Diagnostic Performances of Nuclear Imaging in Infective Endocarditis

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Contributor: Nidaa Mikail

Infective endocarditis (IE) is a life-threatening disease with stable prevalence despite prophylactic, diagnostic, and therapeutic advances. While echocardiography remains the first line imaging technique, especially in native valve endocarditis, the incremental value of two nuclear imaging techniques, 18F-fluorodeoxyglucose positron emission tomography with computed tomography (18F-FDG-PET/CT) and white blood cells single photon emission tomography with computed tomography (WBC-SPECT), has emerged for the management of prosthetic valve and CIED IE.

infective endocarditis | native valve endocarditis | prosthetic valve endocarditis | cardiac implanted electronic device | left ventricular assistance device | vascular graft infection | nuclear medicine | scintigraphy | 18F-FDG | positron emission tomography | white blood c

1. Introduction

Despite significant diagnostic and therapeutic progresses, infective endocarditis (IE) remains associated with high morbidity and mortality [1][2]. IE affects 3–10/100,000/year in developed countries [3], and its incidence is growing in the United States [4]. IE-related mortality reaches 20% at 30 days [5], increasing to up to 40–50% at late follow-up [6][7]. The number of implanted cardiac devices is increasing at a rapid pace, in particular in elderly patients with multiple comorbidities. This population has a high prevalence of sepsis related to secondary infection of the implanted material [1][3][7]. The mortality of IE is related to local complications, such as valve degradation and periannular abscesses, and to distant embolization, which may be fatal, in particular in case of septic embols in the brain [3]. IE treatment may require urgent cardiac surgery, which is associated with a high risk of mortality in this context, even if performed at an early stage of the disease [8][9]. The prognosis remains particularly poor in patients with IE-related stroke, despite adequate reperfusion therapy [10][11].

The diagnosis of IE is challenging. Establishing an IE diagnosis is currently based on the Duke-Li criteria (**Table 1**), which combine clinical, biological/microbiological, and imaging parameters [12]. Based on these criteria, the diagnosis of IE is classified as *definite*, *possible*, or *rejected* (**Table 2**). Given the non-specific value of most clinical and biological criteria, imaging plays a central role in IE management. While echocardiography remains the mainstay exam, in particular for native valve endocarditis (NVE), its diagnostic performance is lower in prosthetic valves endocarditis (PVE) [13], because of acoustic shadowing due to the material and the difficulty to identify perivalvular infection [14]. This also holds true for transesophageal echocardiography (TEE), which despite having higher performances than transthoracic echography (TTE), does not allow ruling out PVE with high confidence in case of negative findings [15][16]. This can delay the diagnosis and the treatment initiation, resulting in poorer clinical outcome [17]. Thus, advanced noninvasive imaging techniques are increasingly used in the management of IE, particularly in case of discordance between the clinical presentation and echocardiography, or in situations where the diagnosis is deemed *possible* based on the Duke-Li criteria [18]. Nuclear medicine imaging techniques, i.e., ^{18}Fluor radiolabeled fluorodeoxyglucose positron emission tomography combined with computed tomography (^{18}F-FDG-PET/CT), and white blood cell (WBC) scintigraphy provide high sensitivity (Se) for the detection of infective foci and have demonstrated their incremental value over TEE for the diagnostic of PVE (**Table 3**). The European guidelines for the management of IE have indeed modified the Duke-Li criteria, incorporating intracardiac findings from ^{18}F-FDG-PET/CT and WBC scintigraphy as major criteria of IE [12]. Following on the modified Duke-Li criteria and the European Society of Cardiology criteria for IE, the International CIED Infection Criteria have also been developed in 2019 [19] (**Table 4**). Non-nuclear medicine imaging techniques, i.e., cardiac computed tomography angiography and cardiac magnetic resonance imaging also play a critical role in the diagnosis of IE. The main specificities of each technique are listed in **Table 5**.

Table 1. Modified Duke-Li criteria for the diagnosis of valve infective endocarditis.

