**REVIEW ARTICLE**

# Current Status of Molecular Imaging in Infections

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**Abstract:** There is an increased need to find non-invasive tools for early diagnosis and follow-up of infections. Nuclear medicine techniques may be used to diagnose, localize and evaluate the severity and the extent of infections before the occurrence of anatomical abnormalities.

This review focuses on different approaches based on radiolabelled cells, peptides and antibodies or [18F]FDG to image infective diseases in agreement with what is being jointly evaluated by the European Association of Nuclear Medicine (EANM).

This is particularly relevant, since the EANM has strated a wide program of collaboration with other European clinical societies to define common diagnostic flow-charts in many of these infective diseases.

It emerges the role of radiolabelled WBC by SPECT/CT for prosthetic joint infections and of FDG by PET/CT for spondylodiscitis. Comparable values of accuracy have been described for WBC and FDG in the diagnosis of vascular fgraft infections, diabetic gfoot, endocarditis and peripheral bone osteomyelitis, with some exceptions.

**Keywords:** Nuclear medicine, radiopharmaceutical, Infection imaging, hybrid imaging.

## 1. INTRODUCTION

In the recent years, we observed an increased need by clinicians to rely on accurate tools for early diagnosis and follow-up of infections, with particular regard to muscoloskeletal and cardiovascular infections. Most importantly, the already available diagnostic techniques need to be correctly positioned in the diagnostic flow-chart of these diseases for a correct management of patients. To this purpose, in the last 10 years the European Association of Nuclear Medicine (EANM), has collaborated with several other European societies (European Society of Radiology, ESR, European Society of Neuroradiology, ESNR, European Society of Cardiology, ESC, European Society) and also with the american Society of Nuclear Medicine and Molecular Imaging (SNMMI).

Several guidelines have been published and others are on the way to be produced. Overall, they emphasize the key role of nuclear medicine techiniques in most occult infections, and most importantly which technique should be peferencially used and when.

Indeed, molecular imaging of infection has been enormously augmented during the past decades, gaining notability in clinical practice for diagnostic and prognostic purposes as well as for treatment decision making. Such strengthening relies on the ability of molecular imaging to point up singular phase of disease onset beside the pure morphological anomalies, generally depicted by the majority of radiological imaging procedures [1].

Computed tomography (CT) and ultrasonography (US) are used for patient's decision making once macroscopic changes are present. However these morphological techniques have some limitations expecially in the early phase of infectious processes when indistinctive sights of disease are manifest and when foreign bodies, implants or prosthesis are present [1].

A large number of radiopharmaceuticals have been developed and used for scintigraphic imaging of infection. Infection specifically refers to the invasion of malignant micro-organisms, whereas inflammation is the response of the immune system against any type of disorder or injury. There may be inflammation without infection or, more rarely, infection without inflammation depending upon the cause of the disease or injury [2].

For infection diagnosis, several radiopharmaceuticals may be used and the choice of the most appropriate mainly depends on pathophysiology and patho-biochemical features of each single disease [2]. In the present scenario, there is no single ideal radiopharmaceutical for imaging infectious diseases. Clinicians must guide their preference according to the purpose of the investigation: when differential diagnosis is the issue, specific radiopharmaceutical should be preferred. In case of low probability of septic disease to define disease extent of a well established diagnosis, less specific molecules may also be considered. Furthermore, distictive propriety to target specifically selected antigen, specific metabolic pathway or cellular process may contribute to therapy decision making and follow-up in different clinical settings. For this scope radiopharmaceutical embracing very high negative predictive value will be preferable. In addition, for the clinically available radiopharmaceuticals that are not targeting the infectious agents, but the immunological response of our body to the infectious noxa, to achieve a differential diagnosis between inflammation and infection specific acquisition parameters and interpretation criteria should be always applied.

Besides the role of well established and novel radiopharmaceuticals, advancements of innovative equipment which have increased spatial resolution allowing the detection of smaller and smaller sites of disease should be also mentioned. Indeed, the event of hybrid imaging, both SPECT/CT and PET/CT has transformed nuclear medicine planar images into 3D functional-anatomical traking of cell function, encouraging the scientific community to a redefinition of their stenght and limitation for a comprehensive patient management. In some clinical condition (i.e. deep structure visualization, post-surgical tissue changes) the use of the CT com-

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ponent of the nuclear medicine procedure is mandatory for the correct interpretation of images. The real challenge of the future will be surely represented by the appropriate definition of the role of multimodal procedures into the complex diagnostic and therapeutic chain allowing the most appropriate and up-to date clinical management.

