both disseminated disease and intracardiac lesions, reducing the number of patients classified as "possible" IE by the modified Duke criteria. In the same guidelines WBC scintigraphy is also suggested over PET in cases where high specificity is required.[51] When compared to intraoperative findings of patients with suspected PVE, WBC scintigraphy showed sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy respectively of 87%, 100%, 100%, 81%, and 92%, respectively.[57] In case of abscess formation sensitivity was reported 83%-100%, specificity 78%-87%, and PPV 43%-71% and NPV 93%-100% even in the early postintervention phase allowing a differential diagnosis between infectious and sterile echocardiographic lesions.[58,59] Furthermore, WBC reduces by 27% the number of misdiagnosed IE classified in the "possible IE" category by modified Duke Criteria.[60] A contribution of the WBC scintigraphy in the identification of proper treatment was also suggested: the indication for cardiac surgery based on a more intense uptake and a safer medical management related to a milder uptake.

The typical setting in which a high contribution of ^{18}F-FDG and WBC SPECT/CT is provided are patients with a high clinical suspicion of IE and a "Possible" or even "Rejected" diagnosis by the traditional criteria, despite a proper clinical and imaging workout, IE.[35,40,61] Indeed, including PET/CT in the ESC 2015 diagnostic criteria has shown to increase sensitivity of Duke criteria from 57.1%-83.5%, with only a relative decrease in specificity (95.8%-70.8%). Most importantly, the presence of ^{18}F-FDG-PET/CT uptakes as a major criterion of the ESC 2015 was found in 40.9% of patients without major echo criteria.[62] In the same study, in the subgroup of patients with high clinical suspicion of EI using 2015 ESC criteria instead of Duke criteria resulted in an absolute increase in true positive findings (+20.9%) higher than the absolute decrease in false positive results (−5.2%). None of the patients with false positive findings had poor myocardial suppression or surgical adhesives was used, in 1 case PET/CT was performed <1 month after surgery, but from 11 to 72 months in the remaining 5 cases. Of interest, in 3 out of the 6 patients uptake was faint and of borderline significance. Adding ^{18}F-FDG-PET/CT was most useful in female patients with negative blood cultures and no clinical embolic events.

The main reason for ^{18}F-FDG-PET/CT false negatives results are prolonged administration of antibiotic treatment before the scan (even though there is no indication to postpone the treatment after the scan execution, in consideration of the severity of the prognosis[63]) and C-reactive protein (CRP) levels <40 mg/dL,[40] expression of a mild inflammatory burden. Simultaneously, it has to be noted that elevated CRP level represents an increased systematic inflammation and not necessarily a localized infection as in PVE. Consequently, CRP levels>40 mg/dL do not strictly exclude the possibility of false negative scan.[64]

False positive results could be related to artefacts due to scatter or beam hardening, therefore every finding should be confirmed in both attenuation correction (AC) and non-attenuation correction (NAC) images.[22] Another confounder is the inflammation related to cardiac surgery: currently the guidelines suggest to wait at least 1[32] to 3 months[22] after surgery before a ^{18}F-FDG-PET/CT execution However, more recent data provided evidences that the pattern of uptake more than the time from surgery is the main determinant to reduce false positive scans. Wahad et al. analysed tracer uptake in patients with aortic valve replacement and no evidence of PVE, by dividing them in three groups, each group scanned at different time interval after surgery (5, 12, and 52 weeks). All the groups showed a similar low to intermediate uptake (mean ± SD SUVmax of 4.1 ± 0.8), mostly circular around the valve.[65] Similar results were obtained by scanning consecutively the same patient[66] or by including also the mitral valve.[67] The distribution of tracer reflects the use of ^{18}F-FDG avid materials, such as surgical adhesives (eg Bioglue),[40] and type of valve. A representative case is the mosaic bioprosthesis: 1 month after implantation no valvular uptake is evident, which instead appears after 6 months, intense and heterogeneous.[68]

