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The "3M" Approach to Cardiovascular Infections:
Multimodality, Multi-tracers and Multidisciplinary

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Abstract (300 words)

Cardiovascular infections are associated with high morbidity and mortality. Early diagnosis is crucial for adequate patient's management, as early treatment improves the prognosis. Hardly diagnosed on the basis of a single symptom, sign or diagnostic test. Rather, the diagnosis requires a multidisciplinary discussion in addition to the integration of clinical signs, microbiology data and imaging data. The application of multimodality imaging, including molecular imaging techniques has improved the sensitivity to detect infections involving heart valves and vessels and implanted cardiovascular devices while also allowing for early detection of septic emboli and metastatic infections before these become clinically apparent. In this review, we describe data supporting the use of a Multimodality, Multitracer and Multidisclinary approach – the 3M approach - to cardiovascular infections. In particular, the role of WBC SPECT/CT and [^{18}F]FDG PET/CT in most prevalent and clinically relevant cardiovascular infections will be discussed. In addition, the needs of advanced hybrid equipment, dedicated imaging acquisition protocols, specific expertise for imaging reading and interpretations in this field are discussed, emphasizing the need of a specific reference framework within a Cardiovascular Multidisciplinary Team Approach to select the best test or combination of tests for each specific clinical situation.

Cardiovascular infections

Cardiovascular infections have been recognized as significant causes of cardiac diseases for many decades. The spectra of micro-organisms causing cardiovascular infections are very broad and include all classes of microbes. They can cause diseases involving various components of the native structure of the heart - pericardium, muscle, endocardium, valves, autonomic nerves and the vessels - as well as implanted devices such as valve prosthesis (all types of prosthetic valves, annuloplasty rings, intracardiac patches, and shunts), cardiovascular implantable electronic devices (CIED), left ventricular assist device (LVAD) catheters and vascular graft.

Due to important technological advance and longevity, the use of implantable devices and surgical biomaterials in medicine has increased significantly during the last decades and is expected to increase further over the next years. If we just take as example historical advancement in pacemaker achieved from the early 50s with the first report on electrical heart stimulation and the production of first generation of devices in 1958 to the most recent leadless, single-chambered pacemaker, they are remarkable. It has been estimated that about 8% to 10% of the population in America and 5% to 6% of people in industrialized countries underwent insertion of an implantable medical device (1). The expected number of heart valve interventions over the coming decades will reach more than 800.000 annual procedures worldwide by 2050 (2). As a consequence, an increased number of complications associated with implanted medical devices are foreseen. Healthcare-associated infections represent the most common non-cardiac complication after cardiac surgery and device implants affecting about 1.7 million patients each year, and are associated with nearly 100,000 deaths in the US (3,4). Infections associated with cardiovascular implants are of particular concern since patients undergoing cardiac surgery are ever older and have many comorbidities. In fact, their infection risk (5,6) is nearly 5% in the first 2 months following cardiac surgery with a 10-fold higher risk for mortality (7).

The severity of cardiovascular infection depends upon the involved microorganism and the maturity of the biofilm (a community of adherent micro-organisms embedded within a self-produced matrix of extracellular polymeric substances) developed on the device (8,9), the location and the type of the biomaterial, and the host defence status. A key common characteristic of cardiovascular infections is that matrix-embedded bacterial communities tolerate efficiently antibiotics and host phagocytic defences. Therefore, often the only opportunity to eradicate effectively the infection is the surgical treatment, including the removal of the infected device.

Cardiovascular infections are hardly diagnosed on the basis of a single symptom, sign or diagnostic test. Rather, the diagnosis requires a clinical suspicion, most commonly triggered by systemic illness in a patient with risk factors, and a careful evaluation performed according to a specific diagnostic flow-chart. The heterogeneity of clinical presentations of cardiovascular infections requires a

multidisciplinary discussion in addition to the application of the diagnostic criteria. Microbiology and imaging are currently the benchmarks for a prompt and accurate diagnosis. The standard practice for the microbiological diagnosis includes routine microbiological sampling consisting of culturing, identification, and antibiotic susceptibility tests that is used also for treatment guidance.

Blood culture is the most important initial laboratory test. If antibiotic therapy has been administered prior to the collection of blood cultures, the rate of positive cultures declines (10). In cases of suspected culture-negative infective endocarditis (IE), other microbiological testing approaches may be useful. Echocardiography is the first-line imaging modality that plays a key role in both the diagnosis and management of IE. Multimodality imaging, including molecular imaging techniques are nowadays widely used to integrate the traditional diagnostic criteria and therefore fill in such uncertainty gap with information on the biochemical burden of these infections.

In this review, we will focus on the use of multimodality, multi-tracer and multidisciplinary approach to the patient with cardiovascular infections. In particular the role of white blood cells (WBC) single photon emission tomography co-registered with computerized tomography (SPECT/CT) and positron emission tomography co-registered with computerized tomography (PET/CT) using fluorodeoxyglucose labelled with fluoride-18 ([^{18}F]FDG) in the most prevalent and clinically relevant cardiovascular infections will be discussed. Some basic, but very critical technical consideration will be reported followed by a specific detailed insight into the topic of infectious IE, CIED and LVAD infections, vascular prosthesis infections (VPI) including composite aortic graft (i.e. vascular tube graft with an attached mechanical or biologic valve). In addition, we will also give some insight in recent new developments that might be of particular interest in the next feature for this field.

The "3M" approach to cardiovascular infections: Multimodality, Multi-tracers and Multidisciplinary

Multimodality and Multi-tracers

Current multimodality procedures used on a large extent in the diagnosis of cardiovascular infections include autologous radiolabeled leukocytes WBC SPECT/CT and [^{18}F]FDG PET/CT. The first technique relies on the direct radiolabeling of autologous leukocytes that accumulate in a time-dependent fashion in late versus earlier images in the focus of an infection. PET/CT is generally performed using a single acquisition time point (generally at 45-60 minutes) after the administration of [^{18}F]FDG, which is actively in vivo incorporated by activated leukocytes, monocyte-macrophages, and CD4+ T-lymphocytes present or accumulating at the sites of infection. PET/MR, an exciting novel multimodality imaging tool which can assess disease activity together with assessments of

cardiac anatomy, function, and tissue composition has been not evaluated yet in the context of cardiovascular infections.

There are several different clinical scenarios in which multimodality imaging can provide important diagnostic information which determine the choice of the preferred procedure and radiopharmaceutical. Patients might be referred to nuclear imager due to a persistent bacteremia or fever despite an appropriate antimicrobial treatment. In this situation, the diagnosis is very challenging since up to one-third of patients with Gram-positive bacteremia and metastatic foci (11,12) have not significant localizing signs and symptoms (13). Active search using [^{18}F]FDG PET/CT and echocardiography in the first 2 weeks of admission, have revealed more metastatic foci in high-risk patients with Gram-positive bacteremia compared to a matched control group managed according to a standard work-up (14). Additionally, treatment modification and reduced mortality were observed (15,16), were observed. Often, in case of *Staphylococcus aureus* bacteraemia heart valve and vessel are affected; if a cardiovascular device is present this might be interested by infection in more than 50% of the patients (17). Therefore, the accurate differentiation of patients with positive blood cultures and underlying cardiovascular/cardiovascular devices infection from those without infections is critical and fundamental for the subsequent patient management. Figure 1 shows an example of [^{18}F]FDG PET/CT imaging contribution to localize the site of occult infection in a patient with *Staphylococcus aureus* bacteraemia.

A different group of patients might require scintigraphy or PET/CT for suspected infection of the cardiovascular system/cardiovascular device, on the basis of clinical presentation and/or laboratory and imaging tests. In this situation, WBC SPECT/CT and [^{18}F]FDG PET/CT are used to increase the likelihood of the diagnosis. By visualizing the presence of uptake at the site of valve/vessel or at the cardiovascular device, diagnosis might be confirmed. 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 or possible sustaining source of infection (identification of the portal of entry). The ability to reliably exclude IE is also a clear advantage of the techniques, both to avoid extended courses of unnecessary antibiotics and also to focus diagnostic considerations onto other possibilities that can be suggested within the same imaging test. Lastly, despite this clinical application is not yet validated, it is possible to use these modalities to assess the response to antimicrobial treatment as well as to identify patients with early recurrence after its discontinuation. Figure 2 schematically represent the possible answer SPECT/CT and PET/CT can provide when applied in this context.

Multidisciplinary

Interdisciplinary discussion of laboratory and multimodality imaging data is necessary to boost their contribution into a clinical planning and decision-making process that delivers quality care within such complex contexts. A multidisciplinary team approach has been recently successfully extended beyond oncology where the work model is successfully established, as in case of valvular heart disease (the 'Heart Valve Clinic'), particularly in the selection of patients for transcatheter aortic valve implantation procedures ('Heart Team' approach) (18,19). The first example of a multidisciplinary approach in the field of cardiovascular infections is represented by the Endocarditis Team (E-Team), a multidisciplinary "round table" system involving specialists in imaging, cardiologists, cardiac surgeons, infectious disease specialists, microbiologists and others (20,21). This approach has been shown to significantly reduce the in-hospital and 1- and 3-year mortality in France, Italy and Spain (22,23). Putting multimodality imaging in a central position in the diagnostic work-up of patients with suspected cardiovascular infections implies a new professional perspective for the "Clinical Imaging Specialist" who is called to be active part and contributor within the E-Team. Therefore, deep knowledge of the technical and clinical critical aspects of multimodalities imaging in this setting as well as attitudes to facilitate inter-specialist communications should be part of the educational planning.

Specific technical considerations: patient preparation, radiopharmaceuticals preparation and acquisition protocols, imaging post-processing and imaging reading/interpretation

WBC SPECT/CT

Patient preparation

In case of CVS infection WBC scan the procedure is very similar to the one used for any other infection. No specific patient preparation is required, besides the standard for WBC imaging. The general rules for the radiolabelling of WBC preparation are also applied.

Radiopharmaceutical: preparation, administered activities and special considerations

The WBC can be radiolabelled either with ^{99m}Tc-hexamethylpropyleneamine oxime ([^{99m}Tc]HMPAO, 370-555 MBq) or with [^{111}In]oxine (10-18.5 MBq), as detailed in the specific guidelines from the European Association of Nuclear Medicine (EANM) (24,25) and the Society of Nuclear medicine and Molecular Imaging (SNMMI) (26,27). It is important to be aware if patient is under antibiotic treatment and consider its' possible effect on WBC uptake when reading the images, but there is no evidence for discontinuation of treatment before the imaging session.

Image acquisition protocol and post-processing

An important aspect of WBC imaging in cardiovascular infections is the image acquisition protocol that should include planar acquisitions at 30 minutes (early images), 4-6 hours (delayed images), and 20-24 hours (late images) after reinjection of [^{99m}Tc]HMPAO/^{111}In-oxine WBC with mandatory inclusion of SPECT/CT acquisition as part of the standard imaging protocol. The importance of including SPECT/CT acquisition is due to the failure of planar images alone to detect the site and the extension of infections in the cardiovascular system (28). Therefore, in this context SPECT/CT images are used not only to confirm and localize findings at planar images consistent with infection (area or increased uptake intensity or size over time), but also to increase the diagnostic accuracy. If semi-quantitative evaluation of WBC is used to reach a diagnosis it's very important that the both planar and SPECT/CT images are always acquired with a "time-corrected for isotope decay" modality. SPECT/CT images should cover the thorax in case of IE and the thorax-upper abdominal area in case of CIEDs and LVAD infections, ensuring that all components of the device are included in the field of view, considering all the possible generator positions (i.e. abdomen). In case of vascular prosthesis, the whole anatomical region where the graft is positioned should be included in the field-of-view, including the region of the native vessels at the proximal and distal prosthetic sites. For abdominal vascular prosthesis acquisition of dynamic images might help in differentiating persistent WBC accumulation from blood pool activity as well images within the first 2 hrs p.i., to minimize the interference due to the HMPAO elimination via the hepatobiliary system. Late SPECT/CT acquisitions are particularly relevant in case of IE, CIEDs infections and thoracic aorta infections since background activity related to the blood pool spill over strongly hampers the detectability of lesions. In addition to this standard protocol, accurate extra-cardiac work-up searching for septic emboli or for the portal of entry should be always performed. This might require additional SPECT/CT acquisitions. The images have to be reconstructed with and without attenuation correction to identify potential reconstruction artefacts.

Image reading and imaging interpretation

When reading WBC imaging some important issues should be taken into consideration. Rarely, false positive findings have been described for WBC imaging in IE and CIED infections, even in case of very early infections. False positive results are more frequent in case of VPI, in particular for those located in the abdominal area, but SPECT/CT has been shown to significantly decrease the false positive rate (29). On the other hand, false negative scans have been observed in the presence of IE caused by some specific strains (28). The same limitation has always to be kept in consideration in case of CIED infections, in particular in the presence of very small vegetation(s) along the electrocatheter. Embolisms at WBC imaging might appear either as area of increased uptake over

time in the brain, lung and soft tissue, or as cold spot when spleen embolism and spondylodiscitis occur. This latter appearance has to be considered non-specific for infectious embolisms since it might be present in other benign or malignant conditions, such as in the case of vertebral crush or metastasis. Therefore, despite these findings in patients with IE are highly suggestive for septic embolism, they should be confirmed by additional diagnostic imaging tests. Due to the limited spatial resolution, reduced sensitivity has been described in case of small embolism (28).

Figure 3 shows a schematic summary of the main steps of the WBC SPECT/CT imaging protocol in cardiovascular infections.

[^{18}F]FDG PET/CT

PET/CT technique has several clear advantages over WBC imaging such as the lack of blood handling, a shorter study time that allows the conclusion of the scan within 1-2 hours after tracer administration and high target-to-background ratio. However, performing a [^{18}F]FDG PET/CT for cardiovascular infections is more complex than a simple translation of the standard protocol used in oncology. Starting from patients' preparation, some specific aspects of the imaging protocol and imaging reading should be considered. An extensive review of the main critical technical issues is provided in the "Recommendation on nuclear and multi-modality imaging in IE and CIED Infections" released by the EANM (30). Briefly, we will discuss here some crucial points for a correct imaging procedure.