Major Criteria	1. Microbiological Criteria
	a. Microorganisms typical of IE evidenced from two separate blood cultures
	- Viridans streptococci, Streptococcus gallolyticus (Streptococcus bovis), HACEK group, Staphylococcus aureus OR - Community-acquired enterococci, in the absence of a primary focus OR
	b. Microorganisms consistent with IE evidenced from persistently positive blood cultures:
	- ≥2 positive blood cultures of blood samples collected >12 h apart OR

	- 3 or a majority of ≥4 separate positive blood cultures (first and last collected > 1 h apart) OR - Single positive blood culture for Coxiella burnetii or phase I IgG antibody titre >1:800
	2. Imaging Criteria
	a. Echocardiogram positive for IE showing one/several of the following typical findings
	- Vegetation - Abscess, pseudoaneurysm, intracardiac fistula - Valvular perforation or aneurysm - New partial dehiscence of prosthetic valve
	b. *Nuclear medicine imaging positive for IE, i.e., abnormal uptake around the site of prosthetic valve implantation*
	- *On ^{18}F-FDG PET/CT if the prosthesis was implanted >3 months* OR - *On radiolabeled WBC-SPECT/CT*
	c. *Cardiac CT*
	- *Paravalvular lesions*
Minor Criteria	1. Predisposing condition such as heart condition, or intravenous drug use
	2. Fever defined as temperature >38 °C

	3. Vascular phenomena *including those detected only by imaging,* major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway's lesions
	4. Immunological phenomena: glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor
	5. 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

18 ...nography; ...; SPECT: ...*difications to the Duke-Li criteria implemented in the 2015 European Society of Cardiology guidelines.* Adapted from Habib et al. [12].

Table 2. Definition of infective endocarditis according to the modified Duke criteria. Adapted from Habib et al. [12].

Definite IE	Histopathological Criteria
	Demonstration of a microorganism from a culture, a cardiac vegetation, an embolized vegetation, or an intracardiac abscess, OR Demonstration of an active endocarditis from a vegetation or an intracardiac abscess
	Clinical Criteria
	2 major criteria, OR 1 major criterion AND 3 minor criteria, OR 5 minor criteria
Possible IE	1 major criterion AND 1 minor criterion, OR 3 minor criteria
Rejected IE	Firm alternate diagnosis, OR

	Resolution of symptoms within ≤4 days of antibiotherapy, OR No pathological evidence of IE (surgery or autopsy) after ≤4 days of antibiotherapy, OR No criteria for *possible IE* as defined above

Table 3. Comparison between ^{18}F-FDG PET/CT and WBC SPECT/CT.

	Advantages	Drawbacks
^{18}F-FDG-PET/CT	High sensitivity for PVE and device-related IE (CIED pocket and extracardiac lead)	Moderate sensitivity for NVE and intracardiac lead CIED-IE
	Good spatial resolution (4–5 mm)	Moderate specificity for infection
	Short protocol (preparation and acquisition <2 h)	Requires a specific diet to suppress the physiological cardiac uptake of ^{18}F-FDG
	Whole-body imaging in 15–20 min. allowing for the detection of device infection and septic emboli	Post-surgery inflammation in case of PVE (cautious interpretation 1–3 months after surgery)
	Identification of possible portal of entry	Limited sensitivity in organs with high FDG uptake, especially the brain
	Identification of alternate diagnosis for infectious or inflammatory syndrome than IE	Possible false-negative results in small vegetations and/or after prolonged antibiotherapy
		Radiation exposure
WBC-SPECT/CT	High specificity	Moderate sensitivity, especially for CIED-IE
	No need for specific diet nor interaction with sugar levels for imaging	Long and complex procedure requiring blood handling

Relatively low spatial resolution (8–10 mm)	Possible false-negative results in small vegetations and/or prolonged antibiotherapy
Lower imaqe quality (late imaging time point and SPECT acquistions)	Radiation exposure
Potential detection of septic emboli, but lower performance than ^{18}F-FDG-PET/CT	Radiation exposure

^{18} [illegible] nplantable electronic device; CT: computed tomography; IE: infective endocarditis; NVE: native valve endocarditis; PVE: prosthetic valve endocarditis; SPECT: single photon emission computed tomography; WBC: white blood cell.

Table 4. Novel 2019 International Criteria for the diagnosis of CIED-IE.