^{18}F-FDG-PET/CT has been also successfully applied in specific subgroups of patients. Of particular interest are patients with transcatheter aortic valve implantation (TAVI) and congenital heart disease (CHD) patients, both categories presenting with mild and nonspecific clinical presentation (mostly persisting fever),[69] limited role of echocardiography and increasing incidence, due to growing numbers of procedures.[70] Despite the limited published studies in the TAVI population, it has been demonstrated that ^{18}F-FDG-PET/CT was able to reclassify 45% of patients defined as possible IE by the Modified Duke Criteria.[71] Adult and pediatric CHD-IE have been largely evaluated, obtaining similar diagnostic performance as in non-CHD patients. In this subgroup the accuracy of echocardiography is limited not only by the postoperative complex anatomy, but also by the frequent development of right-side endocarditis (constitutes 40% of CHD-IE). There are not specifically designed studies in the elderly population, despite, given the mean age in the EURO ENDO population, representative of this cluster, it could already been concluded that ^{18}F-FDG-PET/CT has a major role also in this field. Figures 7-9 represent clinical cases.

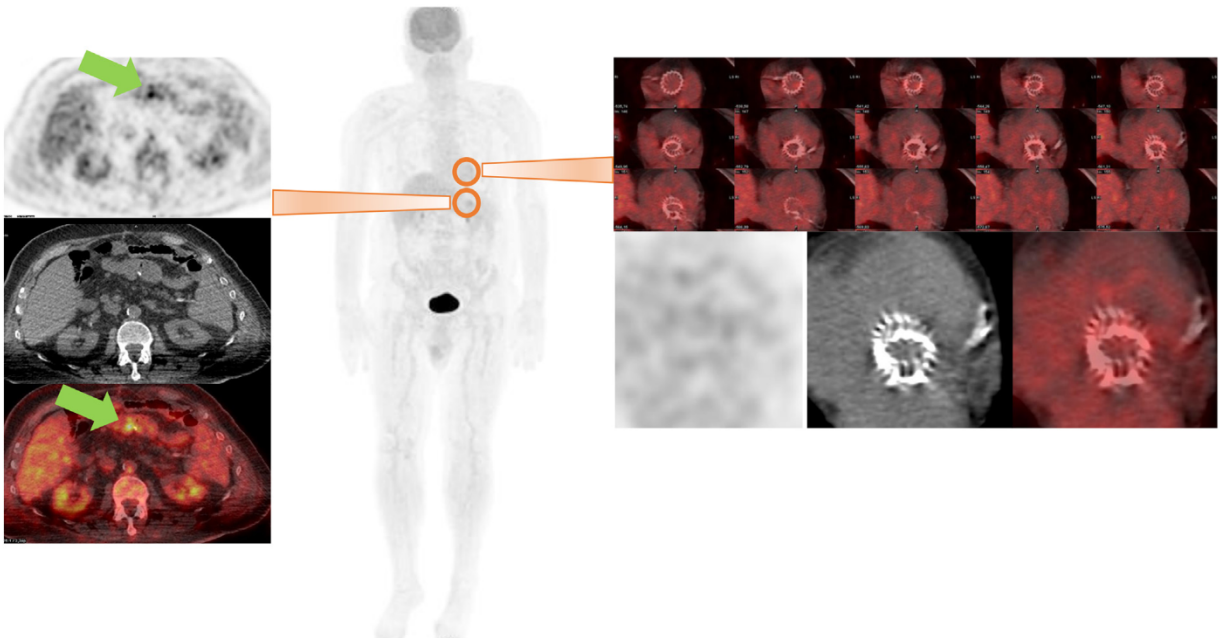

Figure 7 Example of ^{18}F-FDG-PET/CT findings in a patient with fever and a positive blood colture for *Staphylococcus Haemolyticus* arising 1 month after TAVI in a patient with lynch syndrome previously treated with several intestinal resection for cancer. TAVI negative after 1 month from surgery. MIP images are shown in the middle panel. In the left panel (upper row transaxial superimposed PET/CT images at different level and lower row transaxial left valve plane reconstructed images from right to emission, CT and superimposed PET/CT) a normal pattern of uptake at the prosthesis is present which is remarkable due to the very recent procedure while in the left panel (right panel, top-down transaxial emission, CT and superimposed images) a site of uptake at the intestinal wall (green arrow) which was later diagnosed as new cancer lesion.