Patient preparation

Patient preparation is very important to reduce the physiological uptake of [^{18}F]FDG of the myocardium. This can be achieved by the application of a proper fat-enriched diet lacking carbohydrates followed by fasting. Additionally, the use of intravenous heparin approximately 15 minutes prior to [^{18}F]FDG injection, can be used (31). There is a general agreement that high-fat, low-carbohydrate diet for at least two meals with a fast of at least 4 hours is the minimum to obtain a suppression of physiologic myocardial glucose utilization. Table 1 summarized the possible protocols described in literature to prepare patients for [^{18}F]FDG PET/CT in case of IE/CIED infections. Since there is no evidence demonstrating that a specific patient preparation technique is superior to another, each institution should continuously evaluate its' image quality data to ensure that more than 80% of the scans achieve an adequate physiological [^{18}F]FDG myocardial suppression. Efforts should be made to decrease blood glucose to the lowest possible level, although hyperglycemia does not represent an absolute contraindication for performing the study (32). Indeed, in case of infection and inflammation neither diabetes nor hyperglycemia at the time of the study has been demonstrated to increase PET/CT false-negative rate (33).

Radiopharmaceutical: administered activity and special considerations

The [^{18}F]FDG activity recommended in the joint EANM/SNMMI guidelines on PET imaging in inflammation/infection is of 2.5-5.0 MBq/kg (175-350 MBq in a 70 kg standard adult) (32).

Although antimicrobial treatment is expected to decrease the intensity of [^{18}F]FDG accumulation (34), there is no evidence at this stage to routinely recommend treatment discontinuation before performing PET/CT. On the contrary, corticosteroid treatment should be discontinued or at least reduced to the lowest possible dose in the 24 hours preceding the exam (35).

Image acquisition protocol and post-processing

Image acquisition generally starts after an uptake time of 45-60 minutes, the emission time/bed position depends on the sensitivity of the scanner. The field of acquisition, as in oncology, generally includes from skull base to mid thighs (total body). Whole body images including the lower limbs, might be suggested to detect complications of IE such as mycotic aneurysms that may require specific treatment by embolization to prevent rupture (36). An additional separate bed on the cardiac region is useful to record gated images. Diagnostic angio-CT (CTA) scan might be also performed, to maximise the diagnostic information provided by the exam. Despite delayed imaging have been proposed to increase specificity in diagnosing infection of cardiovascular implants (37,38), recent data suggested that in IE delayed images are more prone to false positive results (39).

Figure 4 shows a schematic summary of the [^{18}F]FDG PET/CT protocol we have developed and shared among our partner institutions, based on the extensive experience we developed over the last years. Also in case of [^{18}F]FDG PET/CT, image reconstruction with and without attenuation correction is recommended to identify potential reconstruction artefacts. Metal artefact reduction techniques are useful to minimise overcorrection even if they do not always recover completely PET image quality.

Image reading and interpretation

PET/CT images have to be visually evaluated for increased [^{18}F]FDG uptake, taking into consideration the pattern (focal, linear, diffuse), the intensity, and the relationship to areas of physiologic distribution. PET information is compared with morphologic information obtained by CT and, possible CTA.

Several physiological variants and pathological conditions that enter in the differential diagnosis with IE/CIED infection should be recognized to prevent misinterpretation of a positive scan. Therefore, specific training in the field should be always undertaken before the implementation of the technique in a new center on a daily basis.

A physiological variant that might represent a confounding factor while reading the images, is the presence of increased metabolic activity along the posterior part of the heart, where lipomatous

hypertrophy of the interatrial septum may appear as a fat-containing mass with increased [18F]FDG uptake (40). One of the major finding that should be recognized is the presence of faint and homogeneous [18F]FDG uptake strictly limited to the valve annulus, very similar to the pattern observed in prosthetic vascular graft (41). This pattern of uptake around the prosthetic valve is frequently visible and may have different causes, particularly early after surgery. It most likely results from the persistent host reaction against the biomaterial coating the sewing ring of prosthetic valve. Therefore, to minimize the risk of false positive findings, the European Society of Cardiology Guidelines recommend not to consider (or to consider carefully) [18F]FDG PET results in the 3-month period following valve implantation (20). Focally increased [18F]FDG uptake might be found in many other conditions such as active thrombi (42), soft atherosclerotic plaques (43), vasculitis (44), primary cardiac tumours (45) and cardiac metastasis (46), post-surgical inflammation (47) and foreign body reactions (such as BioGlue, a surgical adhesive used to repair the aortic root) (48) stitches (49) and, in case of Libman-Sacks endocarditis (50). Therefore, it is necessary to adopt accurate patients' selection and inclusion criteria as well as accurate imaging reading to maintain a high specificity for IE using [18F]FDG. As already discussed, antimicrobial therapy and/or vegetation size could account for false negative results on [18F]FDG PET/CT. Analysis by application of the standard uptake value (SUV) is possible. However, conversely to its application in oncology, SUV has not been validated in inflammation and infection. If SUV is used, all the factors influencing its quantification should be carefully considered, including those related to patient preparation (glycaemia, concurrent treatment, etc), time of uptake and the use of positive contrast.

In case of vascular prosthesis, the presence of [18F]FDG uptake along a vascular graft might be rather aspecific. Therefore, PET/CT require specific imaging interpretation criteria for the definition of a positive scan as well as the correlative reading with the CT features (graft wall thickening, oedema, gas surrounding the graft or any other sights) (51). Images are generally evaluated visually using the visual grading scale. The presence of focal [18F]FDG uptake at visual analysis and irregular graft boundary at CT images should be considered as the specific pattern of FDG uptake to differentiate infection from foreign body-related reaction. Indeed, in this latter case faint, diffuse and homogeneous [18F]FDG uptake can persist for years after the implantation of the prosthesis also in relation to the type of implanted material (41). In the case of infection of a composite aortic graft which combine a vascular tube graft with an attached mechanical or biologic valve the diagnosis should consider involvement of the prosthetic valve or of the vascular graft that can also occur at the same time. Therefore, appropriate patients preparation as described in the case of IE is as critical as the imaging interpretation. In fact, the identification of FDG uptake at the aortic valve-root might be accomplished just in case of adequate glucose myocardial uptake suppression. Specific knowledge of

the presence, patterns, and persistence of [^{18}F]FDG uptake in non infected valve prosthesis as well as in vascular prostheses should be also considered to avoid images misinterpretation, particularly when PET/CT is used or imaging is performed very early after surgery.

Infective Endocarditis

Infective endocarditis (IE) is a life-threatening disease, associated with a mortality rate of approximately 10% at initial admission which might rise up to 20% in the first year (51-55). IE is also associated with significant complications among survivors. Globally, in 2010, 1.58 million disability-adjusted life-years or years of healthy life lost as a result of death and nonfatal illness or impairment were associated to IE (56). Therefore, prompt identification of patients at high risk of poor outcome is necessary and urgent in order to make accurate clinical decisions for improving patient prognosis. Although the overall disease incidence has remained stable ranging annually from 3 to 7 per 100 000 person-years in the most contemporary population surveys (57-64), during the least years the epidemiology of IE has become more complex and the epidemiological profile has changed substantially. Currently characteristics of IE patients have shifted toward an increased mean patient age, a higher proportion of prosthetic valves and other cardiac devices, and a decreasing proportion of rheumatic heart disease. At present, 25%-50% of the cases occur in patients older than 60 years (65), an age-related pattern that implies several diagnostic and therapeutic challenges: the usual patient population affected by IE is sicker and older, often with many comorbid conditions. Significant changes in the sustained micro-organism has been also demonstrated with an increased incidence of *Staphylococcus aureus* sustained IE, underlying the increasing importance of the proportion of health care-associated infections. The clinical history of IE is highly variable according to the causative microorganism, the presence or absence of pre-existing cardiac disease, the presence or absence of prosthetic valves or cardiac devices and the presentation. A development of IE requires the simultaneous occurrence of several independent factors: alteration of the cardiac valve surface, bacteraemia and creation of the infected mass or 'vegetation'.

The alteration of the cardiac valve surface as a consequence of specific disease (such as rheumatic carditis), mechanical injury by catheters or electrodes, or injury arising from repeated injections of solid particles in drug abusers facilitates bacterial attachment and colonization. Bacteraemia (the minimum magnitude of bacteraemia is still unknown) with an organism capable of attaching to and colonizing valve tissue lead to the creation of the infected mass or 'vegetation' by 'burying' of the proliferating organism within a protective matrix of serum molecules (for example, fibrin) and platelets. In prosthetic valve endocarditis (PVE) and IE related to CIEDs biofilms formation contributes directly to the evolution of device-associated vegetation propagation. In case of native

valve endocarditis (NVE), the role of biofilm has not been yet established. As a systemic disease, IE results in characteristic pathological changes in multiple target organs (66). Portions of the platelet-fibrin matrix of the vegetation may dislodge from the infected heart valve and travel with arterial blood until lodging in a vascular bed downstream from the heart. IE may present clinically as an acute, rapidly progressive infection, or as a subacute or chronic disease with low grade fever and non-specific symptoms which may thwart or confound initial assessment (67). Therefore, patients may be referred to a variety of specialists who may consider a range of alternative diagnoses.

Diagnostic work-up

In the latest update of the European Society of Cardiology (ESC) Guideline for the management of infective endocarditis (IE), multimodality imaging has been integrated in the diagnostic algorithm of IE (20). Therefore, along with blood cultures and echocardiography, which remains the first imaging test that plays a central role in both the diagnosis and the subsequent clinical management of patients with IE (68), other multimodality imaging techniques were introduced. Cardiac/whole body CT scan, cerebral MRI, [^{18}F]FDG PET/CT and radiolabelled WBC SPECT/CT are positioned central of the diagnostic work-up since they have been demonstrated to contribute to reach an early and accurate diagnosis (20). The value of cardiac CT has also been underlined in the American Heart Association (AHA)/American College of Cardiology (ACC) guidelines (69).

According to the "ESC 2015 modified diagnostic criteria" the echocardiographic findings that are considered major criteria for the diagnosis of IE remained unchanged and include vegetations, the detection of perivalvular abscesses, perivalvular pseudoaneurysms, intracardiac fistulas, valvular perforations, valvular aneurysms, and new prosthetic valve dehiscences (20). Currently, the sensitivity of transthoracic echocardiography (TTE) and transoesofageal echocardiography (TOE) for the diagnosis of vegetations is 70% and 96%, respectively, in NVE and 50% and 92%, respectively. As for abscesses detection, the sensitivity of TTE is about 50%, compared with 90% for TOE with a specificity is higher than 90% in both echocardiographic modalities (70). At echocardiography, the detection of lesions in patients with prosthetic valves is more difficult than in patients with native valves and normal or inconclusive results have been reported in up to 30% of cases. False positive results might also occur. Therefore, in case of PVE other three imaging-based findings are now included as either major or minor criteria as follows: i) the identification of paravalvular lesions by cardiac CT should be considered as a major criterion; ii) in the setting of the suspicion of PVE, abnormal uptake by [^{18}F]FDG PET/CT or WBC SPECT/CT should be considered as a major criterion; iii) the identification by imaging of recent embolic events or infectious aneurysms (silent events) should be considered as a minor criterion.

Prosthetic valve endocarditis

WBC SPECT/CT

Sensitivity of WBC SPECT/CT has been reported overall 64–90% with 36–100% specificity, and 85–100% positive and 47–81% negative predictive values (28,71). In case of abscess formation WBC SPECT/CT presented 83–100% sensitivity, 78–87% specificity, and 43–71% positive and 93–100% negative predictive values (72), even in the early post-intervention phase (28,72). As for [^{18}F]FDGPET/CT, WBC SPECT/CT has an excellent positive predictive value for the detection of perivalvular infection and abscesses in patients with a suspicion of PVE. In addition, the intensity of WBC accumulation in the perivalvular area represents an interesting marker of local infectious activity: patients with a mild activity on the first exam disappearing on the second imaging evaluation seem to have a favourable outcome (72). This open the very interesting perspective of the use of molecular multimodality imaging for the assessment of antimicrobial treatment response. The most recent hybrid equipment allows to perform CTA also during a WBC SPECT/CT scan. However, this potential further development has not been yet evaluated.

Figure 5 presents an example of WBC imaging in a complex patient with a possible endocarditis on an aortic and a mitral mechanical prosthesis. On the basis of the exam IE was condirmed and a portal of entry of the infection was also identified.

[^{18}F]FDG PET/CT

In a recent systematic review on the assessment of PVE, [^{18}F]FDG PET/CT sensitivity and specificity have been reported 73-100% and 71–100%, respectively, with a 67–100% positive and 50–100% negative predictive values (PPV and NPV, respectively). Addition of [^{18}F]FDG PET/CT to the modified Duke criteria increased sensitivity for a definite IE from 52–70% to 91–97% (73) by reducing the number of possible PVE cases. This finding has been confirmed in several series (71,74-79).

[^{18}F]FDG PET/CT have been reported to have similar sensitivities for vegetations, perivalvular sequelae, and prosthetic valve dehiscence compared with echocardiography (74). When ^{18}F-FDG-PET/CT in associated to CT-angiography ([^{18}F]FDG PET/CTA) the diagnosis of infective endocarditis sensitivity and specificity increased to 91% with 93% PPV and 88% NPV (78,80). In association with the Duke criteria [^{18}F]FDG PET/CTA allowed reclassification of 90% of the cases initially classified as ¨possible¨ IE and provided a more conclusive diagnosis (definite/reject) in 95% of the patients. This combined multimodality procedure should be considered in all the patients where echocardiography presents significant limitations. In fact, its ability to provide relevant information on the local extent of the disease such as the presence of pseudo aneurysms, fistulas, thrombosis and coronary involvement are significant for the subsequent clinical and surgical decision-making. In addition, by adding CTA to PET/CT in IE patients it is possible to assess the entire chest identifying

septic pulmonary infarcts and abscesses, evaluate the aorta and the coronary arteries in prevision of surgery. Figures 6 and 7 present two examples of [^{18}F]FDG PET/CT contribution in patients with suspected IE.