Major Criteria	1. Microbiological Criteria
	a. Microorganisms typical of CIED-IE and/or IE (Coagulase-negative staphylococci, Staphylococcus aureus)
	b. Microorganisms typical of IE evidenced from two separate blood cultures
	- Viridans streptococci, Streptococcus gallolyticus (Streptococcus bovis), HACEK group, Staphylococcus aureus OR - Community-acquired enterococci, in the absence of a primary focus OR
	c. Microorganisms consistent with IE evidenced from persistently positive blood cultures:
	- ≥2 positive blood cultures of blood samples collected >12 h apart

	OR - 3 or a majority of ≥4 separate positive blood cultures (first and last collected >1 h apart) OR - Single positive blood culture for Coxiella burnetii or phase I IgG antibody titre >1:800
	2. Imaging Criteria
	a. Echocardiogram positive for CIED-IE:
	clinical pocket/generator infectionlead-vegetation
	b. *Nuclear medicine imaging positive for CIED-IE, i.e., abnormal uptake around pocket/generator site or along leads*
	- *On ^{18}F-FDG PET/CT (caution in case of recent implants)* OR - *On radiolabeled WBC-SPECT/CT*
Minor criteria	1. Predisposing condition such as heart condition or intravenous drug use
	2. Fever defined as temperature >38 °C
	3. Vascular phenomena *including those detected only by imaging,* major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway's lesions
	4. 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 CIED-IE

18 18 ...nography; HACEK: Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella, Kingella; CIED: cardiac implantable electronic device; IE: infective endocarditis; SPECT: single photon emission computed tomography; WBC: white blood cell.

Text in italic font indicates the modifications to the Duke-Li criteria implemented in the 2015 European Society of Cardiology guidelines. Adapted from Blomström-Lundqvist [19].

Table 5. Main advantages/limitations of nuclear/morphological techniques for the diagnosis of IE.

	Echocardiography	CCTA	Cardiac MRI	^{18}F-FDG-PET/CT	WBC-SPECT/CT
Diagnostic Performances for IE Diagnosis	- High spatial and temporal resolution - High diagnostic performances in NVE, lower in PVE	- High spatial and temporal resolution - Good performances for the detection of perivalvular lesions in PVE	- Conflicting data about performances in NVE - Limited data about performances in mechanical PVE	- High sensitivity in PVE - Low sensitivity in NVE	- High specificity in PVE and NVE - Low sensitivity in NVE
Evaluation of Cardiac Complications	- Allows precise evaluation of valvular dysfunction and lesions due to IE	- Allows evaluation of perivalvular lesions (abscess-pseudoaneurysm)	- Allows evaluation of myocardial and valvular function	- Limited evaluation of perivalvular extension	- Limited evaluation of perivalvular extension
Cardiac Presurgical Assessment	- Assessment of cardiac function and evaluation of aortic root	- Allows to evaluate aortic root and coronary arteries	- Assessment of cardiac function and aortic root	-	-
Extracardiac Assessment	- No extracardiac workup	- Detection of peripheral embols if combined with wholebody CTA	- No extracardiac workup	- Detection of septic embols, septic aneurysms and protal of entry	- Detection of septic embols

	Echocardiography	CCTA	Cardiac MRI	^{18}F-FDG-PET/CT	WBC-SPECT/CT
				with high sensitivity	
Contra-Indications	- No contraindication for TTE - Esophageal pathology for TEE	- Pregnancy, allergy to iodinated contrast media, severe renal insufficiency	- Pregnancy, close monitoring in presence of ICD or PM, CI for some old metallic prosthesis, claustrophobia, severe renal insufficiency	- Pregnancy	- Pregnancy
Availability	- Widely and easily available	- Widely available	- Moderate availability	- Moderate availability	- Limited availability
Limitations and drawbacks	- Operator dependent analysis - Metallic artifacts in PVE	- Metallic artifacts in PVE, CIED - Difficulty to discriminate vegetation from thrombus and hematoma from abscess based only on morphological imaging	- Metallic artifacts in PVE - Cardiac and respiratory artifacts	- Lack of specificity - Need for prolonged fasting and dedicated cardiac preparation	- Complex handling of blood products

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2. Rationale for the Use of Nuclear Medicine Imaging