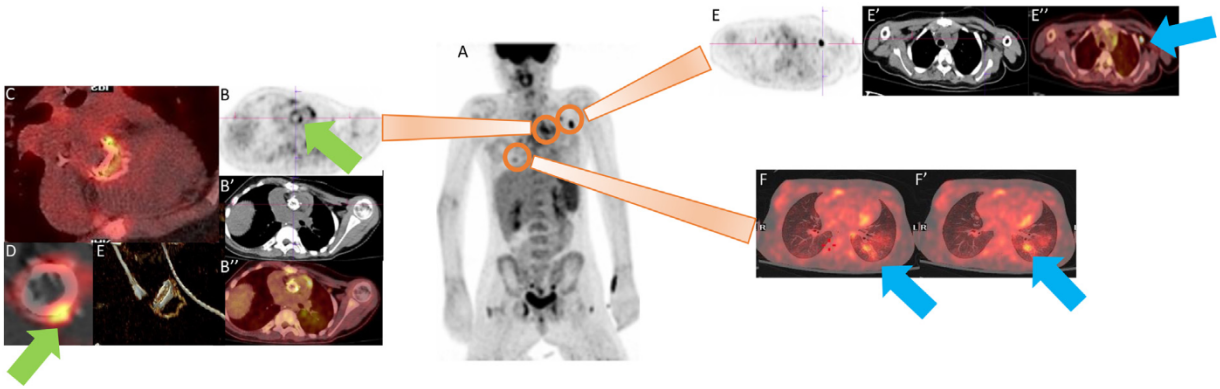

Figure 8 ^{18}F-FDG-PET/CT in a 11 years-old lady with Meyhre syndrome who was treated with Konno procedure to correct the aortic congenital stenosis 1 year prior to the scan due to sudden onset of fever, increased ESR and CRP as well as echocardiographic findings of aortic valve re-stenosis associated with a periprosthetic endoleak. Images (MIP in A, transaxial emission (B), CT (B') and superimposed PET/CT (B"), valve plane reconstructed in C and D and E) showed within a ring on homogeneous uptake the presence of a focal area of [^{18}F]FDG uprake consisten with iIE. Further, whole body images show the presence of systemic involvement of the infection as demonstrated by uptake at multiple axillary lymph nodes (transaxial emission (E), CT (E') and superimposed PET/CT (E") and lung involvement (superimposed PET/CT at different levels in F and F').

Recommended Diagnostic Strategy in PVE

For PVE the following diagnostic algorithm should be applied: performing TTE and TEE systematically in all patients with suspected PVE being aware of an overall sensitivity of 50% for TTE and 92 for TEE. In case of negative findings in particular when performed early in the clinical course they might be repeated within 1 week. However, in case of persistent high clinical suspicion and the lack of echocardiographic proven IE ^{18}F-FDG-PET/CTA or WBC imaging (eventually CTA) are performed to confirm or rule out IE after proper discussion of the case within the Endocarditis Team.

Cardiovascular Implantable Electronic Devices Infections

The term cardiac devices (CD) refers to a heterogeneous group of tools that includes pacemakers (PMs), implantable cardioverter-defibrillators (ICDs) and left ventricular assist devices (LVADs). LVADs have substantial structural differences when compared to PM/ICD and will be treated separately.

Infection is one of the most serious complications of CIED implantation associated in-hospital mortality around 5%-10%[72,73] and 1-year all-cause mortality between 16% and 36% (9, 10) although both appear to be reducing over time.[74] Staphylococcal species, both Staphylococcus aureus and coagulase negative staphylococci, account for about 60%-70% of CIED infections.[75]

CIED infection can be either a superficial incision limited to the skin and subcutaneous tissue infection, with no communication with the pocket; pocket infection, affecting to the generator pocket or an infection involving the leads which can be possibly complicated by IE (right side IE) and disseminated infection. The differentiation among incision infection from the other two entities is key to define the proper treatment since in case of superficial infection shorter antibiotic therapy are sufficient whereas in the case of pocket and/or lead infections the surgical removal of the device as well as longer antibiotic therapy becomes mandatory.[76,77]

Similarly to IE, the crucial role of imaging has been also recognized for pocket or CIED infections. Indeed, the Novel 2019 International CIED infection criteria have move to include both clinical data and imaging findings in patients work out.[77] Indeed, in case of CIED infections, the diagnosis is frequently difficult by both TTE and TEE, particularly when the question is the differentiation between noninfected thrombus and infected vegetation. The main echocardiography drawback is related to the fact that a negative result cannot exclude infection of the extracardiac portion of the device, the assessment of which is beyond the reach of echocardiography. Therefore, additional imaging modalities are necessary: ^{18}F-FDG-PET/CT(A), WBC SPECT/CT and CTA might be used in all cases when right-sided IE (particularly PVE) or CIED involvement are suspected.

