

REVIEW ARTICLE

Detection of Device Infection Using Nuclear Cardiology Imaging

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Abstract

Cardiovascular device-related infections include infections occurring at heart valve prosthesis, cardiovascular implantable electronic devices, left ventricular assist device catheters and vascular graft. Complications, including infections associated with implanted medical devices have been increased. The diagnosis of cardiovascular device-related infections is challenging since symptoms and signs are often inconclusive and clinical presentations may be extremely heterogeneous. Imaging using the “3M” approach (i.e., multimodality, multi-tracers and multidisciplinary) has been integrated into the traditional diagnostic criteria to fill such uncertainty gap with information on the biochemical burden of these infections. The present review aimed to provide an overview of the main applications and results of nuclear cardiology imaging in cardiovascular device-related infections.

Keywords: ¹⁸F-FDG PET/CT, Cardiovascular infections, Multimodality imaging, SPECT/CT

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Cardiovascular device infections (CVSDI) include infections occurring at heart valve prosthesis (PVE), cardiovascular implantable electronic devices (CIED), left ventricular assist device (LVAD) and vascular graft. The use of cardiovascular implantable devices and surgical biomaterials has increased in the last decades and it will increase over the next years due to progresses in medicine, the aging of society and the expanding indications for cardiovascular implants. Accordingly, complications associated with implanted medical devices have been grown (1). CVSDI are of increasing concern. The severity of the infection depends upon the type of pathogen, the biofilm's characteristics, the type and the location of the biomaterial, and the host defense status (1, 2). The diagnosis is extremely challenging due to an extremely heterogeneous clinical picture characterized by aspecific signs and symptoms. The diagnosis relies on careful patient's

assessment according to specific diagnostic flow-chart. A multidisciplinary approach is necessary and has been shown reducing mortality (1, 3-5). Strategies to facilitate early diagnosis are crucial for a favorable clinical outcome. The present review aims to provide an overview of the main applications, technical aspects and results of nuclear cardiology imaging in CVSDI.

Nuclear cardiac imaging in cardiovascular device infections

Nuclear medicine offers useful tools to evaluate patients with suspected or confirmed infectious and inflammatory processes (4). Their role relies on the strength of noninvasive imaging tests that targeting molecular processes provide functional and metabolic information early during the course of the disease. Drawbacks of nuclear medicine procedures related to either the use of radiolabeled tracers or to their rather

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low resolution have been overcome to a large extent during the last decade by the introduction of hybrid imaging (1, 4, 6).

The “3M” approach (i.e. multimodality, multi-tracers and multidisciplinary) has been recently proposed in CVSDI to integrate the traditional diagnostic criteria (1). A multidisciplinary team to discuss laboratory results, multimodality imaging findings and patients’ management has been successfully introduced for the optimal management of cardiovascular infections, resulting in a lower in-hospital and 1- and 3-year mortality reduction across Europe (7-12). Within this Team, the role of the imager has grown, giving the importance of his/her active contribution in the clinical decision making process. Deep knowledge and expertise of both the technical and clinical aspects of multimodalities imaging in cardiovascular infections are more and more important for an active and successful contribution (1, 3).

Nuclear cardiology imaging, including autologous radiolabeled leukocytes (WBC) SPECT/CT and ^{18}F -FDG-PET/CT has been successfully applied in CVSDI diagnosis, particularly in patients not fulfilling the traditional diagnostic criteria for a definitive diagnosis (13-15). The technical aspects of nuclear cardiology imaging in CVSDI are challenging and requires specific patients’ preparation and ad-hoc imaging protocols. An extensive review of these procedures is provided in the Recommendation on nuclear and multimodality imaging in IE and CIED (16). In case of WBC imaging procedures for patient’s preparation, radiolabeling and injection are standard. Acquisition protocol the images should always include SPECT/CT, being aware of including all the portions of the device and of any other additional region of interest. In case of abdominal vascular prosthesis, dynamic acquisition and images within the first 2 hours post injection may be useful. Images with and without attenuation correction reconstruction must be analyzed. The criterion for positivity is a time-dependent increase in radioactivity of an area of abnormal WBC uptake between early and delayed images (17, 18). False positive results, mainly in case of early infections, are quite rare. On the other hand, false negative results may be observed in case of infections caused by low-WBC recruiting microorganism or very small site of infections (i.e. CIED infections along the leads). When interpreting images, antimicrobial treatment intake should always be considered since it may affect the WBC uptake (1, 18-20). In case of ^{18}F -FDG-PET/CT the most relevant issues concern patient’s preparation and protocol acquisition (1, 16). The physiological ^{18}F -FDG myocardial uptake should be the lower as possible in suspected cardiac infections and to achieve that, specific protocols for patient’s preparation should be used (1, 16). All possible sources of doubtful cases and misdiagnosis should be avoided, primarily the presence of a high physiological myocardial background that could mask some