Native valve endocarditis

In case of native valve, despite imaging interpretation might be more straightforward than in PVE, the diagnostic value of [^{18}F]FDG PET/CT has not been well determined. In fact, most studies included mainly PVE or a mixed patient population with both native and prosthetic valves. A recent prospective study in patients with bacteraemia (*Staphylococcus*, *Streptococcus spp* and *Enterococcus spp*) and a very limited proportion of patients with prosthetic valve, showed a limited accuracy (sensitivity 39%, specificity was 93%) of [^{18}F]FDG PET/CT for diagnosing IE (81).

Other smaller studies did not show better results (75,82). The low sensitivity of [^{18}F]FDG PET/CT in NVE is likely to be mainly related to the location and the size of the lesions. In fact, in case of NVE is the presence of a vegetation is the main finding, at least in the initial phase of the disease. Whereas in case of PVE infection it generally spreads along the sewing ring or leads to abscess formation. It should also be noticed that this is a clinical setting where echocardiography presents a very high accuracy, therefore, the use of multimodality imaging is reserved to a limited number of patients, i.e. patients with severe valve calcific degeneration with suboptimal acoustic window. For example, in patients with *S. aureus* bacteraemia due to the high frequency of IE, TTE or TOE are always recommended (83).

Extra-cardiac work-up in Infective Endocarditis

Extracardiac manifestations in IE (both NVE and PVE) are reported in 30 to 80% of patients. Most frequent are embolic stroke or septic embolization to bone, spleen or kidneys (84), although only some of these are symptomatic (58,62,85). The majority of embolisms take place within the first 14 days after treatment initiation (86) and they might appear as the initial symptom leading to the diagnosis, and frequently are recurrent (86). The localization of the emboli and their cerebral/extracerebral proportion vary according to the studies, in particular according to the frequency and modalities of imaging, and the proportion of right-sided and left-sided IE.

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 [ESC Guideline]. This represents another main difference between the ESC and the American Heart Association (AHA) recommendation in which only symptomatic extracardiac localizations of IE are considered as Duke classification minor criteria (69).

A panel of imaging modalities is used routinely to evaluate patients with extra-cardiac infective processes and includes dental radiography, abdominal ultrasound, CT scan of cerebrum, whole-body CT or MRI scan. CT scan (including cerebral) has long been considered the main imaging technique for the diagnosis of embolic events in IE patients and MRI a valuable alternative in case of cerebral embolism with the advantage of a higher sensitivity in detecting recent ischemic lesions, and small ischemic or hemorrhagic lesions, in the absence of iodine injection. A noticeable advantage of [^{18}F]FDG PET/CT and WBC SPECT/CT is the possibility to perform the extra-cardiac work-up within a single imaging procedure, to reveal the concomitant presence of extra-cardiac infection sites as the consequence of both septic embolism as well as primary infective processes (Figure 7, 8 and 9).

[^{18}F]FDG PET/CT

Early detection of embolic events have been reported using [^{18}F]FDG PET/CT with a high sensitivity (87–100%) and specificity (80%) (73), at a reasonable cost-effectiveness, especially in patients with Gram- positive bacteraemia (14). Extracerebral peripheral localizations of IE were found in 24 to 74% among the definite IE population; most of these peripheral localizations were silent (50 to 71%) and revealed by [^{18}F]FDG PET/CT. In a case-control study, [^{18}F]FDG PET/CT detected peripheral localizations in 57.4% of IE patients, representing the only initially positive imaging technique in about half of the patients with embolic events (87). Detection of metastatic infection by [^{18}F]FDG PET/CT led to change of treatment in up to 35% of patients (82) and with a 2-fold reduction in the number of relapses (87). [^{18}F]FDG PET/CT is very accurate in organs with low physiological uptake, therefore not applicable in ruling out the presence of brain embolism (88), where the use of CT/MRI remains fundamental.

WBC SPECT/CT

Radiolabelled leukocytes SPECT/CT shares with PET/CT the possibility of acquiring whole-body images. Moreover, performing additional planar and SPECT/CT spot images constitutes an invaluable aid for detecting septic embolism even in asymptomatic patients (28,89). WBC SPECT/CT has been used in a mixed population of PVE and NVE patients, showing that no cases were undiagnosed when either the echography or the blood cultures were positive (28). However, a recent study from the East Danish Database on Endocarditis comparing the performances of [^{18}F]FDG PET/CT scan and WBC SPECT/CT acquired within 1 week apart and within 14 days of IE treatment initiation, showed [^{18}F]FDG PET/CT to have a significantly higher clinical utility score than WBC SPECT/CT and to be potentially superior to WBC-SPECT/CT in detection of extra-cardiac pathology in patients with IE (90). It should be noted that in this study the the protocol of WBC imaging

acquisition used in the study is not the one recommended by the current EANM guideline, therefore performance of the technique might have been underestimated.

The evaluation of the disease extent by identification of extracardiac complication has consequences on therapeutic management of IE, leading to a reduction of the risk of relapse. This has been shown particularly useful in the identification of unexpected embolic localizations such as in the case of mycotic aneurysms (91), a potential life-threatening complication requiring specific treatment (Figure 2, B). Indeed, [^{18}F]FDG PET/CT has been demonstrated to determine a changed in therapeutic plan in 28% of patients by leading to advance scheduled cardiac surgery or initiation of a specific antimicrobial regimen for the treatment of the embolic foci (92). In addition, in the Kestler case-control study, the systematic use of [^{18}F]FDG-PET/CT was associated with a 2-fold reduction in the number of IE relapses (9.6 vs. 4.2%) (87).

The identification of the infection portal of entry at [^{18}F]FDG PET/CT and subsequent eradication of the sources of infection is particularly important in IE to prevent recurrence either relapse and/or reinfection. The risk of recurrence amongst survivors of IE varies between 2.7 and 22.5% (56,93-99). Relapses are more often due to insufficient duration of original treatment, suboptimal choice of initial antibiotics, and a persistent focus of infection (e.g. periprosthetic abscess). In a large multicenter cohort of patients with IE, history of IE was an independent predictor of repeat IE (100), highlighting the importance of obtaining timely infection source control. The potential portal of entry of a new episode must be searched for in order to eradicate it and thus lower the risk for a new IE episode. This primary infectious site may be suspected based on the common biotope of the bacteria strain (digestive, skin, catheter). Yet published research on this topic is very limited. In a recent study, systematic search for the portal of entry identified the site of primary infection in 74% of patients, mainly cutaneous (40%), followed by oral or dental (29%) and gastrointestinal (23%) (101).

[^{18}F]FDG-PET/CT has been demonstrated able to reveal the source of infection, including cases where the sustaining portal of entry was a neoplasia (colonic cancer) (78). The link between some type of microorganism and colon cancer was first described in 1951(102). Previously categorized as a Lancefield group D streptococcus, an enterococcus, or simply as "*Streptococcus bovis* group", these bacteria have since been differentiated by deoxyribonucleic acid sequencing as *Streptococcus gallolyticus* and *Streptococcus infantarius*. Several studies support the association between bacteremia or IE due to these pathogens and GI pathology: mostly colon cancer (103-106) but also adenomatous polyps (107), diverticulosis (104), and biliary lesions (104,106). Taken together, these evidence highlights the importance of searching for a culprit GI source in case of patients with *S. bovis* group microorganisms. Figure 9 shows an example of the detection of rectal cancer in a patient with IE with spleen embolism sustained by *Streptococcus infantarius*. Multiple portals of entry are

also possible. Once the portal of entry has been identified, risk modification can be attempted. This topic is of clinical importance, as it relates to our understanding of the sources of infection in patients with IE and also influences management of patients. Therefore, from a practical and clinical perspective systematic search for multiple sites of primary infections can be considered as an add element for prevention and treatment planning for IE recurrence and should be always be part of the standard report of a [^{18}F]FDG PET/CT or WBC imaging (Figure 6).

Cardiovascular implantable electronic device infections

Use of cardiovascular implantable electronic devices (CIEDs) has increased significantly over the last decade due to growing evidence of improved quality of life and survival among certain groups of patient (108). The number of devices that are placed is estimated to exceed 1 million per year (109). At least 2% of patients over the age of 65 have a CIED. Simultaneous with the rise in device implantations, the rate of infectious complications is also increasing by an estimated 5% per year (110) reaching an incidence of 1.4 per 1000 device-years (111). This dramatic increase in the rate of device infections coincided with an increase in the prevalence of major comorbidities, including renal failure, heart failure, respiratory failure, and diabetes mellitus in CIED recipients (112). In addition to morbidity for patients, CIED infection has been linked to increased in-hospital mortality by more than 2-fold (113,114). and higher rates of readmission up to 3 years following a device implantation procedure (114-117). CIEDs infections are estimated to cost over US$500 million per year worldwide (116,117). Therefore, strategies to facilitate early diagnosis are crucial for favorable clinical outcome. CIEDs infections include infections that involve the pocket/generator, generally defined as local infections and/or the electrode leads, cardiac valve leaflets, or endocardial surface, this latter condition known as distant infections. These two entities should be distinguished. Infections, either early contamination of the surgical site (118) or late endoplastitis of the lead(s) (17), rarely respond to conservative management with antimicrobial agents alone (119,120); therefore, complete removal of the whole device is usually necessary (121).

Diagnostic work-up

Diagnostic workup of CIEDs infections is problematic, since patients can present with a variety of manifestations including subtle signs of systemic or local infection. The decision whether to medically treat or to remove the device represents a further crucial point, also because it implies evaluation of response to antimicrobial therapy and selection of the optimal time to re-implant. Like in NVE, echocardiography plays a key role in CIEDs infections. Echocardiography helps identifing lead vegetations and defining the size, detecting tricuspid valve involvement and quantifying tricuspid regurgitation. In addition, it might be used for patients' follow-up after lead extraction (20).

However, false negative and false positive echo studies are not rare, and the Duke criteria are difficult to apply in these patients because of lower sensitivity (122), even when the modified Duke criteria are used. Because of the frequently difficult diagnosis of the disease, and because of some limitations of echocardiography, multimodality imaging has been successfully applied in patients with CIEDs infections.

WBC SPECT/CT and [^{18}F]FDG PET/CT

Similarly to what has been described for PVE, WBC SPECT/CT and [^{18}F]FDG PET/CT might be used to confirm/exclude infection and characterize the extension of the infectious process, including extra cardiac work-up. The value of [^{18}F]FDG PET/CT in the diagnosis of CIEDs infection is substantiated by a large body of literature. The diagnosis of local infections is quite straightforward. A recent meta-analysis provides a pooled specificity and sensitivity in this subgroup were 93% (95% CI, 84%–98%) and 98% (95% CI, 88%–100%), respectively, and AUC was 0.98 for [^{18}F]FDG PET/CT (123). The largest study with WBC scan (n=63) reported a sensitivity of 94% and a specificity of 100% (89). By these imaging modalities it is possible to differentiate between superficial and deep pocket infection, which necessitates removal of the generator rather than a medical treatment. Non-attenuation corrected images should be used for final interpretation of the images. Semi-quantitative parameters such as semi-quantitative ratio of maximum count rate of the pocket device over mean count rate of lung parenchyma (124) or normalization of SUVmax around the CIEDs to the mean hepatic blood pool ratio activity (125) might help in differentiated mild post-operative residual inflammation up to 2 months after device implantation versus infection. Finally, those patients with a suspicion of infection but without [^{18}F]FDG uptake has been shown presenting a favorable outcome under antibiotic therapy, suggesting the absence of bacterial colonization of CIEDs. The diagnostic accuracy for lead infections is lower, with overall pooled sensitivity of 65% (95% CI, 53%–76%), specificity of 88% (95% CI, 77%–94%), and AUC of 0.861(123). Such a finding is mainly related to the small size of the vegetations along the leads, which are often under the spatial resolution of the system (126). [^{18}F]FDG PET/CT and WBC scan findings in association with Duke criteria also allowed reclassifying most of cases initially classified as ¨possible¨ IE (78), distinguishing infection limited to the pocket or leads from a more severe infection affecting the whole device (89) and identifying patients requiring device extraction (127).

In addition, also in the case of CIEDs infections accurate evaluation of the whole body imaging might detect septic embolisms and identify possible infection portal of entry, impacting on the subsequent therapeutic management and reducing the risk of relapse (128). Indeed, in CIEDs infection the detection of lung embolisms, considered as a major criterion of the Duke score has shown to increase the diagnostic sensitivity (129).

Therefore, both imaging approaches, WBC SPECT/CT and [^{18}F]FDG PET/CT, can be suggested in patients with CIEDs infections as a guide to clinicians for choosing the most suitable treatment, i.e., conservative treatment (ESC class IIb recommendations) (20). Figure 10 shows an example of [^{18}F]FDG PET/CT extensive work up in a patient with suspected PM infection.