From a technical standpoint the same procedures and considerations previously described [^{18}F-FDG-PET/CT and WBC scintigraphy in IE are also applicable for CIED infections. However, in the evaluation of CDRIE a 150-180 minutes delayed acquisition may be helpful in the detection of lead infection, improving sensitivity (61% vs 24%) without affecting specificity (79% vs 79%) and is therefore a suitable option in patients with a negative 1-hour standard acquisition and a high pretest probability of pacing lead infection.[34] Another difference worth a mention is the cut off for semiquantitative PET/CT assessment in CIED infections

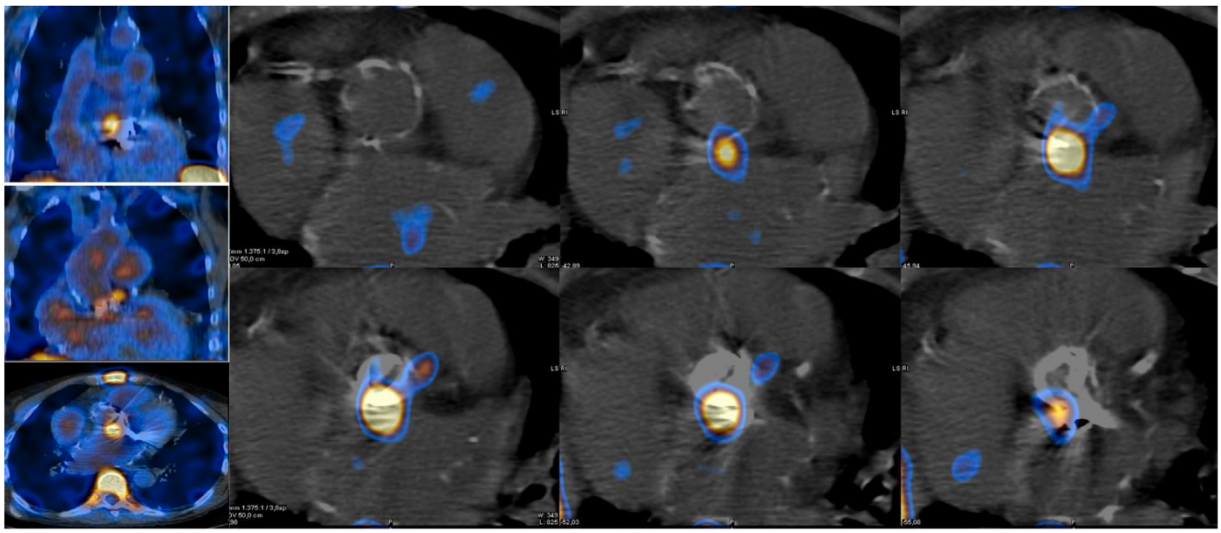

Figure 9 shows an example of WBC SPECT/CT findings (^{99m}Tc-HMPAO WBC, right panel top-down sagittal, coronal and transaxial superimposed view or the thorax at 6 hours after the WBR injection and left panel valve plane reconstructed superimposed images at different levels) in a patient with suspected late PVE after with mitral and aortic valve replacements. In this case a "possible IE" based on the Duke Criteria has been transformed in a "Definite IE" based on the 2015 ESC Criteria by adding WBC uptake as a major criteria to a positive blood culture (*Enterococcus faecalis*).