This review focuses on the current state of the art of nuclear medicine imaging in the most clinically relevant infectious diseases.

## 2. MOLECULAR IMAGING OF INFECTION

### 2.1. Bone Infections

#### 2.1.1. Peripheral Bone Osteomyelitis

Osteomyelitis is most commonly caused by pyogenic bacteria and mycobacteria. Hematogenous osteomyelitis is typical of children as consequence of a contiguous focus of infection or associated with vascular insufficiency. Its manifestations are heterogeneous, depending on the age of the patient, specific causative microorganism, anatomic area of involvement, segment of affected bone, route of contamination, systemic and local host factors, as well as the presence of underlying co-morbidities [3-5]. Laboratory tests are generally abnormal in case of acute disease. X-ray is used to exclude other diseases that can mimic osteomyelitis such as fractures and tumors. However, X-ray may take time (10 to 21 days) to identify bone changes since 30% to 50% reduction of bone density is necessary to be detectable (sensitivity 43-75% and specificity 75-83%) [3, 6]. MRI is extremely useful for the diagnosis of osteomyelitis and it is the preferred imaging modality when plain radiographs are negative also allowing evaluation of complications (i.e. subperiosteal and soft-tissue abscesses). MRI is highly sensitive for detecting osteomyelitis as early as 3 to 5 days (sensitivity 82-100% and specificity 75-96%). Bone scintigraphy can be performed when symptoms are not localized or there is clinical suspicion for multifocal osteomyelitis [3, 6, 7]. Bone scan is extremely sensitive in diagnosing osteomyelitis (> 90%) with high specificity in case of underlying normal bone while it decreases to 35% in case of post-traumatic disease or after surgery. SPECT/CT acquisitions further increase specificity [6, 8]. Leukocyte scintigraphy presents excellent diagnostic accuracy up to 89% with value of sensitivity and specificity ranging from 83% to 89% and 84% to 90% [9-13] (Fig. 1). Accuracy is further improved by the use of time decay corrected protocols for imaging acquisition and by the use of semiquantitative analysis for imaging interpretation [14, 15]. Similar performances (81% sensitivity and 84% specificity) were observed for antigranulocyte scintigraphy with MoAbs with higher sensitivity rates observed for peripheral lesions compared with axial lesions [16]. A new murine IgG1k antibody BW 250/183, $^{99m}$Tc-besilesomab (Scintimun®) against granulocytes and granulocyte precursor non-specific cross-reacting antigen 95 has been more recently introduced for imaging peripheral osteomyelitis. Results of a phase III clinical trial demonstrated that Scintimun® performed similarly to $^{99m}$Tc-HMPAO-WBC, with higher sensitivity (74.8% versus 59.0%) and at slightly lower specificity (71.8% versus 79.5%, respectively), particularly in chronic osteomyelitis [17]. However, human anti-murine antibodies (HAMA), detected in 14% of patients after scintigraphy [17] may limited its application in case of repeated studies. When SPECT/CT is added to planar and tomographic acquisitions, improvement both in diagnosis and localization of infectious site is reported for $^{67}$Ga and labeled leukocyte (either $^{111}$In and $^{99m}$Tc-HMPAO) in up to 55% of patients assessed for osteomyelitis [18] or relapsing osteomyelitis on bone with structural abnormalities after trauma [19, 20]. The main value of hybrid technology is essentially related to the precise anatomic localization of infection and delineation of the extent of the infectious process after the initial identification with planar images [6]. Radiolabeling of leukocyte with [$^{18}$F]FDG has been proposed, but data on patients with osteomyelitis are few [21] (accuracy of 46% according to Rini