Left Ventricular Assist Device Associated Infections

Implantable left ventricular assist device (LVAD) represents a major medical development for end-stage heart failure in selected patients (130). This treatment is currently used as a bridge-to-transplantation, a bridge-to-recovery, or as destination therapy as the last resort in patients with neither perspectives of recovery, nor heart transplant. Implantable LVAD intended for long-term use rely on a percutaneous driveline, to carry electric signals and energy from the controller and batteries to the implanted pump. As with any other implantable foreign device, it is subject to LVAD-related infections. The presence of a driveline piercing the skin places the patient at continual risk of infection that can affect the exit site, the subcutaneous tunnel, the abdominal pocket (if present) and the implanted pump, and that can disseminate through bloodstream infection. The transition from pulsatile to continuous-flow LVAD, significantly improved the clinical outcome (131), and decreased the risk of infectious complications. Nonetheless, LVAD-related infections are still common with a prevalence that ranges from 23 to 58%, being associated with a high mortality rate (15-44%) (132). The major sites of infection comprise the mediastinum drivelines and device surface, identified as LVAD endocarditis (133). The major pathogens involved in these emerging foreign device-related infectious diseases, where the 'big five' are - as could be expected - *Staphylococcu* aureus, *Enterobacteriaceae*, *Pseudomonas aeruginosa*, *Coagulase-negative Staphylococci*, and *Corynebacterium spp* (134). The management of LVAD infections, due to the few data currently available in literature and the lack of specific guidelines, is poorly standardized, and is mainly derived from the available recommendation of other CIEDs infections, prosthetic valves or vascular prosthesis, although their characteristics significantly differ. The only available specific recommendation to assist therapeutic decisions (i.e., the use of anti-microbial treatment and surgery) in this challenging context, is based on observational studies and expert opinion (135).

Diagnostic work-up

The use of CT as main diagnostic imaging in these patients rely on the possibility to detect the presence of edema as primary sign of infection, a finding that is often unspecific. The usefulness of WBS SPECT/CT and [^{18}F]FDG PET/CT in the diagnosis of LVAD-related infection has been shown in small patient groups under routine clinical conditions. Molecular imaging allows precise anatomic location and accurate extent of a suspected infection (132) with sensitivity of 100% and a specificity

of 94% in case of [^{18}F]FDG PET/CT (136). The use of the metabolic volume has been recently reported to be associated with increased diagnostic accuracy as compared to the SUVmax in a series of 48 patients. In particular, the NPV and sensitivity increased up to >95% by using the metabolic volume compared to 87.5% when using SUVmax (137).

Vascular prosthesis infection

Vascular prosthetic infection (VPI) is the most serious complication following surgical or endovascular implantation. Despite a relative low incidence that has been reported between 0.5 and 5% (138), it represents one of the most challenging post-surgical medical complication affecting the prognosis of the patient with very high morbidity and mortality rates (around 50% and 25%-75%, respectively). It's more common in the inguinal region (about 13%) followed by aorto-bifemoral bypass and femoro-popliteal bypass. Prosthetic graft infection following thoracic aortic procedures has significantly lower rate compared to abdominal aortic surgery or peripheral vascular interventions. The development of endovascular aortic repair (EVAR) devices has granted the possibility of aneurysmal repair to a large number of high-risk patients otherwise ineligible for an open procedure due to age or significant comorbidities. Therefore, the patient population undergoing aortic repair has extended to include those previously unable to tolerate the sequelae of a traditional surgical approach. This can explain why despite the shift in trends of aortic repair in the past two decades with increased proportion of endovascular repairs (139) the expected reduction in the rates of VPI did not occur (138, 140). While the incidence of VPI has not been significantly altered by the endovascular revolution, the advent of aortic stent-grafts has almost certainly dictated a change in the patient populations affected by VPI after both open and endovascular repair. The qualities of endovascular grafts render them appealing tools for addressing the more urgent sequelae of VPI (141), but also cause management of infection affecting these endoprostheses to be more challenging (140-143).

Management of infected vascular grafts depends on several factors, including the position of the infected prosthesis, the extent of infection, and the underlying microorganism (144). Removal of the infected graft or stent-graft is required in the majority of the cases. However, even if surgery get successful morbidity may still be significant or even increased.

An appropriate perioperative prophylactic strategy and expedient surgery are important factors to prevent graft infection. Prophylactic antibiotic administration is recommended before vascular and endovascular prosthetic implantation since it has been demonstrated decreasing the risk of wound infection, a possible risk factor for subsequent graft infection (145).

Infection might arise as a consequence of vascular graft or stent-graft perioperative contamination or during bacteremia with consecutive seeding of the implant material. Mechanical erosion of the graft/stent-graft into an adjacent structure (esophagus, bronchial system and duodenum) is a very rare but challenging complication (146). Depending on the timing of clinical presentation, prosthetic graft infection can be classified as early versus late or very late infections, the threshold for late infection being 4–6 months after the primary surgery or endovascular intervention. The nature of late infection is more indolent without signs of septicemia; one of the most suggesting signs is the absence of graft incorporation with surrounding tissue and the presence of perigraft fluid (and gas particles) containing large amounts of leucocytes (147).

The majority of cases of VPI are due to Staphylococcus aureus, Escherichia coli and S. epidermidis are responsible whereas, *Klebsiella*, *Pseudomonas*, *Enterobacter* and *Proteus* accounts for most of the remaining portion (144-147). Patients with suspected graft infection usually present with local pain, redness, a palpable lump, and/or secretion in the area of the surgical wound, associated with blood chemistry values consistent with infection (increased leukocyte count, ESR and CRP values). Microbiological cultures (obtained by a CT-guided needle aspiration, if technically feasible) may confirm the diagnosis. However, from a microbiological standpoint, blood culture is positive in approximately 35% of the cases, higher in aortic and early VPI since bacteria adhering to the vascular graft are organized in a biofilm, confining to a quiescent state (146,148). Such nonspecific presentation makes the diagnosis and treatment of these infections a real challenge, and success of surgical intervention is closely dependent on an early diagnosis.

Diagnostic work-up

Diagnosis is difficult. No single diagnostic procedure has 100% of accuracy, therefore, a combination of physical examination, laboratory tests, and several imaging techniques is mandatory. In fact, patients may report a variety of clinically equivocal complaints. Furthermore, blood chemistry parameters can only show moderately elevated WBC counts, ESR and/or CRP values, a common, non-specific finding (147). Once a vascular graft infection is suspected, prompt and accurate detection is required for the correct choice of therapeutic procedures. It is critically important to avoid complications such as sepsis, aneurismatic ruptures, gastrointestinal bleeding and suture line disruption (149,150). Therefore, graft revision to remove infected material by an aggressive surgical treatment is urgent. Delay in treatment can lead to life-threatening sepsis and/or bleeding. Lyons et al. recently proposed a case definition of aortic graft infection including clinical/surgical, radiological and laboratory criteria (150).

Success of surgical intervention is closely dependent on an early diagnosis. CT angiography is the technique of choice for both confirmation of the infection and the detection of complications. CT

sensitivity and specificity are 94% and 85%, respectively (151). Whereas the presence of fluid and air surrounding the aortic graft is a normal finding in the early postoperative period, the finding of gas in the periprosthetic tissue on CT-scan should be considered abnormal beyond 6-8 weeks after surgery. Despite several advantages (high specificity, guidance for needle aspiration and microbiological analysis, speed of execution), the main limitations of CT imaging are the low sensitivity in detecting early post-surgical infections and low-grade (152). Ultrasonography with color flow doppler is often a first-line imaging procedure. This noninvasive technique does not involve any risk of contrast allergy and nephrotoxicity, does not expose the patient to ionizing radiation, and is in general highly cost-effective (153). However, particularly in case of aortic graft the predictive value is limited both by air content in the intestinal lumen and, sometimes, by abundant subcutaneous fat of the patient. Magnetic Resonance Imaging (MRI) provides multiparametric information which is especially useful for tissue characterization. In case of VPI MRI allows to distinguish between perigraft fluid and perigraft fibrosis, thanks to signal intensity differences between T1 and T2 weighted images. However, sensitivity in detecting of peri-graft infection has not been thoroughly investigated, and is probably similar as that of CT (154). MRI shares the same limitations as CT imaging for the differential diagnosis of peri-prosthetic fluid accumulation in the early postoperative period because of non-specific uptake in the vicinitiy of the perigraft. However, MRI accuracy increases to 90–95% when it's performed 3-4 months after surgery. Nuclear medicine techniques have been generally reserved to cases with equivocal conventional imaging findings or to patients managed by high-expertise multidisciplinary groups including nuclear medicine physicians (155). Molecular multimodality imaging has demonstrated high accuracy in detecting graft infection in patients with aortic graft and without specific signs of infection (low-grade phases) (29,156).

WBC SPECT/CT

Overall, WBC imaging presents a sensitivity ranging from 53 to 100%, with 50-100% specificity. [^{99m}Tc] WBC is the preferred imaging agent with a sensitivity of 82-100% and a specificity of 75-100%. The extensive use of SPECT/CT allows accurate characterization of pathological foci and extension visualization, confirming or rejecting graft involvement even in presence of post-surgical distortions and in complex anatomical sites (29,157-159). The use of SPECT/CT is associated with a significant reduction in the false positive results (i.e. abdominal aspecific accumulation). High specificity is maintained even when scintigraphy is performed during the first month after surgery (160) and also in case of late low grade VPI (29). A comparative study between MRI and [^{111}In]-WBC reported similar performances of the two methods (positive and negative predictive value of 95% and 80% for MRI and 80% and 82% for [^{111}In]-WBC) (161). WBC scintigraphy may be used to determine the response to treatment. The evidence of the resolution of infection prevents the risk

of adverse drug reactions as well as the acquisition of resistance related to long-term antibiotic treatment (162). Figures 11 and 12 shows examples of the use of WBC imaging in VPI infections

[^{18}F]FDG PET/CT

[^{18}F]FDG PET/CT has emerged as a valuable tool for the evaluation of suspected VPI (163,164). By using the presence of focal [^{18}F]FDG uptake around the prosthesis as diagnostic criteria it's possible to reach sensitivity of about 93%, and a specificity of 70-91%, respectively with positive and negative predictive values of 82-88% and 88-96% (165). The presence of focal [^{18}F]FDG uptake at visual analysis and irregular graft boundary at CT images has been identified as an independent significant predictor of low-grade VPI with erroneous classification occurring in less than 5% in the majority of patients (75%) (166). Figures 12-14 shows examples of the use of these criteria in the diagnosis of VPI infections and, also, some comparative example between [^{18}F]FDG PET/CT and WBC imaging in the same patient. Semi-quantitative approach, by mean of SUVmax and/or the tissue-to-background ratio might be also used. The combination of these parameters is associated with high sensitivity (up to 91%), but a relatively low specificity (up to 64%) (51,164,165,167,168). No recommendations on a specific cut-off value for SUVmax in the perigraft area can be made since quantitative measures has been shown to be of modest utility in the diagnosis of VPI (169) . There is a significant overlap in infected and uninfected central vascular grafts (170). More accurate quantification methods are also possible and recently textural analysis has been proposed to evaluate [^{18}F]FDG uptake heterogeneity in aortic VPI. Several textural features were found to be robust for inter-observer variability in delineation of the prosthesis and seem to be suitable for VPI prediction. Short-run-high-grey-level-emphasis, which is highly dependent on the occurrence of short runs (and thus a heterogeneous [^{18}F]FDG uptake) with high grey levels, was the only textural feature to distinguish proven from non-proven VPI. The short-run-high-grey-level-emphasis demonstrated higher values for the infected compared to the uninfected prosthetic grafts. The short-run-high-grey-level-emphasis was most efficient in identifying AGI within the suspected group, whereas for the same task the performances of SUVmax, TBR, and VGS measurements were all limited (171).

Composite aortic graft

A particular case of cardiovascular infections are the ones arising after the corrections of aorta defects with a special surgical approach, the Bentall procedure. This procedure consists in the positioning of a composite aortic graft (combining a vascular tube graft with an attached mechanical or biologic valve) to replace the proximal ascending aorta and the aortic valve. Circulation of the coronary arteries is maintained by implanting the proximal end of the coronary arteries into openings made in the aortic graft (172). The main indications for performing a Bentall surgery are the presence of aortic

regurgitation, Marfan's syndrome, aortic dissection, and aortic aneurysm. Possible complications associated with the Bentall procedure are air embolus, arrhythmias, atelectasis, bleeding, pneumonia, transient confusion, wound infection, graft infection, embolization (172). Rarely aortic abscesses can be present (173). In a recent meta-analysis, major adverse valve-related events are reported after the Bentall procedure with a cumulative incidence of 26.6% at 10 years, including major bleeding and thromboembolic complications, accounting for a combined cumulative incidence of 14.1% at 10 years (174). Infections after Bentall is reported in about 3% of the cases (175), but despite their relatively low incidence they are severe. From a microbial perspective, there is a predominance of *Staphylococcus aureus* infections (35%), with a recent 20% increase in *Methicillin-resistant Staphylococcus aureus* infections (176) associated with VPI.

Diagnostic work-up

The scope of diagnostic imaging is to demonstrate ad differentiate the presence of aortic valve-root involvement or of infection localized to the vascular aortic graft. These two conditions might also coexist and involve the surrounding structures such as the mediastinal soft tissue and the sternum. VPI, as well as the status of surrounding tissue infection extent is crucial for the subsequent treatment planning. Identification of patients with infection limited to the vascular portion of the thoracic aortic grafts (VPI, about 2%) (177) is very important since the ideal treatment, the replacement of the graft, carries a high mortality (178), especially in cases of long-lasting infections or severe co-morbidities. Therefore, alternative options including graft salvage through aggressive debridement and irrigation or non-surgical management with antibiotics alone (179) might be considered. Similarly, identification of the presence of mediastinitis, (incidence ranging between 0.4 to 5%) is another key information imaging should provide due to the related high mortality rate (27-50%) (180). Of notice, such condition represents a major diagnostic challenge particularly when the suspicion arises in the early postoperative period (181).

No specific guidelines for the management of aortic valve-root-vascular prosthesis infections are available, being usually followed the standard recommendations for diagnosis of infectious endocarditis and prosthetic graft infections, including echocardiography and ce-CT and/or MRI in short interval. TEE plays a key role in the assessment of IE, but is not always conclusive due to the numerous artifacts related to the presence of the prosthesis. In most of the published reports, the diagnosis of infection in composite aortic grafts needs a combination of TTE, TEE, CT and PET/CT (175,178,182-184). Figure 9 presents an example of a [^{18}F]FDG PET/CT in a patient with suspected infection of a aortic valve and ascending aorta prosthesis (St. Jude medical). Also in presence of infection after Bentall procedure in relation to possible comorbidities, the risk of distant sites of infections as should not be underestimated. Prompt extra-cardiac work out will allow identification

of both embolic events or concomitant source of infection/inflammation. Examples of this occurrence is represented by patients affected by active large vessel vasculitis who presented fever and increased CRP/ESR or patients with orthopedic prosthesis or CIED infections.