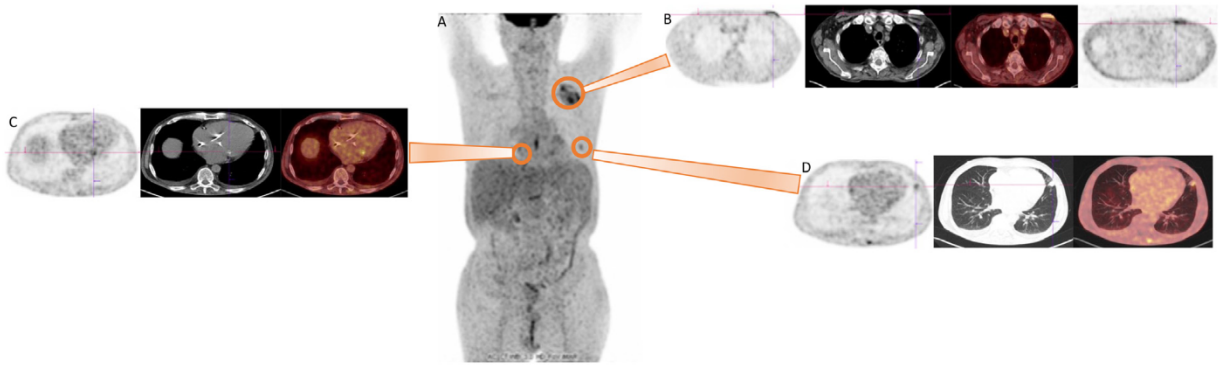

Figure 10 shows an example of ^{18}F-FDG-PET/CT in a patient with persistent fever despite proper antimicrobial treatment for MSSA mitral valve IE. Possible involvement of the CIED was suspected. The images (MIP in A) showed clear involvement of the CIED both at the pocket, the lead as well as lung embolism (B, C, and D from right to left transaxial emission, CT, superimposed PET/CT and non-attenuated corrected, respectively).

for which no general threshold has been identified despite the ratio to the mean hepatic blood pool has been proposed as the more reliable and repeatable index as compared to the ratio to mean mediastinal blood pool or lung.[37]

^{18}F-FDG-PET/CT(A) has proven useful in patients with evidence of pocket infection and negative microbiological and echocardiographic examination as well as in all cases of positive blood cultures but negative echocardiographic results. Overall, ^{18}F-FDG-PET/CT pooled sensitivity and specificity for CIED infection is 87% and 94%, respectively. However, with significant differences has been reported in the evaluation of pocket/generator infections for which sensitivity and specificity are of 93% and 98% and infections of the device leads for which the value of sensitivity and specificity significantly reduced to 65% and 88% as a direct consequence of the size of the lesions.[78,79] Overall, it can be safely assumed that ^{18}F-FDG-PET/CT is a reliable tool in identifying pocket infection, but a negative result at lead level cannot exclude IE, especially in the presence of disseminated disease. Moreover, ^{18}F-FDG-PET/CT has proven a prognostic value: the "Cold Closed Pocket" define as a concomitant endovascular infection and a pocket with no skin erosion/perforation or ^{18}F-FDG uptake is associated with all-cause mortality.[80] Figure 10 shows an example of ^{18}F-FDG-PET/CT in a patient with CIED infection.

WBC scintigraphy also plays a role in the diagnosis of CIED infections. In a recent systematic review, the range of sensitivity, specificity, NPV and PPV were reported respectively as 60%-93.7%, 88%-100%, 84.6%-93.9%, and 74%-100%.[81] It has been also been proven an association between a positive WBC scintigraphy and a worsening of the prognosis in term of increased in hospital mortality, complications and removal procedure.[82]

When ^{18}F-FDG-PET/CT and WBC are compared (48 patients with suspected CIED infection to both tests within 30 days), as expected, WBC showed better specificity (100%