*et al.* [9]) and the application still remains experimental. Radiolabeled antibodies performed poorer compared to autologous leukocyte scintigraphy (accuracy ranging from 75-86%), while no data on the use of [$^{18}$F]FDG-PET and PET/CT in primary appendicular osteomyelitis are available (exect for chronic, see below) [10]. $^{99m}$Tc-ciprofloxacin (Infecton™, a radiolabeled broad-spectrum fluoroquinolone that inhibits the DNA-gyrase and/or 8 topoisomerase IV of bacteria) have been used in pediatrics patients with clinical suspicion of osteomyelitis (98% sensitivity and 100% specificity, with a 100% positive predictive value and a 87% negative predictive [22]) despite the low specificity for osteoarticular infections (aspecific accumulation in growth plates, non-infected prosthetic knees, pseudoarthrosis, palindromic rheumatism, and postoperative fibrosis of the lumbar spine, avascular hip necrosis, fibrous dysplasia, non-union fracture, and uninfected prosthetic joints [23-28] (those resultshad also been reported in animal model with another radiolabeled quinolone, $^{14}$C-sparfloxacin [29]). Preliminary results of $^{68}$Ga-citrate PET/CT compared to different combinations of diagnostic procedures (MRI, radiography, CT, or labeled WBC scintigraphy), biopsy (when diagnostic), and follow-up data (at least 1 year), have been reported in 31 patients with suspected osteomyelitis or diskitis. $^{68}$Ga-citrate PET/CT resulted in sensitivity 100%, specificity 76%, positive predictive value 85%, negative predictive value 100%, with an overall accuracy of 90%) [30] suggesting its possible role in the diagnosis of bone infections, especially based on its favorable characteristics. Differently from to acute osteomyelitis, low-grade and chronic infections are more difficult to diagnose using current imaging modalities. [$^{18}$F]FDG-PET has been reported as the most sensitive and specific technique (88-100% and 73-95%) as compared to bone scintigraphy (70-89% and 16-36%), leukocyte scintigraphy (43-76% and 63-87%) and to combined bone and leukocyte scans (72-100% and 75-93%). Sensitivity of WBC scan for chronic osteomyelitis of the peripheral skeleton maintains high value (72-91%) while it decreases significantly for the axial skeleton (11-38%) [10, 31-33]. PET success relies on the ability of [$^{18}$F]FDG to be avidly taken up by activated macrophages in the chronic phases of infection. According to the literature, osteomyelitis can be virtually rule out by a negative [$^{18}$F]FDG-PET scan [34-37].

More recently, early dynamic PET/CT using [$^{18}$F]NaF or [$^{18}$F]FDG has been tested in chronic osteomyelitis suggesting that data on the early radiotracer distribution may provide additional information than standard acquisition however results to be validated prospectively in larger trials [38, 39].

In case of osteomyelitis of the peripheral skeleton leukocyte scintigraphy (either autologous leukocytes or antigranulocyte MoAbs) presents excellent diagnostic accuracy with important advantage when SPECT/CT is performed. For chronic osteomyelitis of the peripheral skeleton WBC and [$^{18}$F]FDG-PET perform similarly with a potential advantage in sensitivity of this latter related to the extremely high negative predictive value.

#### 2.1.2. Sternum, Jaw and Skull Osteomyelitis

Post-surgery sternal wound infection (both superficial and deep) is a potential life-threatening condition requiring a prompt diagnosis for optimal treatment. The differential diagnosis between superficial and deep infections is crucial since their prognosis is extremely diverse. Superficial infection has a good prognosis when tempestively treated while deep infection presents an unfavourable prognosis [40]. Several radiopharmaceuticals ($^{67}$Ga, $^{99m}$Tc-MDP, $^{111}$In-WBCs, $^{99m}$Tc-HMPAO-WBC, $^{99m}$Tc-MoAb anti-granulocyte antibodies and [$^{18}$F]FDG) have been used in patients with sternal infections because of limitation of CT findings (low specificity and sensitivity in early phase) and aspirate pitfalls in the immediate post-surgical setting (inflammation), but the real element affecting the diagnostic accuracy of nuclear medicine procedures is the acquisition of tomographic images (included CT co-registration) [41]. Clinically the most extensively used radiopharmaceuticals are $^{67}$Ga
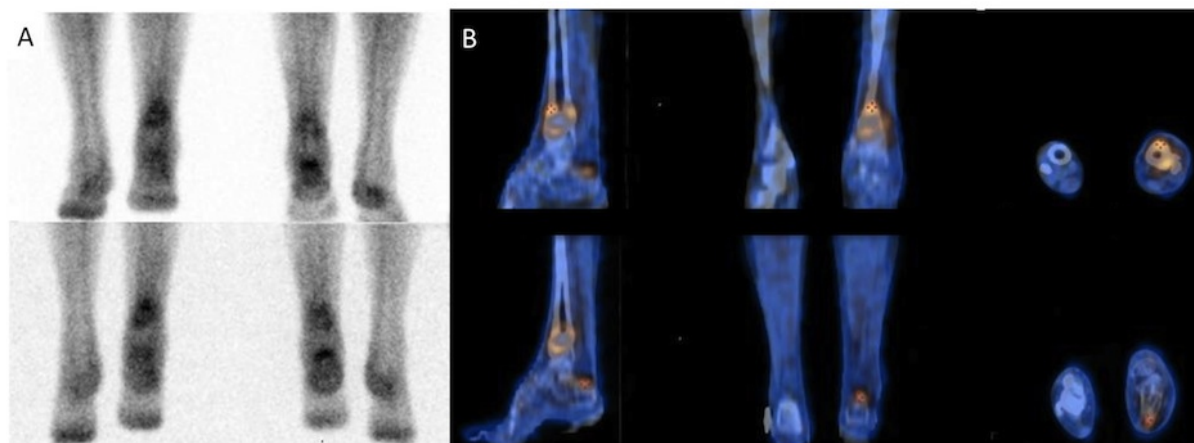
**Fig. (1).** Post-surgical osteomyelitis in a patient with traumatic fracture of the left tibia. Radiolabelled WBCs planar images at 4 (A upper panel, left anterior view and right posterior view) and 24 hrs (A lower panel, left anterior view and right posterior view) show the presence of a infective foci that at the subsequent SPECT/CT images (B superimposed SPECT/CT images, from left to right sagittal coronal and transaxial images, respectively) was localized at the distal aspect of the tibia and the soft tissue of the calcaneus.