Conclusions

Overall in this review, we describe data supporting the use of a Multimodality, Multitracer and Multidisclinary approach – the 3M approach - to cardiovascular infections. The application of multimodality imaging has improved the sensitivity to detect infections involving valves and vessels and devices while also allowing for early detection of septic emboli and metastatic infections before these become clinically apparent. This further increases the importance of the early implementation of multimodality imaging in the diagnostic work-up, as they allow a prompt diagnosis and immediate initiation of appropriate antimicrobial treatment. Specific expertise and advanced equipment and required in this field, emphasizing the need of a specific reference framework within a Multidisciplinary Team Approach.

Novel trends in radiopharmaceuticals developments as well as significant progress in technology, new insights on the various mechanisms that play a role in cardiovascular infections will likely to provide in the next future new diagnostic and therapeutic targets for further developments in the field.

Table 1: different protocols for patients' preparation for [^{18}F]FDG PET/CT to obtain suppression of the myocardial physiological [^{18}F]FDG uptake.

Type of approach		Effects	Scheme	Ref
Pharmacologic Approaches	Intravenous LMVH administration	Promotes lipolysis and availability of FFA	50 UI/kg bolus i.v. 15 mins before [^{18}F]FDG	88
	calcium channel blockade	block Intracellular calcium which increase glucose uptake	120 mg orally 1 h before [^{18}F]FDG	189
Dietary Approaches	Fasting, different duration	Reduces insulin release and promotes systemic lipolysis	4-6 hrs	44,185,187,190,192-194
			6-8 hrs	
			> 12 hrs	
	No carbohydrate diet + fasting		12 hrs fast	194
	Low carbohydrate diet		24 hrs	195
	Low carbohydrate diet + fasting		At least 12 hrs fasting	187,191,196
			24 hrs prior > 8 hrs fast	191
	+ high fat beverage		24 hrs	44
	HFNC diet + fasting	suppressing insulin release, increase serum FFA	2 meals + 4 hrs fast	197,198
	HFLC dieat	suppressing insulin release, increase serum FFA	2 meals + 4 hrs fast	193
			18 hrs fast	189
			2 days + 12-14 hrs fast	190
	HFLC or HFNC diet + high-fat drink (vegetable oil) prior to [^{18}F]FDG			189,196
Mix regimens	Fasting + Pharmacologic		Heparin bolus after 6-14 hrs fast	78,185,186

LMVH = low molecular weight heparin; FFA = free fatty acid; HFNC = high-fat-no-carbohydrate; HFLC = low--fat-no-carbohydrate
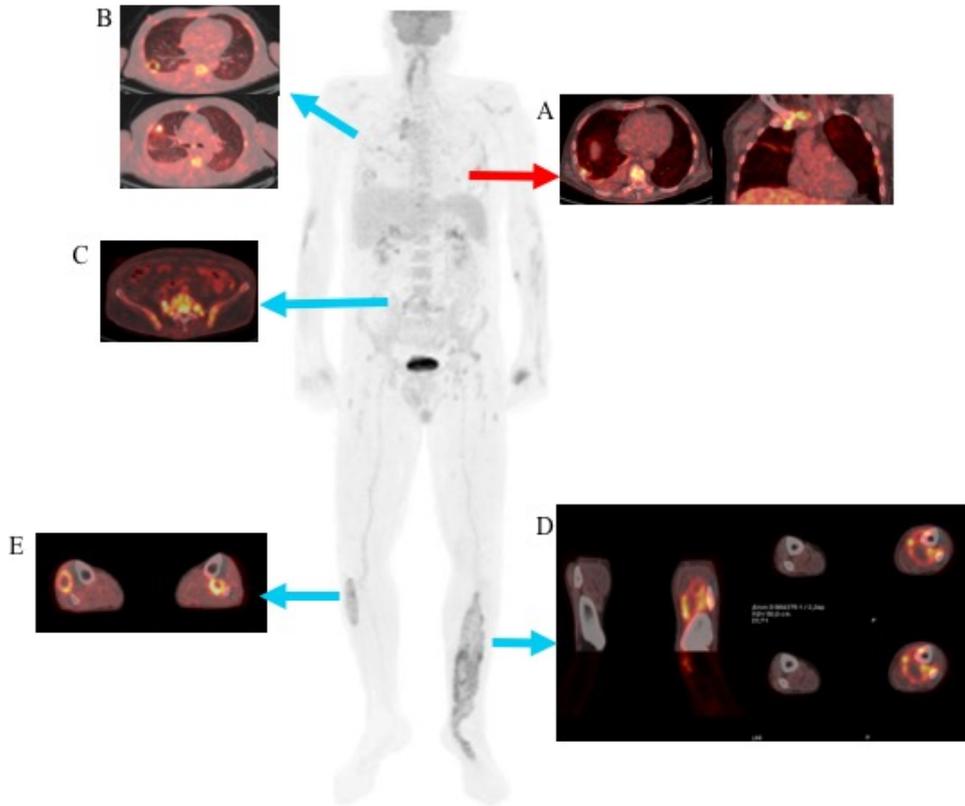
Figure 1 [^{18}F]FDG PET/CT scan in a 26 years man, HIV positive with *Staphylococcus aureus* sepsis. Echocardiography was negative. The patient was prepared with LCHF diet for 48hrs, resulting in a complete suppression of the myocardial [^{18}F]FDG uptake. Normal pattern of uptake was found at the cardiac region (A, from left to right transaxial and coronal superimposed PET/CT). On the contrary, whole body images show metastatic infection at lung (B, transaxial supeimposed PET/CT at two different levels), mediastinal lymphnodes, bone (C, transaxial supeimposed PET/CT) and muscles (E, F, transaxial supeimposed PET/CT).
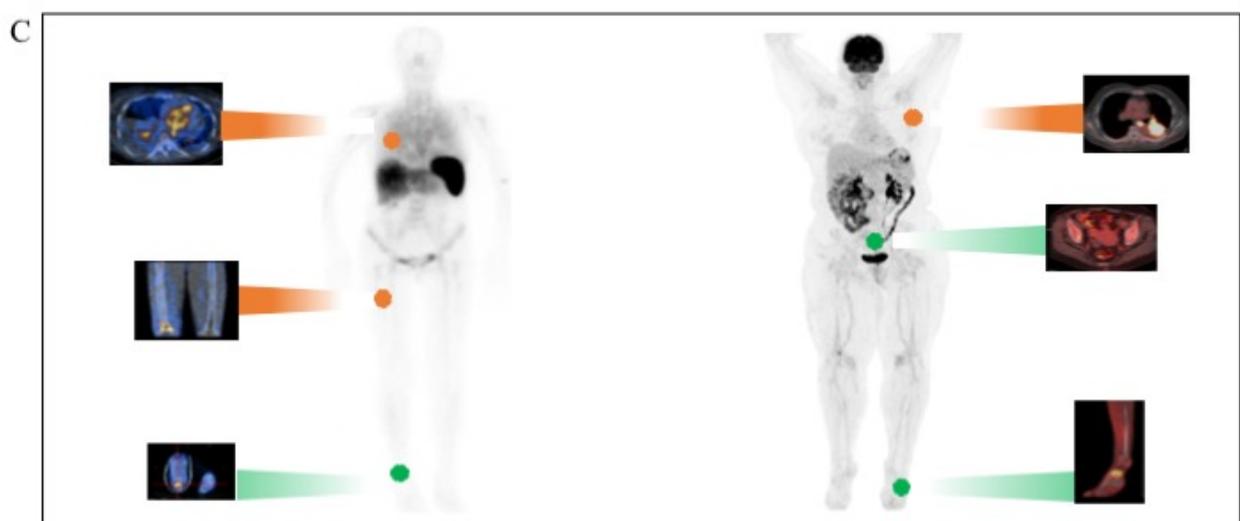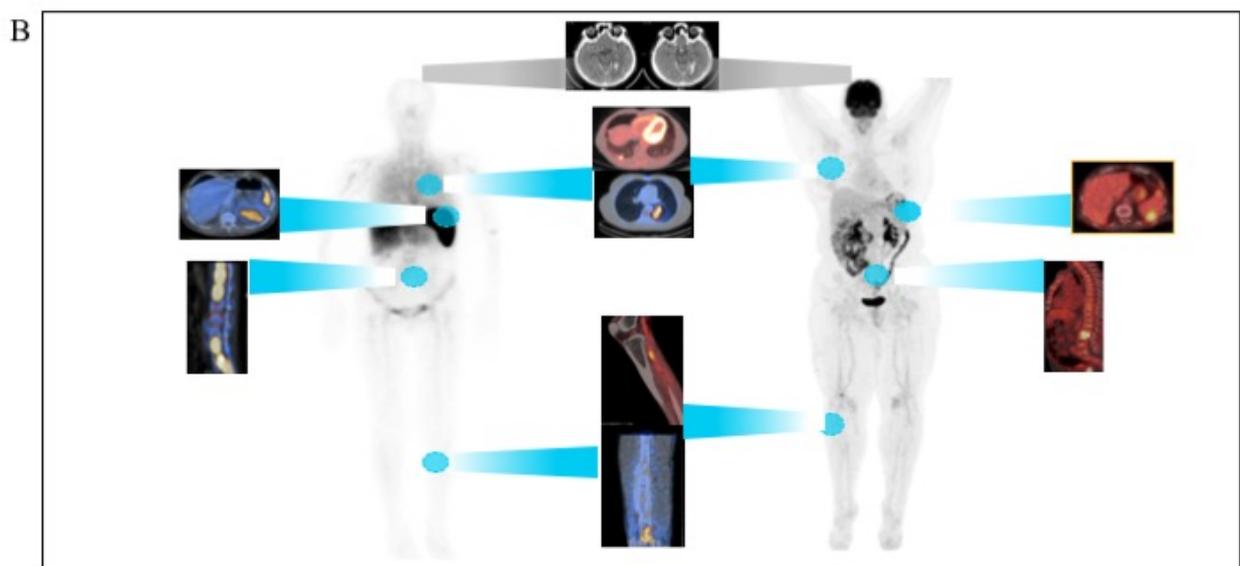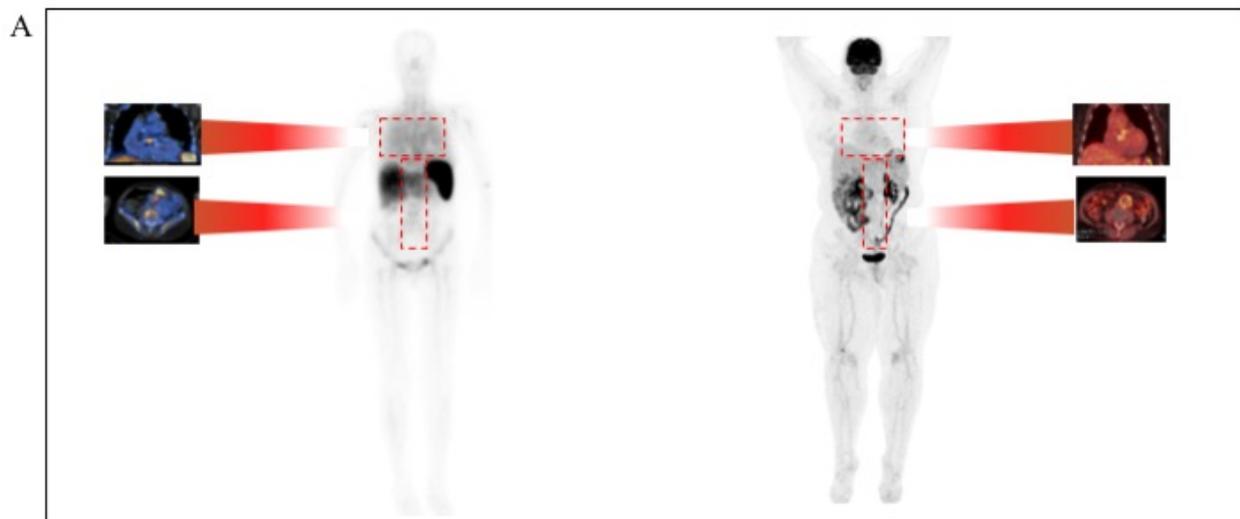
Figure 2 Possible scenarios of the use of WBC SPECT/CT and [^{18}F]FDG PET/CT in the context of cardiovascular infections. Images should be evaluated to search involvement of valve/vessels and cardiovascular devices such as prosthetic valve, CIED and/or prosthetic graft to diagnose infection as shown either by accumulation of WBC (A, left) or [^{18}F]FDG (A, right). Subsequently, whole body images should be analysed to identify possible sites of embolisms or metastatic infections at lung, spine, peripheral vessels, distal bone or spleen. In this case the different pattern at WBC images of photopenic area at spine and spleen (*cold spot*, B left) as compared to the pattern of increase uptake (*hot spot,* B right) at [^{18}F]FDG should be always considered. Lastly, whole body images might provide the evidence for the portal of entry (C lower panel) of the infection as well as exclude the valve/vessel/device infection identifying alternative disease, i.e. lung or bone infection (C left upper and middle panel) or lung or colorectal cancer (C right upper and middle panel).
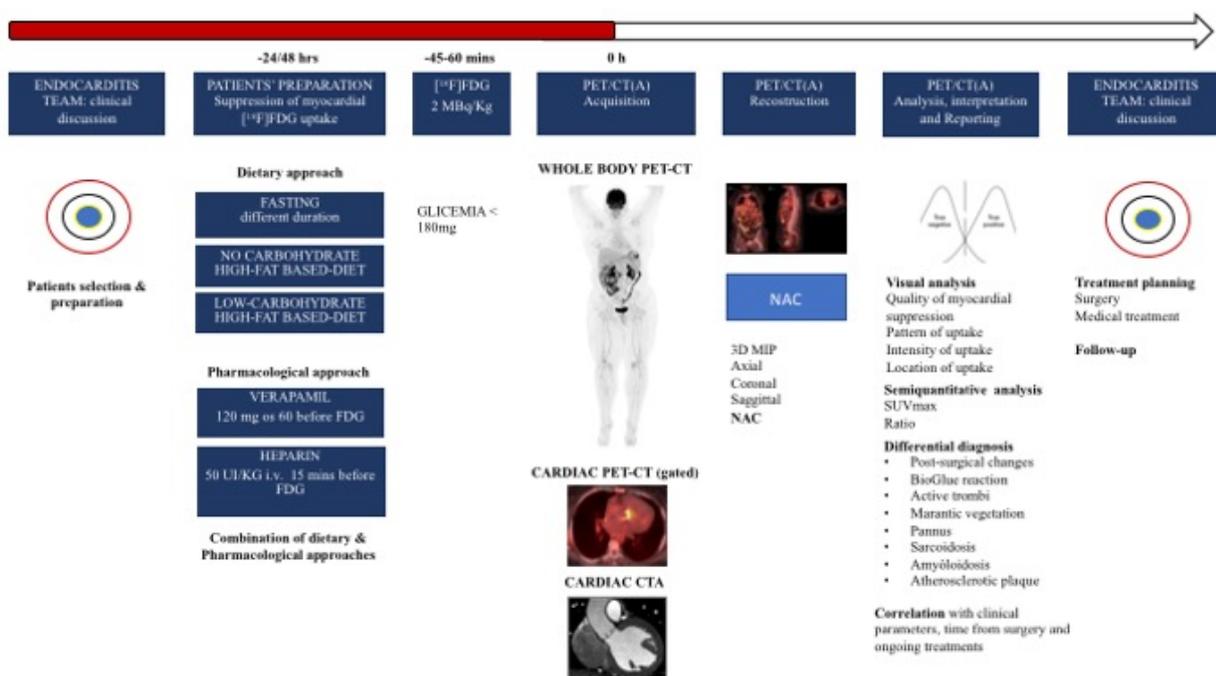