pathological area, especially if small. 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, and avoid vigorous exercise during the 24 h before the examination are interventions recommended with high evidence for cardiac ^{18}F -FDG-PET/CT (16). Blood glucose should be settled to the lowest possible level, even though hyperglycemia not represents an absolute contraindication (neither diabetes nor hyperglycemia at the time of the study has been demonstrated to increase PET/CT false-negative rate in case of infection and inflammation) (1, 21). Total body images (i.e. from skull base to mid thighs) should be acquired 45-60 minutes after ^{18}F -FDG injection. Whole body images including the lower limbs, might be useful to detect some complications (1, 16, 22). An additional bed on the cardiac region is foreseen, in particular if gated images and diagnostic angio-CT (CTA) scan. Images with and without attenuation correction reconstruction must be analyzed. Techniques to reduce metal artefact may be useful even though some impact on image quality may occur (1, 23). In case of increased ^{18}F -FDG uptake area(s), the pattern (focal, linear, diffuse), the intensity, and the relationship to physiologic tracer distribution should be considered and compared to morphologic information provided by CT or CTA. Semi-quantitative analysis should be carefully used to interpret images since SUV and other parameters are not validated in the domain of inflammation and infection (1, 16). Many physiological variants and pathological conditions should be recognized to prevent misinterpretation of positive scan in case of cardiac uptake (1, 4). Results of ^{18}F -FDG-PET/CT within 3 months after prosthetic valve’s replacement should be carefully discussed within the multidisciplinary Endocarditis Team due to the risk of false positive results (1, 7). Small vegetation could account for false negative results in case of cardiac infections. In case of vascular graft, specific pattern of ^{18}F -FDG uptake should be considered to differentiate VPI from foreign body-related reaction that can be observed for years after the implantation of the prosthesis (1, 24). There is not any evidence to recommend antimicrobial treatment discontinuation even if it is expected that it may affect ^{18}F -FDG uptake. Steroids should be interrupted or at least reduced to the lowest dose 24 hours before the exam (1).

Nuclear medicine techniques may be successfully used to monitor antimicrobial treatment response despite there are no many evidences on this (1, 20, 25). The main concern for applying WBC scintigraphy and ^{18}F -FDG PET/CT imaging is probably related to the possibility of false negative results, however our experience (unpublished data) supports their use opened the possibility to apply molecular imaging procedures in treatment decision making.