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2.1. F-FDG PET

^{18}F-FDG is a radioactive analog of glucose, in which a hydroxyl group has been replaced by ^{18}F, a positron-emitting radionuclide [20]. Similar to glucose, ^{18}F-FDG enters the cell via GLUT membrane transporters, thereby indicating cells with increased metabolic activity. However, unlike glucose, ^{18}F-FDG does not undergo further glycolysis, which is blocked by ^{18}F. Consequently, ^{18}F-FDG accumulates in the cell—a phenomenon coined metabolic trapping. Therefore, the concentration of ^{18}F-FDG reflects the actual concentration of glucose in the tissue, enabling an absolute quantification of its metabolic activity. Owing to this, the higher the metabolic activity of the tissue, the higher the accumulation of ^{18}F-FDG and the detected signal on the PET images [21]. ^{18}F-FDG, which has initially arisen in the field of oncology, is nowadays used routinely for inflammatory and infectious diseases [22].

In the setting of cardiac imaging, an important parameter is the metabolic fuel of the myocardium on the day of the exam. Indeed, the myocardial metabolism consists mainly of a balance between glucose and free fatty acids [23]. Depending on several physiological and pathological factors, the cardiac metabolism can predominantly switch to glucose, a situation characterized by a diffuse myocardial ^{18}F-FDG uptake. A diffuse myocardial ^{18}F-FDG uptake can mask a pathologic focal ^{18}F-FDG uptake, for example located on a cardiac valve, thereby inducing false negatives. To avoid this, several tools have been developed, considering prior fasting conditions, diet, and blood insulin levels [24]. Carbohydrate consumption prior to the exam leads to increased insulinemia, which activates the expression of GLUT transporters at the surface of cardiomyocytes, favoring a predominantly glucose heart metabolism. Conversely, a high fatty diet will inhibit glucose metabolism and switch the cardiomyocyte metabolism towards free fatty acids consumption. Therefore, the European guidelines recommend specific cardiac preparation before cardiac ^{18}F-FDG-PET.

2.2. WBC Scintigraphy

Radiolabeling leukocytes allows tracking their accumulation in infectious sites, making WBC scintigraphy a widely used tool for the detection of infection. Two main radiotracers are available to label WBC: ^{111}Indium-oxine (^{111}In), which is the first historical tracer in this indication, and ^{99m}Technetium-hexamethylpropyleneamine oxime (^{99m}Tc-HMPAO) [25][26]. However, ^{99m}Tc-HMPAO is currently preferred, owing to its higher image quality (higher signal/noise ratio and spatial resolution), and lower radiation exposure compared to ^{111}In [24]. Both ^{99m}Tc-HMPAO and ^{111}In are lipophilic, a property which enables them to penetrate through the WBC membrane, before attaching to cytoplasmic components. To selectively label WBC, a sample of ca. 50 mL of blood is collected; WBC (either only granulocytes alone or all leukocytes) are separated from other blood cells; cells are incubated with the radiolabeled tracer (^{111}In-oxine or ^{99m}Tc-HMPAO) and then reinjected in a vein of the patient. This whole procedure should be performed in sterile conditions. In addition, it is recommended to avoid radiolabeling WBC of different patients the same day on the same location, to prevent transfusion accident [25][26].

3. Diagnostic Performances

3.1. ^{18}F-FDG PET/CT

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The performances of ^{18}F-FDG-PET/CT highly depend on the type of IE [27]. Therefore, we will distinguish in the following section the different clinical situations.

3.1.1. Native Valve Endocarditis

The literature that specifically evaluated the role of ^{18}F-FDG-PET/CT in NVE is limited. A recent meta-analysis identified seven studies addressing this issue, amongst which only two focused solely on patients with a suspicion of NVE, the other consisting of mixed populations of suspected NVE and PVE [28].