Figure 3 Schematic summary of the main steps of the WBC SPECT/CT imaging protocol in cardiovascular infections.
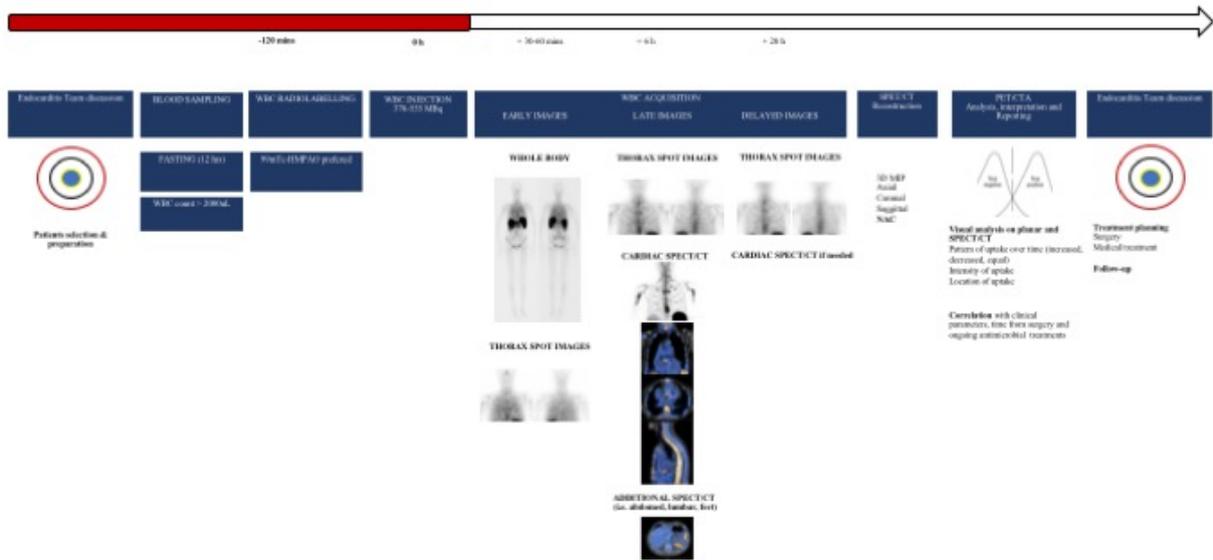
Figure 4 Schematic summary of the [18F]FDG PET/CT protocol we have developed and shared among our partner institutions
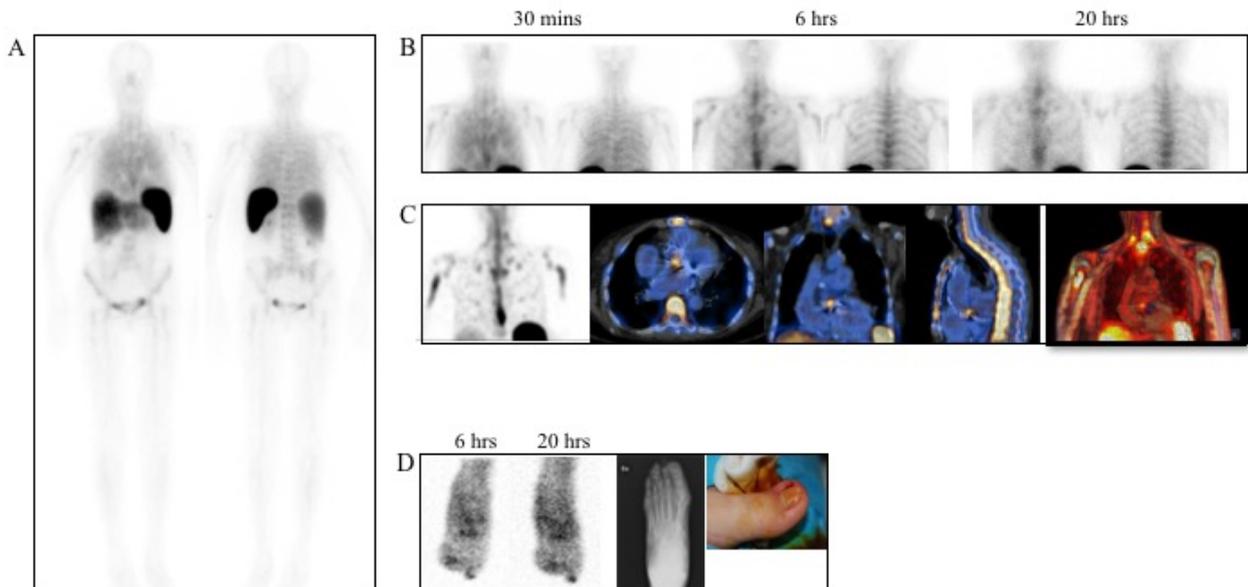

Figure 5 Man, 74 years with an aortic and mitral mechanical prosthesis positioned in 1995 and 1974, respectively. Rheumatic polymyalgia, atrial fibrillation and obliterative vasculopathy of the lower limb are also present. The patient presents fever, increased CRP and ESR, negarive RF.

Ecocardiography, both TEE and TOE were negative. Due to a positive urine culture with isolation of P. Mirabilis and positive blood culture with isolation of *Enterococcus faecalis*. WBC scan was performed. SPECT/CT shows a focal area of increased uptake the perivalvular aortic region, at the medial aspect (C from left to right MIP, transaxial, coronal and sagittal view and reconstructed 3D images, respectively). In this case, the add value of SPECT/CT images is clearly evident since planar images alone are not able to diagnose IE due to the activity of the sternum that cover the valvular uptake. In addition to that, at whole body images (A, anterior view at left and posterior view at right) a focal area of mild uptake is evident at the distal 1° right tooth, better evident at planar images (D, anterior view). Plain X-ray (D) shows a corresponding area of osteolysis. This finding most likely represents to be the portal of entry of the infection. Treatment with antimicrobial was intiated and right tooth amputation performed.
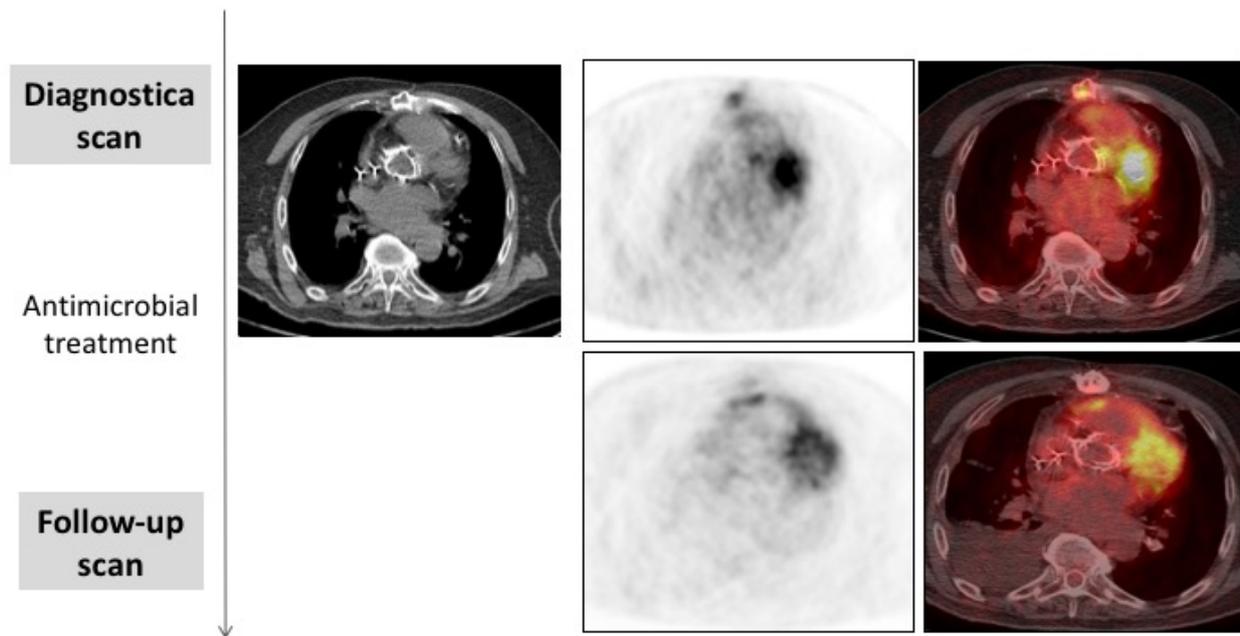

Figure 6 Man of 50 years with a aortic biological prosthesis positioned 2 years before. The patient developed fever, increased ESR and positive blood culture with isolation of *Enterococcus faecalis*. Ecocardiography was negative. The patient was referred for [18F]FDG PET/CT.