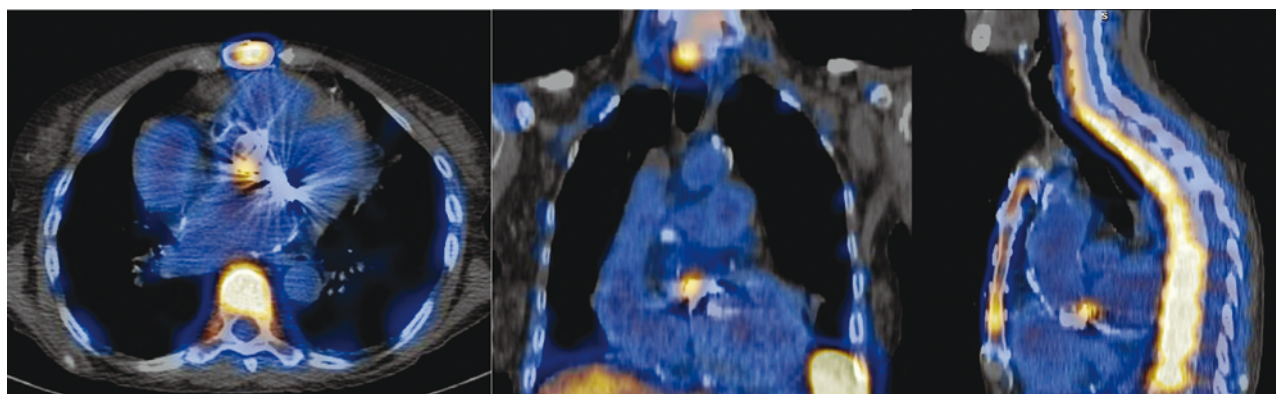


Fig. 1 Radiolabeled WBC scan in a patient with aortic and mitral mechanical prosthesis. The patient presented fever, increased CRP and ESR, negative RF and echocardiography (both TEE and TOE). Positive urine culture with isolation of *P. Mirabilis* and positive blood culture with isolation of *Enterococcus faecalis* were found. SPECT/CT shows a focal area of increased uptake the perivalvular aortic region, at the medial aspect (from left to right transaxial, coronal and sagittal view, respectively).

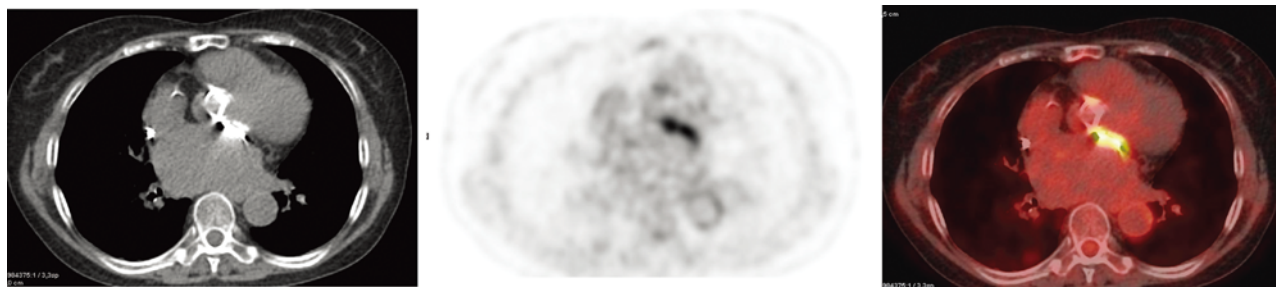


Fig. 2 ^{18}F -FDG PET/CT in a patient with suspected IE. Mitral and aortic mechanical prosthesis positioned 5 years before. The patient developed fever, increased ESR and positive blood culture with isolation of MSSA. Ecocardiography was negative. Images shows increased uptake the perivalvular region of the aortic prosthesis (from left to right transaxial CT, emission and superimposed images). Therefore, by adding the criteria of “abnormal uptake around the site of prosthetic valve implantation” the patient was classified as “Definite IE” and treated with antimicrobial treatment. PET/CT was performed after 24 hours of LCHF diet.

Prosthetic valve endocarditis

PVE is the most severe form of infective endocarditis associated with high rates of morbidity and mortality. With the increasing frequency of valve replacement and an aging population, PVE represents an increased proportion of overall endocarditis cases (20%) (26-28) and the rates of undesirable outcomes, including mortality, remain unacceptably high (26, 27). Echocardiography plays a crucial role in infective endocarditis diagnosis but its accuracy decreases in presence of a prosthetic valve (normal or inconclusive results in up to 30% of cases). The “ESC 2015 modified criteria” have been implemented with non-echo imaging-based findings (i. e. paravalvular lesions by cardiac CT, abnormal WBC or ^{18}F -FDG uptake at SPECT/CT or PET/CT and recent embolic events or infectious silent aneurysms detected by imaging) to increase the diagnostic accuracy in suspected PVE (1, 7). WBC SPECT/CT has been reported to be more specific than sensitive in PVE (95-100% versus 64-83%) (19, 29, 30), conversely, ^{18}F -FDG PET/CT had similar performances in

terms of sensitivity (73-100%) and specificity (71-100%) in PVE diagnosis providing complementary information to echocardiography (15). Fig. 1 and 2 present examples of WBC imaging and ^{18}F -FDG PET/CT in patients with “possible PVE.”