and radiolabeled WBC. Gallium-67 is useless both for high suspicion of sternal bone osteomyelitis and borderline cases (about 74% sensitivity) [10, 42]. Labeled WBC scintigraphy has been demonstrated as the most useful technique to differentiate superficial from deep wound infection with higher value of sensitivity, specificity and accuracy (also in the early post-surgical setting) when technetium-99m radiolabeling is used (sensitivity around 100% and specificity 88%) [10, 43, 44]. Additionally, in case of suspicion of mediastinitis relapse a negative labeled WBC scintigraphy is able to rule out infection, potentially impacting on therapeutic management in patients with poor clinical status [45].

Jaw ostemyelitis, either acute or chronic (suppurative, nonsuppurative, osteoradionecrosis bisphosphonate-related, Garre` osteomyelitis, chronic recurrent multifocal, and sclerosing), are uncommon infections often difficult to diagnose resulting in treatment delays and increase morbidity [46-50]. Because pre-therapeutic symptom duration is one of the most significant factors influencing the curability [51] accurate early diagnosis is critical for patients management. Given its frequent odontogenic origin, the initial imaging manifestations of acute osteomyelitis are often observed on plain dental or panorex radiographs. However, X-ray images require a loss of up to 50% of bone mineral density to reveal disease and these studies may be normal for up to 8 days or even as long as 3 weeks from symptom onset [52]. Three-phase bone scan findings may be abnormal as early as 2 to 3 days after symptom onset [53] and uptake during blood flow phase is not usually observed in chronic forms [54]. However, specificity of the bone scan is poor (79%) [55]. Recently, the performance of a novel flat-panel SPECT/CT has been evaluated in patients with suspected jaw osteomyelitis in comparison with conventional orthopantomography, planar bone scintigraphy and CT alone [56]. The specificity of planar bone scintigraphy was improved by the use of SPECT/CT acquisition (71% versus 86% with an accuracy of 95% and 98%, respectively) [56]. Additionally SPECT/CT was superior to CT alone (79%) and conventional orthopantomography (66%) to assess the presence of steomyelitis of the jaw [56]. Specificity of radionuclide examinations is better (especially in patients with indwelling surgical hardware) when using radiolabeled WBC [44] (around 100% sensitivity, 67% specificity, 62% positive predictive value, and 100% negative predictive value) [55]. In treatment-responsive disease, abnormal uptake on WBC scans resolves earlier than CT abnormalities. Additionally, in patients who have contraindications for MRI or those with surgical hardware artifacts that adversely affect MRI quality, WBC scintigraphy is an excellent alternative for treatment surveillance. Whole-body imaging is also useful for de-

tection of multiple sites of disease involvement in cases of non-suppurative primary chronic mandibular osteomyelitis associated with systemic diseases or chronic recurrent multifocal osteomyelitis. If surgical treatment is planned, high-resolution CT is required to specify the degree of cortical destruction, the presence of sequestra in particular, and to define the extent of osseous removal required [49]. Comparative studies of the various modalities are not currently available.

Infections of the skull both primary and post-surgical are generally diagnosed by neurologic examination, laboratory tests and radiological imaging (CT and MRI); however in particular case additional tests are required. Osteomyelitis of the skull is a typical case of improved detection by means of SPECT and SPECT/CT acquisition [57-59]. Nevertheless, few clinical data are available and radiolabeled dyphosphonates and [18F]FDG the most commonly used radiopharmaceutical, primarily for otogenic cranial base [60] and chronic osteomyelitis [61, 62].