Despite an suboptimal suppression of myocardial [18F]FDG uptake, PET/CT shows a focal area of increased uptake the perivalvular region, at the medial aspect (upper panel, 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. The follow-up PET/CT demonstrates the disappearance of the uptake (lower panel, from left to right transaxial CT, emission and superimposed images).
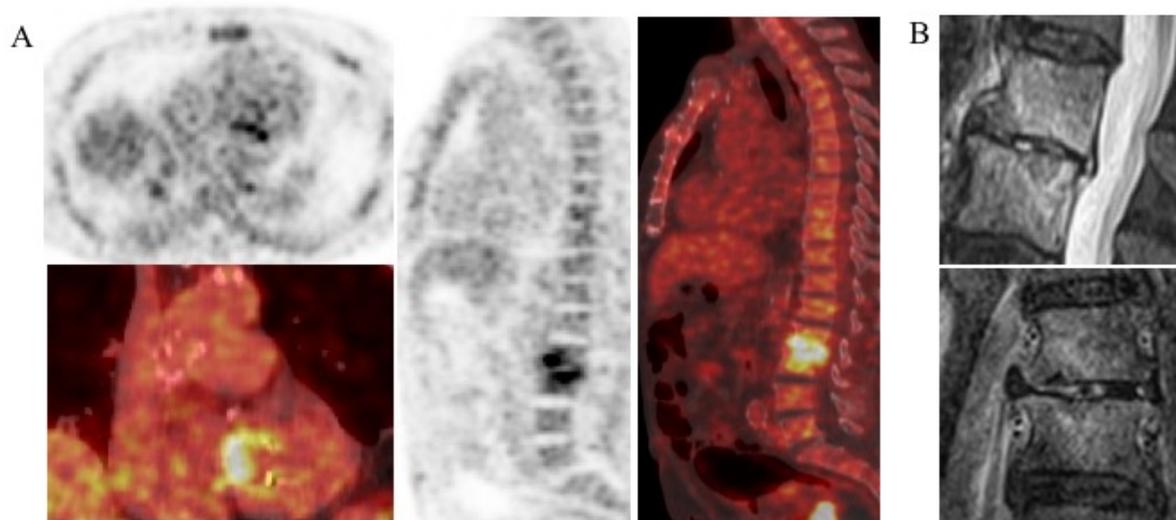
Figure 7 Man, 80 years; history of aortic valve replacement with a biological prosthesis 3 years before. The patient developed fever, back pain, increased CRP and ESR, positive blood culture with isolation of *Lactococcus garvieae*. Ecocardiography was negative. [^{18}F]FDG PET/CT shows a focal area of increased uptake the perivalvular region, at the upper-medial aspect (A, upper left panel transaxial emission and lower left panel coronal superimposed). In addition, whole body images demonstrate intense [^{18}F]FDG at the spine, involving L2-L3 suggesting the presence of spondilodiscytis (A middle panel emission sagittal, right panel sagittal superimposed images). The finding was confirmed by MR (B, T2 weighted images in sagittal view) which shows oedema at the corresponding vertebral bodies.
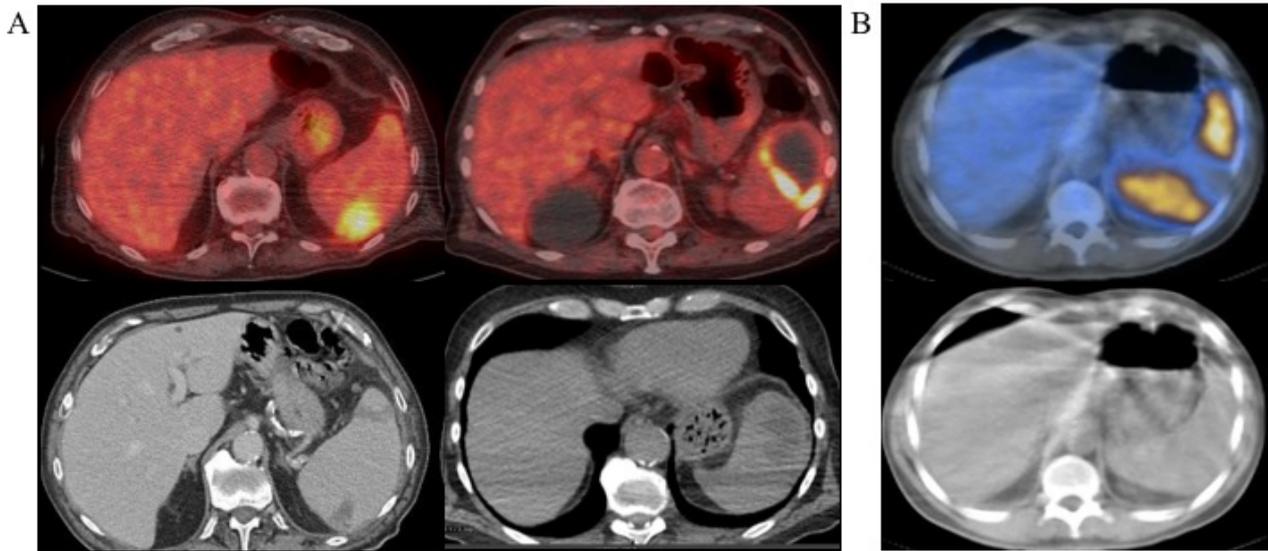
Figure 8 Examples of different pattern of uptake in patients with IE and spleen embolisms at [^{18}F]FDG PET/CT ((Discovery 710 PET/CT GE Healthcare; A, upper panel superimposed PET/CT images, lower panel CT images) and radiolabelled WBC imaging (Infinia, GE Healthcare; B, upper panel superimposed SPET/CT images, lower panel CT images). At PET/CT spleen embolisms might presents increased homogeneous [^{18}F]FDG uptake (A, left, upper panel) corresponding to a segmental wedge-shaped low-attenuation defect at TC (A left lower panel) or a rim of high uptake surrounding a wide photopenic area as consequence of colliquation (A, right lover panel), corresponding to a low-attenuation area at the CT images (A, right lover panel). At radiolabelled SPECT/CT imaging due to the physiological accumulation of the radiolabelled WBC in the spleen, the typical pattern of splenic embolism is a segmental wedge-shaped cold area (B, upper panel; lower panel the corresponding CT image).
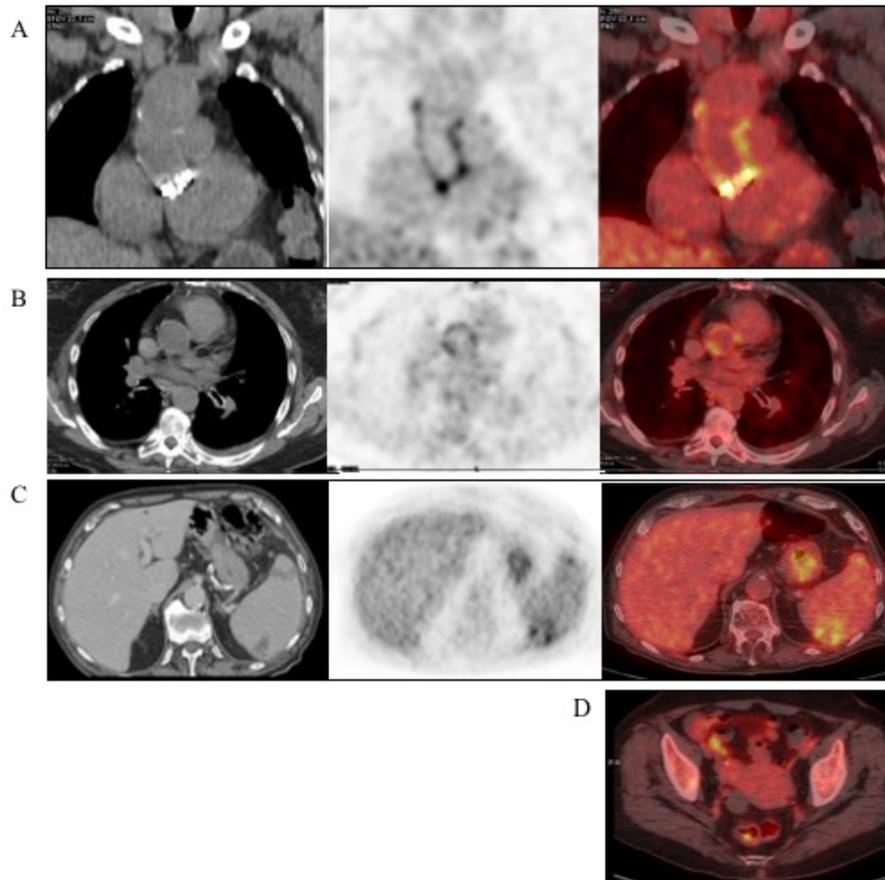
Figure 9 [^{18}F]FDG PET/CT (Discovery 710 PET/CT, GE Healthcare) images in a 36 years old women with severe aortic steno-insufficiency treated with aortic valve + ascending aorta replacement (St. Jude medical 25/28) 10 years ago. The patient developed hyperpyrexia with gastric pain and finger paresthesia and undervent empiric antimicrobial treatment. ESR and CRP were mild increased and blood culture was positive with isolation of *Streptococcus infantarius*. Echocardiography was negative. PET/CT was performed after 24 hours of LCHF diet. Images show suppression of myocardial [^{18}F]FDG uptake. An area of uptake was found at the aortic valve prosthesis (B, transaxial view from left to right CT, emission and superimposed PET/CT) associate with linear and homogeneous uptake at the ascending aortic prosthesis (A, coronal view from left to right CT, emission and superimposed PET/CT). In addition, spleen uptake (C, transaxial view from left to right CT, emission and superimposed PET/CT) as well as at the rectal posterior-left wall (B, transaxial view from left to right CT, emission and superimposed PET/CT) were also found. The final clinical and histopathological findings confirmed the presence of IE with spleen embolism and rectal cancer. Due to the pattern of uptake the finding at the vascular thoracic aorta proathesis is considered aspecific.
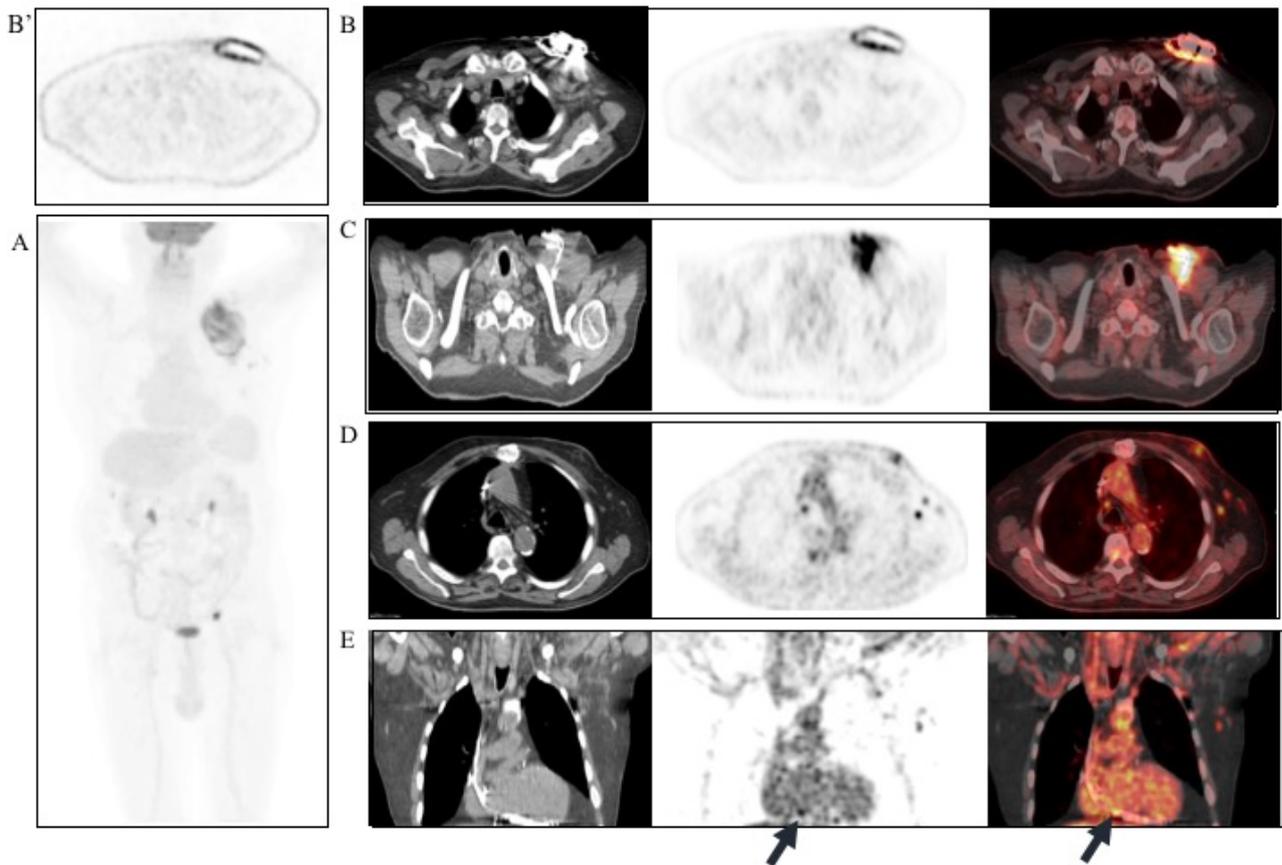
Figure 10 Woman, 73 years PM since 3 years and fever from several weeks with mild increased CRP and ESR. Ecocardiography was negative. Antimicrobial treatment was initiated.