In practice, echocardiography outperforms ^{18}F-FDG-PET/CT for the detection of intracardiac evidence of IE. In a prospective study carried out with 120 patients with suspected IE, including 34 NVE, TEE showed a 95.0% Se for the detection of NVE versus 17.0% for ^{18}F-FDG-PET/CT [27]. Nevertheless, the addition of ^{18}F-FDG-PET/CT may be useful in patients with NVE to detect peripheral FDG uptake corresponding to septic emboli that are often missed by conventional imaging and are considered as a minor criterion of IE in the modified Duke-Li criteria [12]. Consequently, adding ^{18}F-FDG-PET/CT in patients with NVE improves the Se of the modified Duke-Li criteria without affecting its high Sp [29][30][31][32]. The prospective multicenter TEPvENDO study reported that, in addition to reclassifying patients with NVE, ^{18}F-FDG-PET/CT resulted into a change in the therapeutic management (antibiotic or surgical strategy) in about one third of patients [31].

Several explanations account for the low Se of ^{18}F-FDG-PET/CT in NVE. While PVE are often related to inflammatory perivalvular abscesses, NVE frequently consist of small (<10 mm) fibrotic vegetations on the valve, with low inflammatory infiltration [1][30]. The relatively low spatial resolution of PET imaging (~5mm) represents an important limitation for the detection of small vegetations with continuous cardiac movements. The Se of ^{18}F-FDG-PET may be improved by respiratory and ECG-gated cardiac PET acquisitions compared to static PET acquisitions [33]. The sensitivity of ^{18}F-FDG-PET imaging for cardiac infective foci is further decreased in case of failure to suppress ^{18}F-FDG uptake in the myocardium. In a study by Abikhzer et al., the exclusion of patients with inadequate myocardial ^{18}F-FDG suppression from the analysis resulted in an increase of the Se of ^{18}F-FDG-PET/CT with preserved high Sp [29]. Because of the low Se of ^{18}F-FDG-PET and the high Se of TEE, ^{18}F-FDG-PET/CT is not recommended as a first-line exam for the diagnosis of NVE [12], but may help in case of inconclusive TEE.

3.1.2. Prosthetic Valve Endocarditis

The literature on the role of ^{18}F-FDG-PET/CT for the diagnosis of PVE is increasing at a rapid pace [34][35][36][37]. A recent meta-analysis including 15 studies with 333 cases of PVE showed respective pooled Se and Sp of 86% and 84%, and respective PLR and NLR of 3.23 and 0.21 with a diagnostic OR of 22.0 [34]. Interestingly, the performances of ^{18}F-FDG-PET/CT are comparable for mechanical and biological prosthetic valves [38][39][40].

The use of antibiotics prior to imaging influences the diagnostic performance of ^{18}F-FDG-PET imaging in IE. The intensity of systemic and local inflammation decreases in parallel to the duration of antibiotherapy, resulting in false-negative ^{18}F-FDG-PET/CT results [41][42][43]. The timing of imaging after prosthetic valve surgery is also

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important [24][44]. Indeed, the healing of tissue after surgery generates local inflammation, which can lead to false positive findings. In addition, surgical adhesives and glue induce a sustained inflammatory reaction in the surgical site [45], which may persist several years after prosthetic valve implantation [41][46][47][48]. Consequently, the European Guidelines recommend performing ^{18}F-FDG-PET/CT after an empirical minimal delay of 1–3 months following surgery [12][47], a delay that can be reduced to <3 weeks in case of non-complicated valve surgery and depending on the risk of infection [24].

Given its high sensitivity and specificity, the 2015 European guidelines recommend ^{18}F-FDG-PET/CT in patients with suspected PVE and diagnostic uncertainty, i.e., PVE classified as *possible* or as *rejected but with persistent high clinical suspicion* based on the Duke criteria [12].

An alternative to ^{18}F-FDG-PET/CT in case of diagnostic uncertainty is computed tomography angiography (CTA) [12], which can show vegetations on valve leaflets [49]. However, ^{18}F-FDG-PET/CT can detect early inflammatory signs before the apparition of anatomical modifications [41]. Combining ^{18}F-FDG-PET with CTA improves the diagnostic performances compared to PET with nonenhanced CT (respective Se, Sp, positive predictive value (PPV) and negative predictive value (NPV) of 91%, 90.6%, 92.8%, and 88.3%, versus 86.4%, 87.5%, 90.2%, and 82.9%). In addition, ^{18}F-FDG-PET/CTA significantly reduces the rate of doubtful cases from 20% to 8% [39]. CTA is in fact particularly performant to detect complications of PVE, such as pseudoaneurysms and perivalvular abscesses [41][50]. CTA also improves the visualization of valvular thrombi/vegetation as well as the detection of septic emboli [24]. Therefore, ^{18}F-FDG-PET/CTA is interesting to detect complications and coronary arteries involvement prior to surgical treatment [41]. Transcatheter-implanted aortic valve (TAVI) procedure is an increasingly used method of valve replacement, especially in the elderly population [51]. TAVI can be complicated by IE [52], a situation where ^{18}F-FDG-PET/CTA could be useful. Indeed, detection of TAVI-related IE by echocardiography is limited due to metal artifacts. A recent study showed that while ^{18}F-FDG-PET with nonenhanced CT had a low Se to diagnose TAVI-related IE (58%), adding CTA significantly improved the Se (83.3%), reclassifying patients with *possible* IE to either of the two other groups (*definite* or *rejected* IE) [53].