### 2.1.3. Spondylodiscitis

Spine infection (also defined as spondylodiscitis, SD) can be primary (haematogenous) or secondary (prevalently due to spine surgery). An early diagnosis is mandatory to establish a proper therapy that when delayed can result in irreversible neurological impairment [63]. The clinical suspicious of spine infection must be confirmed or ruled out by diagnostic imaging, including radiological and nuclear medicine procedures [64, 65]. MRI is the technique of choice in patients with suspected spinal infection especially in haematogenous SD [63]. Nevertheless, post-surgical structural changes may hamper correct interpretation of MRI, thus its diagnostic role during patients follow-up and disease monitoring is questioned [63, 66-69]. CT-guided biopsy has high specificity (100%) but it not routinely employed since its sensitivity ranges between 58% and 91% [70, 71]. Bone and Gallium-67 scans performed similarly (sensitivity of 81% and 41%, specificity of 86% and 36%, respectively). Radiolabeled WBC scintigraphy sensitivity and specificity have been reported ranging from 63% to 84% and from 55% to 100% [10, 14]. SD appears as a "cold" spot at WBC scan (Fig. **2**). [18F]FDG-PET is considered the most sensitive technique for spine infection diagnosis (about 100%), but lower specificity (88%) is the main the limitation of the technique [10, 35]. False positive findings are possible in case of degenerative lesions, bone tumours and post-surgical changes [72]. More recently Fuster *et al.* [73] proposed a pattern of [18F]FDG uptake to increase PET/CT accuracy. Accordingly to this visual criterion, PET/CT was considered positive when [18F]FDG uptake was higher than bone
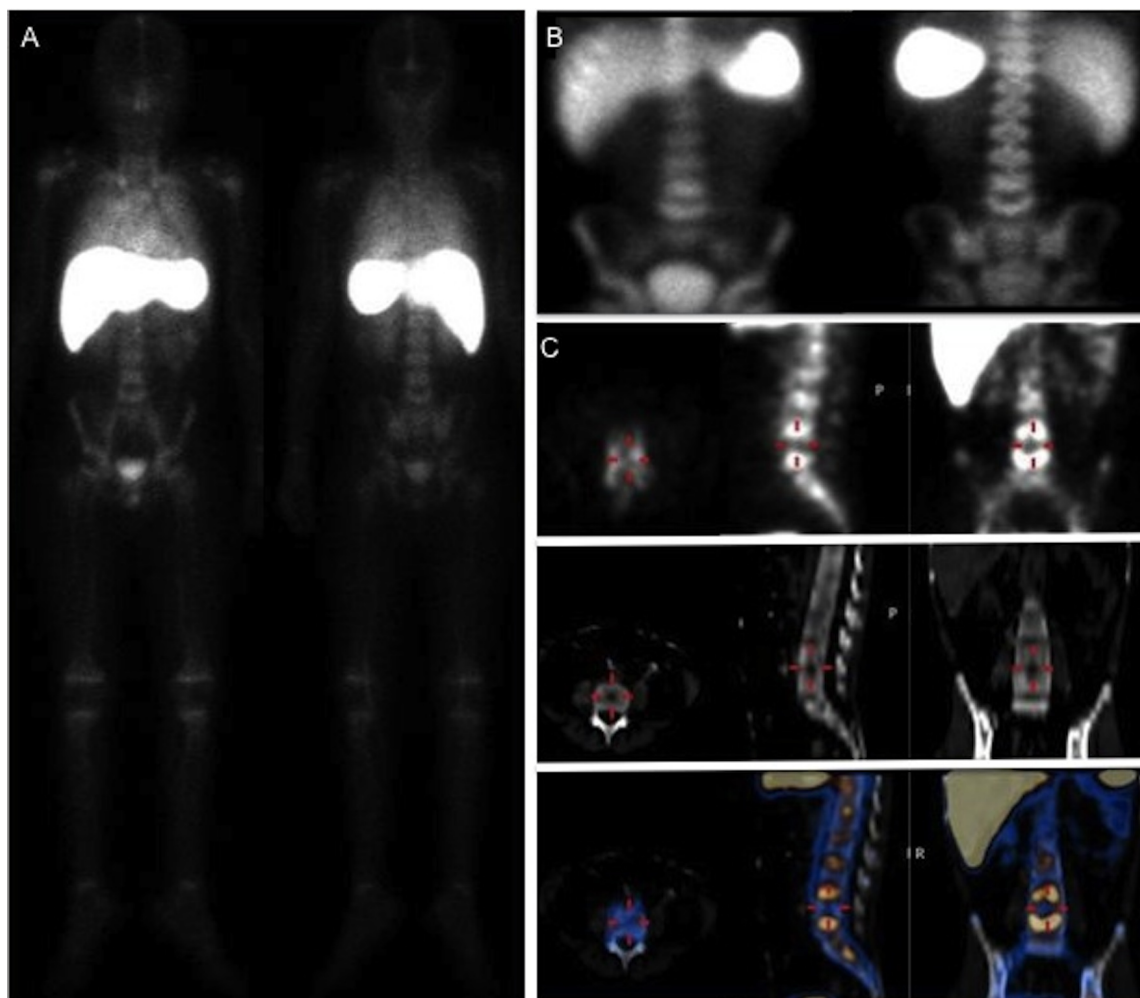
**Fig. (2).** Radiolabeled WBC scintigraphy in a patient with haematogenous spine infection. Whole-body images 30 minutesa after the radiopharmaceuticals administration (A, at left anterior and at right posterio), planar spot images of the admonel-upper pelvis (B, anterior at left and posteriori at right) and SPECT/CT images (C, upper panel emission, middle panel CT and lower panel superimposed SPECT/CT from left to right transaxial, sagittal and coronal and images, respectively) show a "cold" spot in the lumbar spine at the level of L4-L5.