In addition, by using WBC scan and ^{18}F -FDG PET/CT, it is possible to perform an accurate extra-cardiac work-up. In fact, an extracardiac involvement may result as a consequence of embolic events which may occur in 30 to 80% of patients, or possible sustaining source of infection (identification of the portal of entry). The search for asymptomatic embolic events through systematic extracardiac imaging has become a very important topic, due to the fact that the detection of asymptomatic embolic events is now considered a minor Duke criterion in the 2015 ESC criteria (8). Detection of metastatic infection by ^{18}F -FDG PET/CT led to change of treatment in up to 35% of patients with a 2-fold reduction in the number of relapses (31).

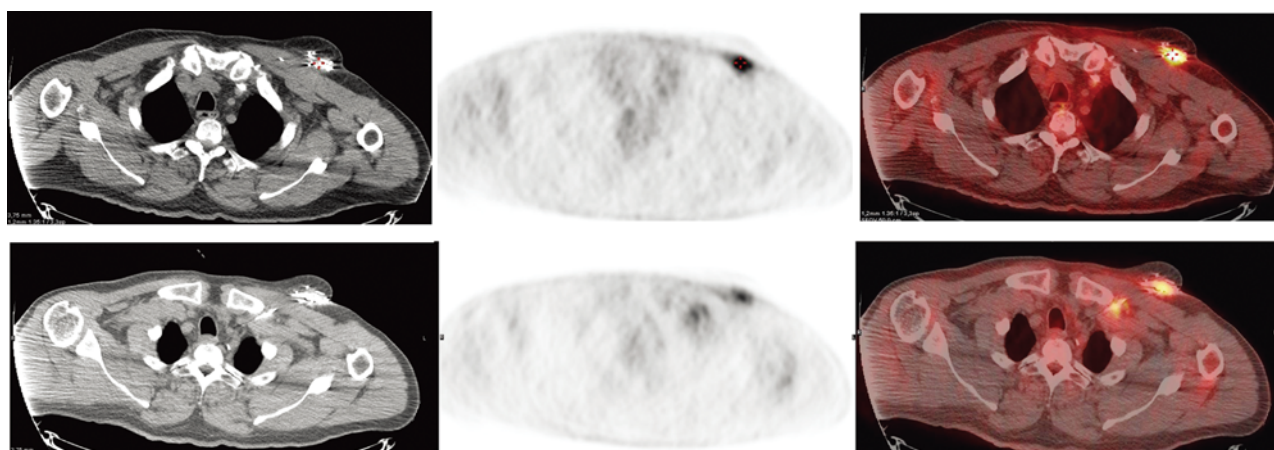


Fig. 3 ^{18}F -FDG PET/CT images of an infected CIED performed after 24 hours of LCHF diet. showing involvement of both the pocket/generator (upper panel from left to right transaxial CT, emission and superimposed images) and the intravascular portion of the EC (lower panel, from left to right transaxial CT, emission and superimposed images).

CIED infection

The use of CIED has increased significantly over the last decade (1, 32). Accordingly to the rise in device implantations, the rate of infectious complications is also increasing by an estimated 5% per year (33). CIED-infections are linked to high in-hospital mortality, rates of readmission and costs (1). Therefore, strategies to facilitate early diagnosis are foreseen for a favorable clinical outcome. The diagnosis of CIED-related infection is a hard task in which multimodality imaging may be successfully applied to confirm/exclude the presence of infection and define its extent, including embolic and metastatic foci (1, 13, 14). The largest study with WBC SPECT/CT in CIED-infection diagnosis reported a sensitivity of 94% and a specificity of 100% (18). ^{18}F -FDG-PET/CT has been extensively used in CIED infection resulting in good diagnostic performances (pooled sensitivity of 83-87% and pooled specificity of 89-94%), better for the diagnosis of generator/pocket infections (sensitivity of 93-96% and specificity of 97-97%) as compared to infections along the leads (sensitivity 65-76% and specificity 83-88%) (13, 14, 34), as a consequence of the very small size of the vegetations along the leads (35). Fig. 3 present an example of ^{18}F -FDG-PET/CT in a patient with CIED infection.