3.1.3. Cardiac Implanted Electronic Device Infective Endocarditis (CIED-IE)

Several studies have specifically investigated the performances of ^{18}F-FDG-PET/CT for the diagnosis of CIED-IE [54][55][56][57][58][59]. Two recent meta-analyses reported respective Se 83% and Sp 89%, and Se 87% and Sp 94% [36][54]. Although ^{18}F-FDG-PET/CT considerably increases the diagnostic accuracy of the modified Duke criteria, its overall Se remains low in CIED-IE [43][60]. In fact, a distinction must be made between CIED-IE involving the extracardiac components of the device (pocket, extracardiac portion of the leads) and CIED-IE involving the intracardiac portion of the leads [44]. In case of insufficient metabolic preparation, the myocardial uptake of ^{18}F-FDG may mask a lead infection, resulting in false negatives [59]. Comparing the performances of ^{18}F-FDG-PET/CT in these two settings, Jerónimo et al. reported a Se 72.2% and Sp 95.6% for the diagnosis of pocket infection vs. Se 38.5% and Sp 98.0% for lead infection, despite adequate myocardial suppression in both groups [61]. This is in line with the results of a meta-analysis, reporting the results of subgroup analysis obtained from studies incorporating both pocket and lead IE and showing respective Se 96% and Sp 97% for pocket IE vs. Se 76% and Sp 83% for

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lead IE [54]. Additional explanations for the false-negative findings in lead-infections include prior antibiotherapy and the small size of lead vegetation [61]. In case of suspicion of lead infection, delayed acquisitions (3 h post-injection) could improve the diagnostic accuracy compared to standard imaging (70% vs. 51%, respectively) [62]. Additionally, combining ^{18}F-FDG-PET with CTA performs better than nonenhanced CT, reclassifying more patients initially deemed *possible* IE and detecting more patterns of IE than nonenhanced CT [39][63]. Furthermore, ^{18}F-FDG-PET/CTA may help distinguishing infectious from inflammatory periprosthetic 18F-FDG uptake [64].

3.1.4. Left Ventricular Assistance Device Infective Endocarditis (LVAD-IE)

Left ventricular assistant devices (LVAD) are a circulatory support therapeutic option for end-stage heart failure, often in anticipation of heart transplantation. LVAD usually consist of two main parts, which both can be infected: a pump implanted at the left ventricle apex and a driveline. Device infection can occur in about one out of five patients with LVAD [65], and is associated with high morbi-mortality [66]. Diagnosing LVAD-IE can be challenging, and ^{18}F-FDG-PET/CT can be helpful in this setting [67]. In a recent meta-analysis by Ten Hove et al. [68], pooled results of 8 studies including 256 exams found Se, Sp, LR−, LR+, and diagnostic OR of 95%, 91%, 0.14, 3.54, and 38.43 for the diagnosis of either pocket and/or driveline infection, respectively. Similarly high performances were reported by Tam et al., with respective Se and Sp of 92% and 83%, and an AUC of 0.94 [69]. Focusing on driveline infection, ^{18}F-FDG-PET/CT's corresponding performances were 97%, 99%, 3.93, 0.13, and 92.46, respectively. For pump infection, the corresponding diagnostic performances were 97%, 93%, 0.12, 5.56, and 49.43. ^{18}F-FDG-PET/CT stigmas of LVAD IE are also associated with an increased mortality, in particular in case of central infection [70]. Interestingly, using the metabolic volume performs better than SUVmax and visual grading for the diagnosis of LVAD-IE [71].