marrow uptake in adjacent vertebras and/or in presence of soft tissue uptake [73]. Additionally, $SUV_{max}$ in an area surrounding the lesion suspected of infection and the background $SUV_{mean}$ in a preserved area of the spine were calculated in all patients. In this series of patients, [$^{18}$F]FDG uptake (quantified as $SUV_{max}$) was significantly higher in patients with spondylodiscitis ($p < 0.005$) using an estimated threshold of 5.324 (95 % CI 4.465 - 6.183). The use of $SUV_{max}$ corrected by the background $SUV_{mean}$ led to a higher level of significance than the use of $SUV_{max}$ alone ($p < 0.001$) with an estimated threshold of 2.2 (95 % CI 2.113 - 2.287). The use of $SUV_{max}$ and $SUV_{max}$ corrected by the background $SUV_{mean}$ showed sensitivities of 56% and 89%, respectively, with 100% specificity for both [73]. Using [$^{18}$F]FDG-PET/CT a strong impact on patients clinical management due to the guidance of the most suitable therapeutic strategy (i.e. start antibiotic therapy or surgical intervention) has been demonstrated in up to 52% of cases [74, 75]. The use of semi-quantitative parameters (e.g. $SUV_{max}$) may be useful to discriminate infection of the spine from other processes [73, 75]. The high negative predictive value of [$^{18}$F]FDG-PET/CT make it a useful method for the discrimination of residual and non residual spine infection during and after treatment (i.e. with use of quantitative indexes % deltaSUVmax) [76-80]. Fig. **3** shows an example of PET/CT in a patient with haematogenous spine infection by MRSA.

Preliminary results with $^{99m}$Tc-ubiquicidin$_{29-41}$ have been reported in patients with suspected SD. The sensitivity and specificity for detecting SD were 100% and 87%, respectively with a positive predictive value of 95% and a negative predictive value of 100%. Although this method was useful in this group of patients to reach at a certain diagnosis, the role of this method in the diagnostic protocol of the patient with suspected SD has not yet been defined [81]. The use of $^{99m}$Tc-ciprofloxacin has been extended to axial skeleton infections without conclusive results: high sensitivity (100%) with a maximum specificity of 74% when SPECT is acquired, but with high false positive rate particularly in the early post-operative setting [35]. An infection specific radiopharmaceutical, $^{111}$In-Biotin has been extensively studied in patients with spine infection showing (n=180) high accuracy (92-93%) [63, 82]. However, this radiopharmaceutical is still in-home experimental preparation and it is not yet commercially available.