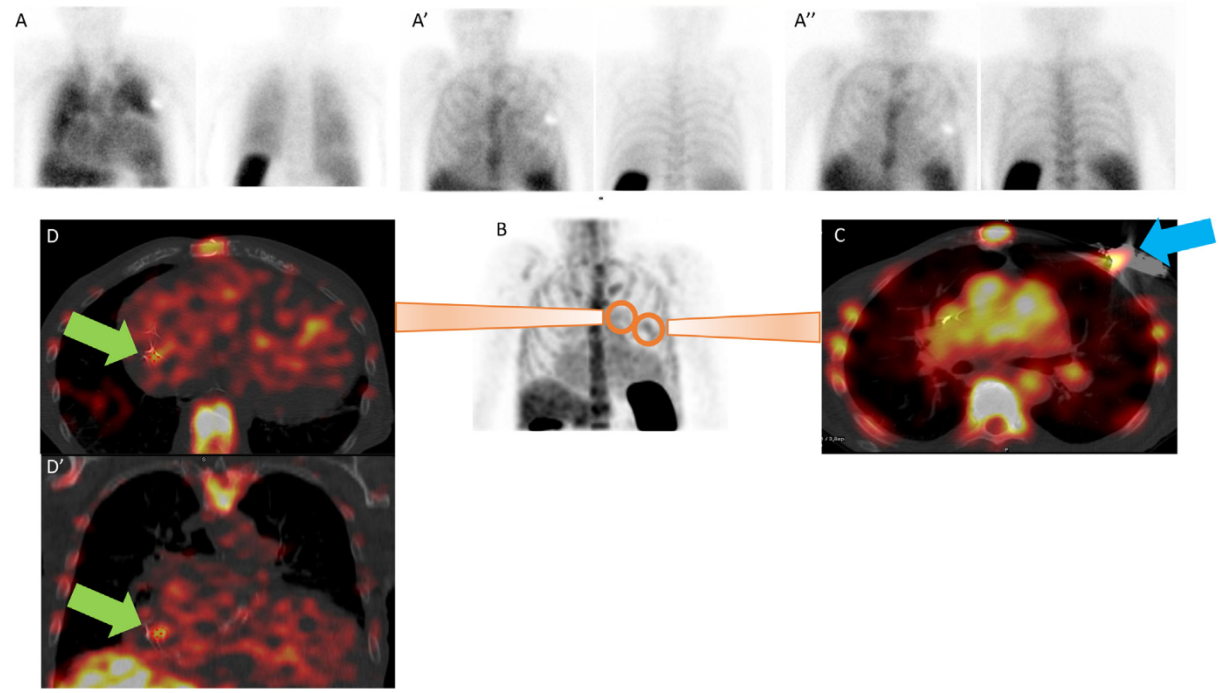

Figure 11 Example of WBC imaging (^{99m}Tc-HMPAO WBC) in CIED infection in a patient with suspected CIED infection. Planar images of the torax (at 30 minutes in A, 6 hours in A' and 20 hours in A") after the injection of the radiopharmaceutical show an area of pathological leukocyte accumulation that at SPECT/CT (MIP in B) which localized at the level of the ICD pocket in the deep posterior portion (blue arrow in C transaxial superimposed SPECT/CT) and at the level of the electro-catheter in the right intravascular and interatrial tract (green arrow in D and D', superimposed SPECT/CT transaxial and coronal views, respectively).

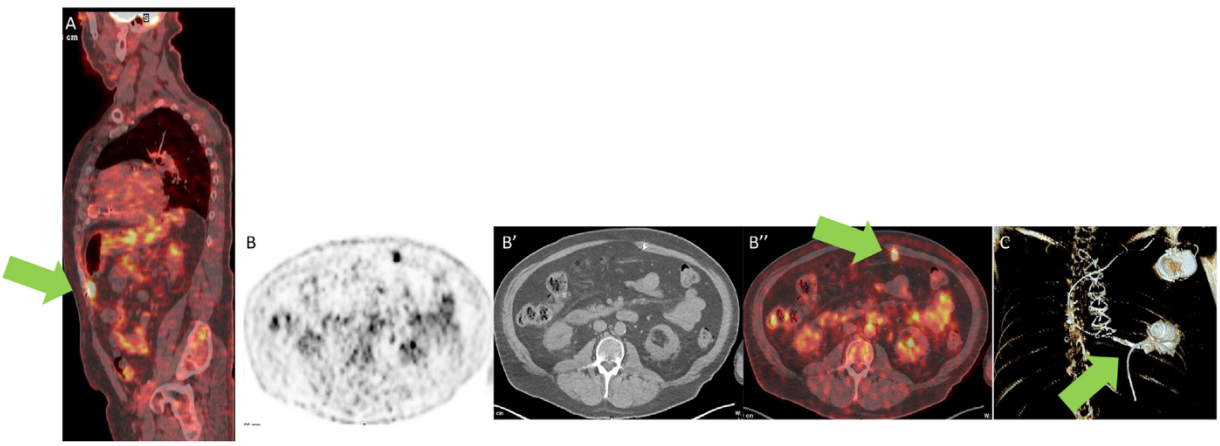

Figure 12 is presented an example of ^{18}F-FDG-PET/CT infection detection in a patient with sepsis. Images (A sagittal superimposed SPECT/CT, B-B' and B" trabinsaxial emission CT, superimposed PET/CT and reconstructed images D) show focal uptake at the level of the distal outflow-tract and drive-line.

vs 91% of ^{18}F-FDG-PET/CT) and PPV (100% vs 80% of ^{18}F-FDG-PET/CT), while ^{18}F-FDG-PET/CT presented higher sensitivity (80% vs 60%, WBC scintigraphy) and NPV (91% vs 85% of WBC scintigraphy).[83] In Figure 11, it is presented an example of WBC imaging in CIED infection.