3.1.5. Vascular Graft Infection

The diagnosis of vascular graft infection (VGI), which includes native vessel and endoprosthetic infections, is challenging. Symptoms are often nonspecific and obtaining direct culture material from the vessel is risky. ^{18}F-FDG-PET/CT can help in this setting [72][73], with respective pooled Se and Sp of 90–95% and 59–81%, depending on the diagnostic criteria [74]. Comparing three different diagnostic methods, i.e., ^{18}F-FDG uptake intensity, ^{18}F-FDG pattern, and SUVmax, a focal ^{18}F-FDG uptake pattern is the most accurate method for diagnosis of VGI [74].

3.2. WBC Scintigraphy

3.2.1. PVE and NVE

Data about the usefulness of WBC scintigraphy in IE are limited and mostly retrospective and mono-centric. In a landmark study by Erba et al. [75] in 51 patients with suspected IE (16 on native valves, 35 on prosthetic valves), WBC scintigraphy showed a 90% Se and a 100% Sp. No differential analysis based on the type of valve (NVE, PVE) was reported in this study. In a preliminary study, we reported the added value of WBC for PVE with inconclusive TTE [76]. In a subsequent study performed in 39 patients with suspected PVE, WBC scintigraphy showed respective Se, Sp, PPV, NPV, and accuracy of 64%, 100%, 100%, 81%, and 86% [77]. The high Sp of WBC scintigraphy was confirmed in three subsequent studies, with respective Sp of 88%, 100%, and 87% [43][78][79]. In

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the study by Kooshki et al. where all WBC-SPECT results were confronted to surgical findings, adding the results of WBC-SPECT to the modified Duke-Li score correctly re-classified 25% of patients from *possible* to *definite* PVE [78]. Interestingly, this study showed that the intensity of ^{99m}Tc-WBC uptake depends on the type of infection, with high signal in abscesses and low signal in non-abscessed lesions, which could partly explain the relatively low Se of WBC scintigraphy [78]. The performances of WBC scintigraphy can also be decreased by former initiation of antibiotherapy. Consequently, WBC scintigraphy should be performed as early as possible to avoid false negatives [43]. In addition, high intensity uptake is associated with a worse outcome, which could have prognostic value and help defining the best management strategy [76][79]. SPECT-based imaging of IE could also benefit from the development of cardiac-dedicated cameras based on cadmium-zinc-telluride (CZT) detectors. CZT cameras offer higher sensitivity than classical Anger cameras thanks to a higher photon counting sensitivity and to the heart-focused disposition of detectors [80][81]. Compared to planar WBC-SPECT, CZT WBC-SPECT significantly improves the detection of WBC signal in patients with IE, with respective Se of 83% vs. 58%, and Sp of 95% vs. 70% [82]. A meta-analysis pooling the results of studies performed with either planar SPECT [75][76][77] and CZT [82] cameras found respective pooled Se and Sp of 86% and 97%, and an excellent accuracy with an area under the curve of 0.957 [36].

3.2.2. CIED-IE, LVAD-IE and VGI

Few studies have specifically investigated the diagnostic value of WBC scintigraphy in CIED-IE and/or in LVAD-IE [43][60][83][84]. The reported diagnostic performances range within Se 60–93.7% and Sp within 81–100%. The additional value of WBC-SPECT/CT is particularly marked in case of CIED-IE deemed as *possible* based on the Duke-Li criteria [43]. Adding the results of WBC-SPECT to the Duke criteria improved the diagnostic accuracy from 83% to 88% [60]. A small study performed in patients with LVAD-IE showed a 100% Se with no false positive results [85]. A more recent study reported performances comparable to those in CIED-IE, with respective Se, Sp, PPV, NPV, and accuracy of 71.4%, 100%, 100%, 33.3%, and 75% [83]. In the setting of suspected VGI, the diagnostic performances of ^{99m}Tc-WBC-SPECT range within Se 82–100% and Sp 75–100% [84]. The performances remain in case of late or a low-grade late prosthetic VGI [86] and when SPECT/CT is performed within the first month after surgery [87].

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