In conclusion [$^{18}$F]FDG-PET/CT should be considered the first choice radionuclide test in the presence of high suspicious of spine infection and potentially for the follow-up of patients after antibiotic treatment. The pattern of uptake should be used to increase the diagnostic accuracy. However, it fails in differential diagnosis between infection and others bone pathologies (i.e. spine metastasis, osteoarthritis), thus making an infection specific radiopharmaceutical the really warrant.
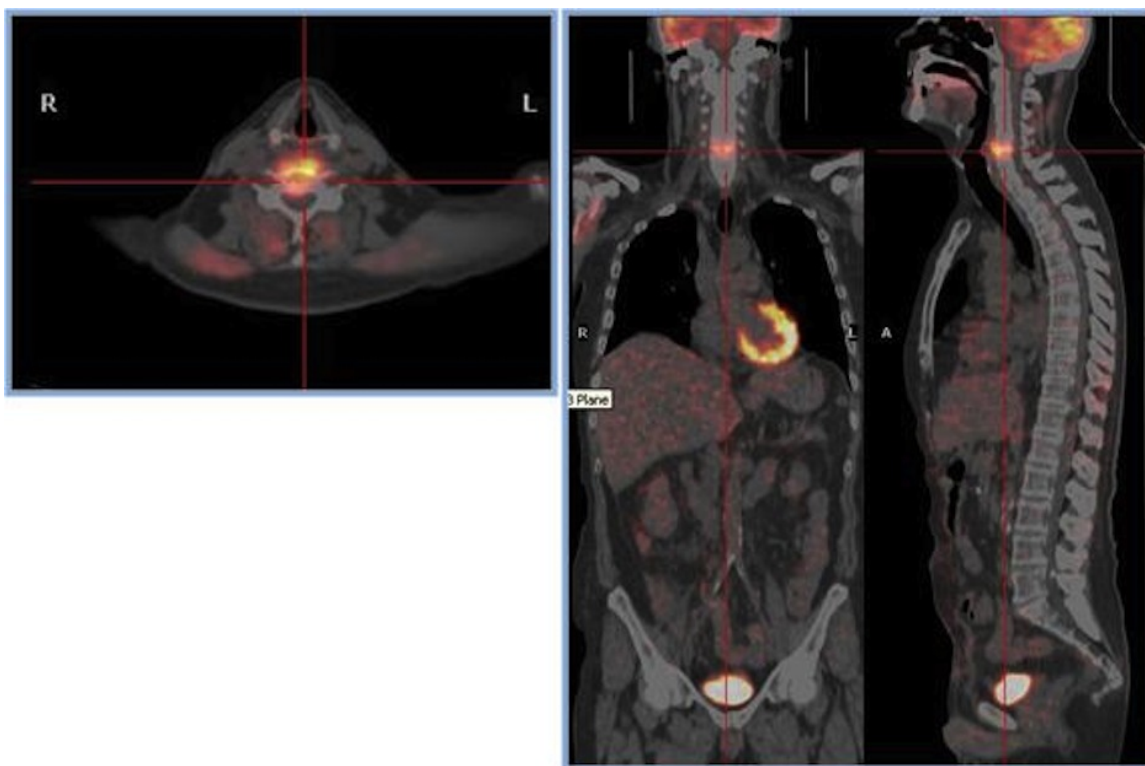
**Fig. (3).** [$^{18}$F]FDG PET/CT in a patient with suspected haematogenous spine infection by MRSA. Fused transaxial (left panel), coronal (middle panel) and sagittal (right panel) PET/CT images show an area of increased radiopharmaceutical uptake at the cervical spine. Linear pattern of uptake at C5-C6 consistents with the clinical suspicious of spine infection.

### 2.1.4. Diabetic Foot Infection

Osteomyelitis of the foot is one of the most commonly encountered complications in diabetic patients. Early diagnosis of diabetic foot infection is crucial to define the treatment [6]. Three-phase bone scintigraphy demonstrated extremely high sensitivity even in the absence of signs and symptoms (69-100%) [6]. Nevertheless, fracture, the neuropathic joint, and even the pedal ulcer all can yield positive 3-phase bone scans making the specificity of the method relatively low (28-62% with lower value of 10% in only one series) [83-92]. To improve sensitivity different attempts have been made. The acquisition of 24 hours image (4-phase) was able to increase specificity (87% versus 73%) with a lack in sensitivity (80% versus 100%) and 85% accuracy adding to semiquantitative analysis [93, 94]. Evaluation of perfusion at 3-phase bone scan in site of suspected infection (arterial hyperperfusion associated with ostepmyelitis venous hyperperfusion with soft tissue infection) allowed to obtain 94% sensitivity and 79% specificity [95].

Sensitivity and specificity values of radiolabeled WBC in the diagnosis of diabetic foot infection ranging from 75% to 100% and from 69% to 89% [83, 87, 96] for $^{111}$In-oxine labeling while for $^{99m}$Tc-HMPAO labeling range from 86% to 93% and 80% to 98% [88, 89, 97].