^{18}F-FDG-PET/CTA and WBC SPECT/CT have also largely replaced ventilation-perfusion scintigraphy for the diagnosis of septic lung embolism, allowing the contemporary assessment of right- and left-sided valves and sites of distant embolisms and portal of entry also in case of CIED infections.

Recommended Diagnostic Strategy in CIED Infections

The status of the pocket at inspection is extremely important to guide the subsequent imaging management. In the presence of a clinically positive pocket echocardiograph is indicated, which often remains the only imaging tests needed. In all suspected CIED infection, even if only pocket infection is suspected blood cultures and echocardiographic should be performed. When negative in patients without evidence of

pocket infection, no additional imaging is needed. However, in patients with positive blood cultures and negative echocardiographic WBC imaging and ^{18}F-FDG-PET/CT have proved a significant impact for the final diagnosis and they were incorporated in the Novel 2019 International CIED infection criteria.[77]

LVADs

LVADs are more complex devices, consisting of several components. A control unit with its batteries, located outside the patient, is connected via a driveline through a small hole in the abdomen to the pump of the central device. The pump in turn is the connector between the inflow cannula (which receives the blood from the left ventricle) and the outflow graft (which redistributes the pumped blood to the systemic circulation via the aorta). Image interpretation may be challenging due to artefacts related to beam hardening and to the use of surgical adhesives to reinforce the inflow and outflow cannulas (it has to be mentioned that not all the surgical procedures requires these glues, therefore is advisable to properly check case by case).[84] Nevertheless, ^{18}F-FDG-PET/CT has proven to be a robust method to correctly identify both the infection at the driveline (sensitivity of 97% and specificity of 99%) and at the central device (sensitivity of 97% and specificity: 93%)[85] even though specificity may vary strongly among different studies.[86] ^{18}F-FDG-PET/CT is even superior to CT in predicting patient outcome.[87] By grouping patients according to the presence of central and peripheral infection or non-infection as shown by ^{18}F-FDG-PET/CT patient outcome differed significantly among central (cannula and pump pocket), peripheral (exit wound site or driveline), and noninfected groups. In particular, it has been shown a significantly higher mortality in FDG-avid central versus peripheral infection groups: none of the noninfected patients died; by contrast, 50% of the infected patients died.[88] In Figure 12, it is presented as example.

On the contrary, the possible role of WBC scintigraphy in LVAD infection is still under debate.[89] A retrospective study on 24 patients has showed similar results as in CIED: with sensitivity, specificity, PPV, NPV, accuracy of 95.2%, 66.7%, 95.2%, 66.7%, 91.6% for ^{18}FFDG-PET/CT and 71.4%, 100%, 100%, 33.3%, 75% for WBC scintigraphy.[90]

Recommended Diagnostic Strategy in LVADs Infections

When LVADs infection is suspected the initial imaging study are chest x-ray and echocardiography starting with TTE and in case of negative findings a TEE. If the suspicion is a pocket infection an abdominal US and/or chest and abdomen ceCT should be perfomed. In case of negative findings, but persistent high clinical suspicion of infection ^{18}F-FDG-PET/CT is the imaging modality of choice to prove or reject the final diagnosis.

Conclusion

^{18}F-FDG-PET/CT and WBC imaging are of utmost value in the diagnosis and management of IE, having demonstrated to be useful in suspected and definite IE. Their indications when to perform is different based on the type of endocarditis, that is, prosthetic versus native versus cardiac device related, the clinical status of the patient, and the possible limitations in the use of contrast agents. The selection of the most appropriate imaging test as well as the integration of the imaging results into the patients' clinical management should be made in light of the endocarditis team in which the nuclear cardiac imaging experts is actively involved.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests.

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