PET/CT images (Discovery 710 PET/CT, GE Healthcare) show increased uptake of [^{18}F]FDG around the pocket (A MIP images; B, transaxial images from left to right CT, emission and superimposed PET/CT). NAC images confirmed the uptake (B', transaxial images). Infection involved also the intravascular portion of the electrocateters (C, transaxial images from left to right CT, emission and superimposed PET/CT) and the intracardiac portion of the electrocatetr (E, black arrow; coronal view from left to right CT, emission and superimposed PET/CT), very limited in extension. This latter finding demonstrate the difficulties in identifing very small foci of infection around the catheters, particularly when the patient is under antimicrobial treatment. Increased [^{18}F]FDG uptake in also present at mediastinal and left axillary lymph-nodes (D transaxial images from left to right CT, emission and superimposed PET/CT). Based on the scan results, the patient was treated with removal of the device and prolonged antimicrobial treatment.
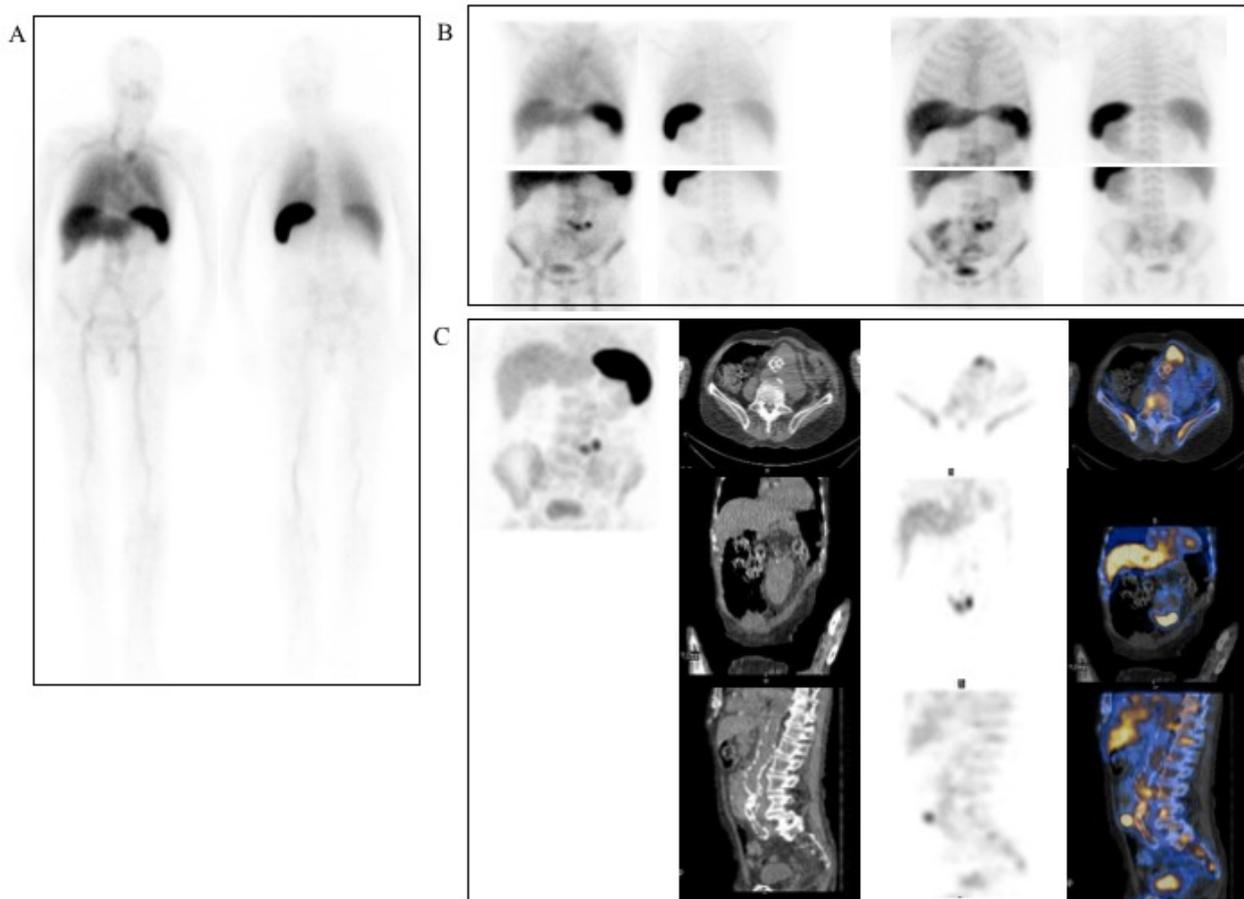
Figure 11 Radiolabelled WBC scan of a patient with suspected infection of a aorto-bisiliac prosthesis. Whole body images (Discovery 670 SPET/CT, GE Healthcare) were acquired at 30 minutes (A) followed by planar spot images of the thorax (B upper pane, left at 30 minutes and right at 6 hours) and the abdomen (B lower panel, left at 30 minutes and right at 6 hours). Intense uptake in the abdomen is evident, further localized at SPECT/CT images at the anterior aspect of the vascular prosthesis collection (C, left panel 3D, MIP images and left panel from top to bottom transaxial, coronal and sagittal views, from left to right CT, emission and superimposed SPECT/CT). Based on the scan result, the patient was treated with surgical removal of the prosthesis.
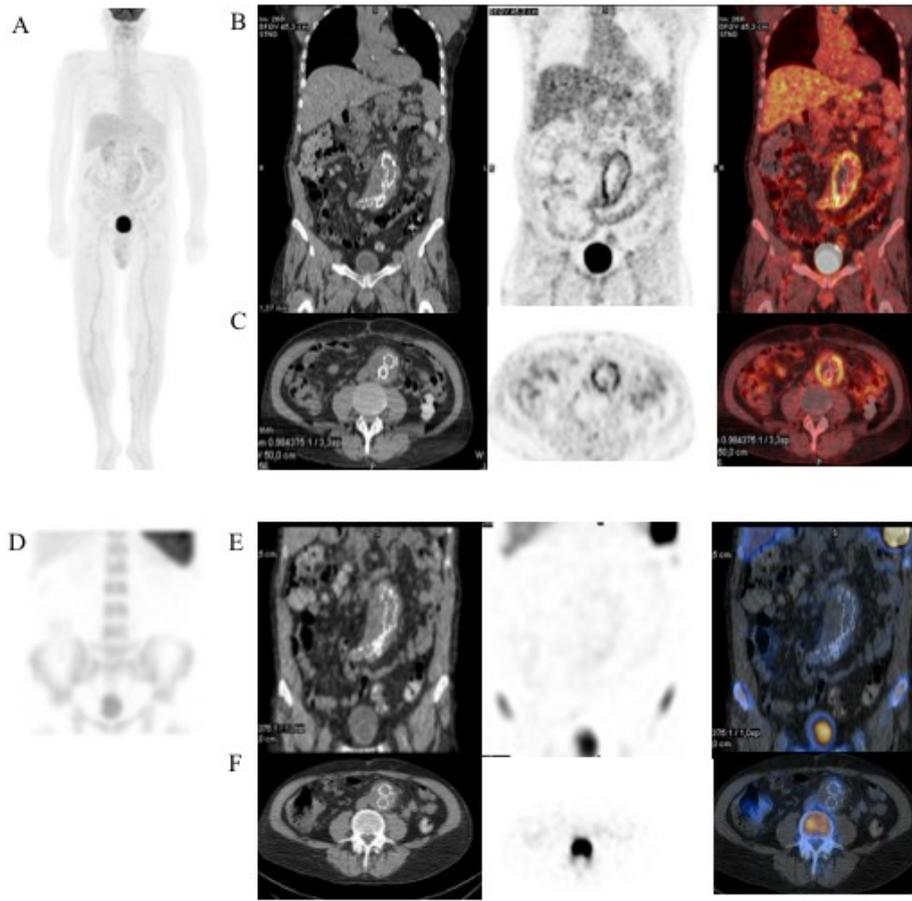
Figure 12 Man, 64 years old. HIV positivity and history of drug abuse, previous liver transplantation and AAA treated with EVAR in 2014. In March 2015, the patient develop fever. ESR was moderately increased whereas CRP was negative.

We first performed PET/CT (upper panel, A MIP images Discovery 710 PET/CT GE Healthcare). Images show an area of uptake linear and homogeneous all around the native aneurismatic vessel wall (B and C coronal and transaxial view, respectively; from left to right CT, emission and superimposed PET/CT). The finding suggested intense inflammation at the vascular wall, but no sign of focal uptake as in case of infection were evident. Within 5 days the patient underwent also radiolabelled WBC scan (lower panel, D, MIP images of the abdominal area, E and F coronal and transaxial view, respectively; from left to right CT, emission and superimposed SPET/CT) which resulted negative, confirming the PET/Ct findings.
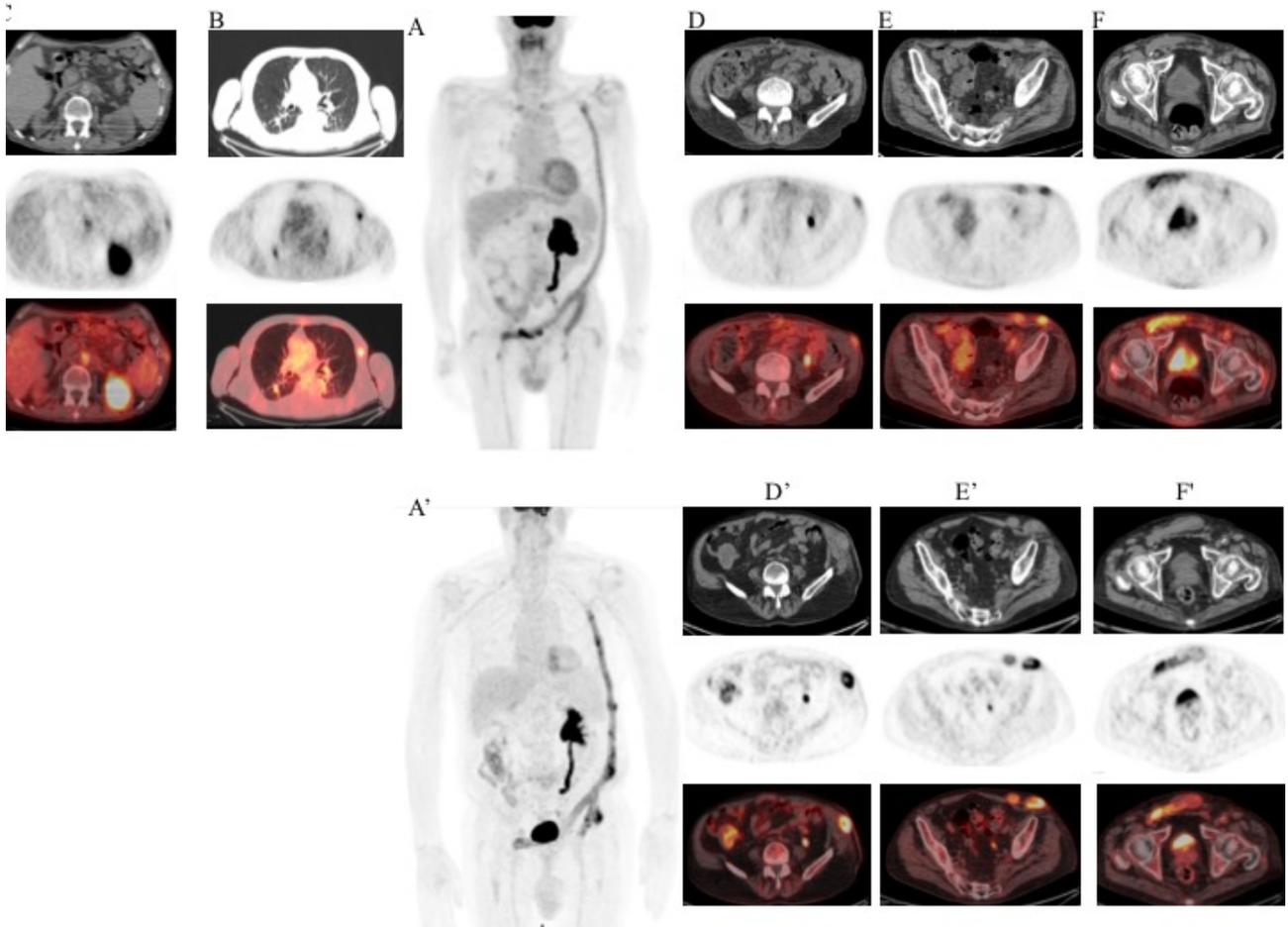
Figure 13 Man, 70 years old. With infection of an aorto-bisiliac graft, surgically removed and subsituted with axillary-bifemural graft in 2012. After surgery, the patient presented recurrent fever with dyspnoea, increased ESR and normal CT findings. PET/CT was performed 6 months after surgery (A, MIP images - Discovery ST PET/CT GE Healthcare) to evaluate possible source of infection. Images show an area of uptake at the right lung upper lobe (B, from top to bottom transaxial CT, emission and superimposed PET/CT images, respectively) and in the abdomen, just below the celiac tripod, at the vascular and perivascular space (C, from top to bottom transaxial CT, emission and superimposed PET/CT images, respectively), consistent with persistent infection. As collateral finding intense visualization of the left kidney and left ureter. Of interest, the pattern of uptake along the vascular graft is characterized by diffuse, linear and homogeneous uptake. This finding is due to foreiner body response and should not be confounded with infection.

The patient was treated with antimicrobial treatment.

After 3 years during follow-up echography showed periprotesic collections. The patient shortly after develop fever with increased ESR and PCR. Therefore, a new PET/CT scan was performed (A' MIP images, Discovery 710 PET/CT GE Healthcare). Diffuse, linear and homogeneous uptake along the vascular graft is still present, but several areas of focal uptake are evident corresponding to perigraft collections at CT (D', E', F' from top to bottom transaxial CT, emission and superimposed PET/CT images respectively). For comparison images obtained at the same level at the first Pet/CT are shown inD, E an F (from top to bottom transaxial CT, emission and superimposed PET/CT images, respectively) Based on the PET/CT result, antimicrobial treatment was initiated. The finding at the left kidney was unmodified.
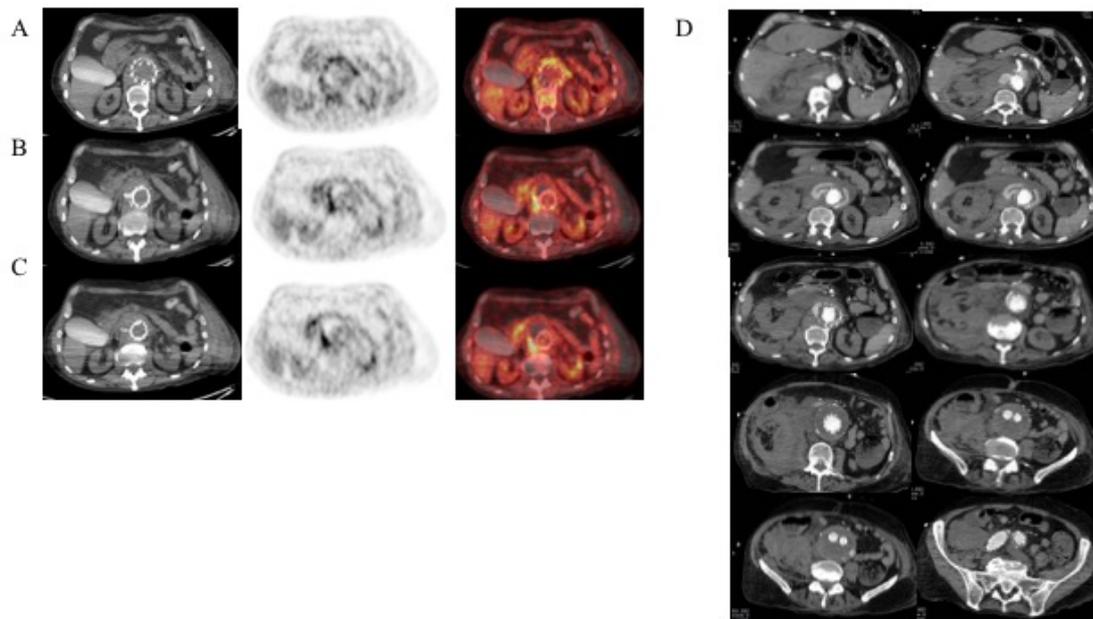
Figure 14 Man, 74 years abdominal pain, increase of ESR and CRP. Empiric antimicrobial treatment was initiated. The patient suffers from IBD and was in treatment with steroids, in 2014, he underwenr apical left lung resection for SCLC and aorto-bisiliac endoprosthesis. Shortly after, the patient developed a pseudoaneurysm of the abdominal aorta above the endoprosthesis which was rapidly enlarging, that was treated with EVAR positioning. In the suspicion of infection, PET/CT was performed (Discovery 710 PET/CT GE Healthcare). Area of increased [^{18}F]FDG uptake with focal pattern were found around the distal portion of the aorto-bisiliac endoprosthesis, both at anterior (A from left to right CT, superimposed PET/CT and emission images, respectively) and posterolateral aspects (B, C from left to right CT, superimposed PET/CT and emission images, respectively).
ce-CT performed shortly after to follow-up the patients showed blushing of the contrast agent, as for prosthesis leakage

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