LVAD infection

LVADs are becoming a more frequent life-support intervention. As more devices have been implanted, LVAD infections, associated with substantial morbidity and mortality, have become an increasingly serious problem (36). Infection frequently complicates LVAD placement (22% overall) and is a continuing problem despite the use of newer, smaller devices since the 1 year mortality is 5.6 times greater in patients with than without infections (37). Besides mortality, LVAD infections are associated with increased risk of complications,

longer hospital stay, need for LVAD exchange, and failure to transplant (36). The usefulness of WBC SPECT/CT and ^{18}F -FDG-PET/CT in the diagnosis and management of LVAD-related infection has been shown in small cohort of patients (38-45). Semi-quantitative analysis may be used to improve ^{18}F -FDG-PET/CT performances (41, 42). Therefore, nuclear medicine imaging, when properly applied (i. e. accurate selection of patients, appropriate interpretation of images, and accurate definition of disease burden), may impact in LVAD patients' management and outcome since both treatment and survival differed in patients with central, peripheral or without LVAD infection (39).

Vascular graft infection

Infection of vascular prosthesis (VPI) is quite rare (incidence of 0.5%-6% depending on surgical site) but it is associated to a significant increase in morbidity and mortality risk as well as to high costs (46, 47). VPI's management is challenging (46). Therefore, early and accurate diagnosis is required for the correct choice of the best therapeutic strategy (1). Sensitivity and specificity for WBC scintigraphy increased when $^{99\text{m}}\text{Tc}$ -radiolabeling is used (82-100% and 75-100%, respectively) (1, 48). The use of SPECT/CT resulted in an accurate definition of site and extent of infection and reduced the false positive rate (1, 4, 20, 49-52) (Fig. 4). High specificity is also observed when scintigraphy is performed early after surgery and in case of late low grade VPI (1, 20, 53). PET/CT had high sensitivity in VPI diagnosis when focal ^{18}F -FDG uptake around the prosthesis is used as diagnostic criterion (93% with a specificity of 70-91%) (1, 4, 52, 54). Diffuse ^{18}F -FDG uptake has been reported in 92% of noninfected vascular prostheses (especially in Dacron grafts) (55) pointing out that this pattern should be carefully considered when interpreting PET/CT images. Fig. 5 shows an

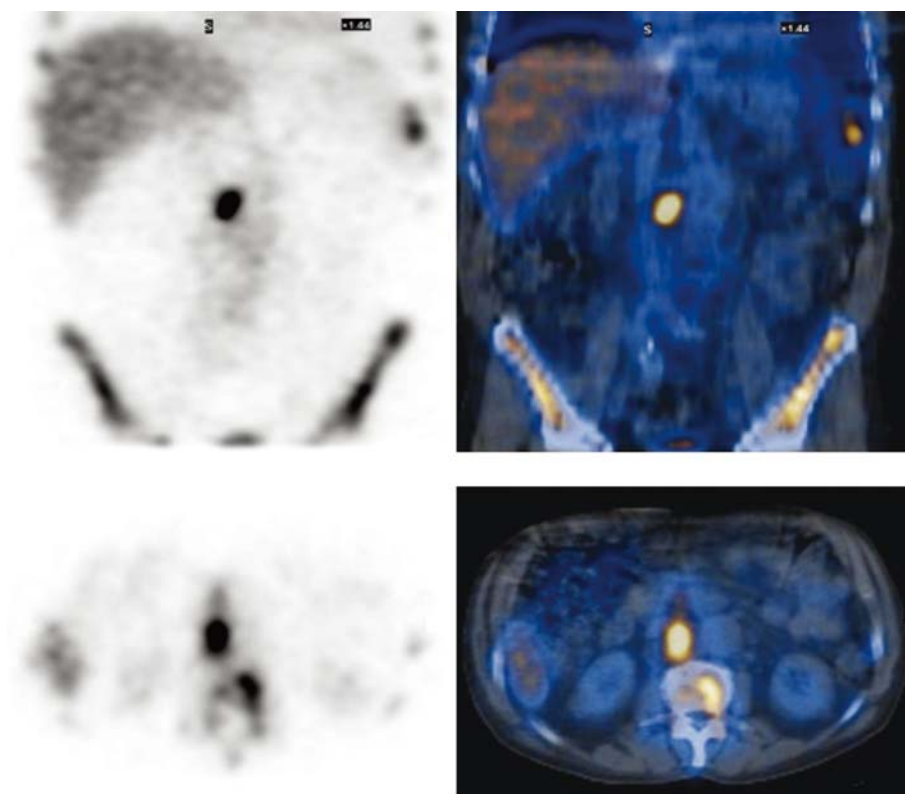


Fig. 4 Examples of radiolabelled WBC imaging (Infinia, GE Healthcare; B, SPET/CT images upper panel coronal view and lower panel transaxial view, from left to right emission and superimposed SPECT/CT) in a patient with infection of the aorto-bisiliac vascular prosthesis. Images show radiolabelled WBC accumulation at the site of the aortic prosthesis.

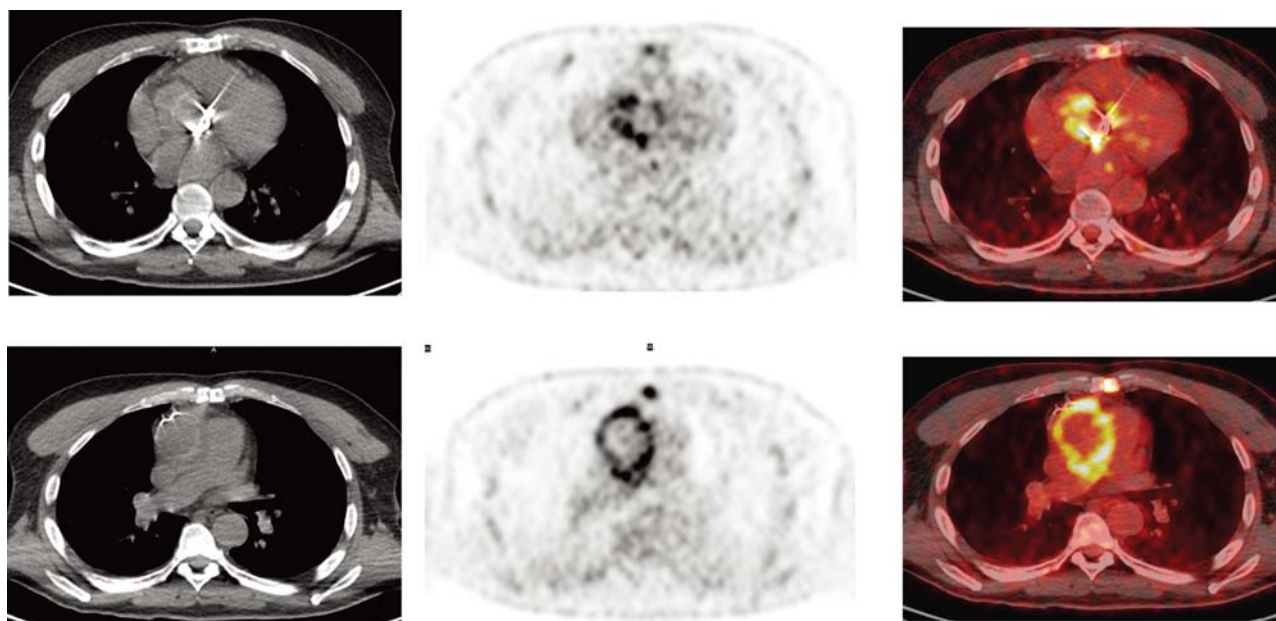


Fig. 5 ^{18}F -FDG PET/CT (Discovery 710 PET/CT, GE Healthcare) images in a patient with aortic valve and thoracic aorta prosthesis. PET/CT was performed after 24 hours of LCHF diet. Images show uptake at the aortic valve prosthesis (upper panel transaxial view from left to right CT, emission and superimposed PET/CT) associate with intense uptake around the ascending aortic prosthesis (lower panel, transaxial view from left to right CT, emission and superimposed PET/CT).

example. Dual-time-point images and a five point visual grading ^{18}F -FDG score, improving image quality, and enhancing delineation of the infected aortic grafts, may be used to enhance the diagnostic accuracy (4, 52, 56, 57). Both WBC scintigraphy and ^{18}F -FDG PET/CT may be used to evaluate antimicrobial treatment response in VPI (1, 20).

Conclusions

Nuclear cardiology imaging is helpful to detect device infections. The “3M” approach (i. e. multimodality, multi-tracers and multidisciplinary), recently proposed to integrate the traditional diagnostic criteria in cardiovascular device infections, facilitates early diagnosis, impacts in patients’ management, and improves the outcome.

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Conflicts of interest

Paola Anna Erba was a member of the 2015 Task Force for the Management of Infective Endocarditis of the European Society of Cardiology. No other potential conflict of interest relevant to this article.

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