Compared to bone scan, leukocyte imaging demonstrates higher sensitivity (89% versus 69%) and specificity (69% versus 39%) [86, 98]. All studies are based on the evaluation of planar early and delayed images (4 and 24 hours) with some specific interpretation criteria (i.e. radiotracer uptake increased from early to late images). Using bone scan as anatomic reference, sensitivity and specificity may be improved (up to 100% and to 97%, respectively) [89, 96]. SPECT/CT may contribute to increase the specificity of the labeled leukocytes imaging substituting CT acquisition to the injection of $^{99m}$Tc-MDP; the ability to discriminate bone involvement from the sole soft tissue localization of infection results in a modification of the interpretation of images in up to 53% of cases both with Gallium-67 and radiolabeled WBC [18, 99]. Despite proved utility, the small size of metatarsal and foot toes may hamper difficulties in the evaluation and discrimination of bone form soft tissue even with SPECT/CT; probably the use of new generation SPECT/CT equipment with multislices CT detector might overcome these obstacles. Additionally, radiolabeled WBC SPECT/CT showed higher specificity and positive predictive value than three-phase bone scintigraphy in predicting osteomyelitis relapse after antibiotic treatment discontinuation (91% versus 12% and 71% versus 15%, respectively) [100]. Dual-isotope SPECT/CT ($^{99m}$Tc-HMDP plus $^{111}$In-WBC) has been compared to conventional imaging (plain radiography, CT, planar bone scan, planar $^{111}$In-WBC scan, and MRI) in a similar number of patients (227 versus 232). In this large population of diabetic patients with suspected foot infection, dual-isotope SPECT/CT was more accurate in diagnosing and localizing infection compared with conventional imaging. Nonetheless, it provided clear guidance, promoted many limb salvage procedures, and was associated with considerably reduced length of hospitalization compared with conventional imaging impacting also on health economics [101].

Combined 4-phase MDP and $^{99m}$Tc-HMPAO-WBC resulted in higher sensitivity and specificity (91% and 67%) compared to MRI (78% and 60%) and microbiological examination (92% and 60%) using histopathologic bone tissue specimens as gold standard [102]. More recently, MRI has been fused with $^{111}$In-WBC/$^{99m}$Tc-HDP SPECT/CT in a small series of diabetic foot infections patients in order to better localize the infection helping in conservative treatment planning and limbing salvage procedures [103].

Radiolabeled anti-granulocytes antibodies have demonstrated value of sensitivity and specificity of about 93% and 78% for MAb

BW 250/183 [104], 90% and 67% for murine IgM mAb (against CD15, Fanolesomab) [90] and 95% and 70% for an anti-granulocyte antibody murine IgG anti-NCA-90 (Leukoscan®) [105].

The combination of Leukoscan and $^{99m}$Tc-MDP bone scan shows better sensitivity and specificity when compared to bone and $^{67}$Ga scan combination (67-86% and 84-85% versus 44% and 77%, respectively) [106, 107]. As compared to $^{99m}$Tc-MDP 3-phase scintigraphy performances $^{99m}$Tc-IgG demonstrated similar sensitivity with higher specificity (63% versus 54%) and accuracy (83% versus 74%). Specificity may be improved by 24 hours images evaluation (77%) at the price of decrease of overall accuracy (70%) [108]. Infecton™ has also been evaluated in diabetic foot osteomyelitis, mainly in association with 3-phase bone scintigraphy (accuracy around 72%); false negative results generally occours in case of ciprofloxacin-resistant bacterial flora [25, 109-111]. $^{99m}$Tc-labelled nanocolloids scintigraphy has also been used in a limited series of diabetic patients with neuropathic foot disease showing high sensitivity (100%) and low specificity (about 60%) mainly as a consequence of the aspecific mechanism of accumulation in infectious site (extravasation through the capillary basement membrane, followed by phagocytosis or adsorption of the particles by granulocytes and macrophages) [112].

Aslangul *et al.* [113] evaluated a method for definitively diagnosing osteomyelitis in patients presenting with a foot ulcer and clinically suspected osteomyelitis but without soft tissue infection. They used a combined approach using $^{67}$Ga-SPECT/CT plus a percutaneous bone puncture. In case of postive scan and positive bone culture patients recieved culture-guided antimicrobial treatment while patients with negative imaging or with positive imaging but negative bone culture were not treated. This approach resulted in high sensitivity and specificity (88% and 94%) for diagnosing diabetic foot osteomyelitis, obviating the need for antibiotic treatment in more than half of suspected cases.

More recently, the utility of $^{99m}$Tc-ubiquicidin$_{29-41}$ scintigraphy in combination with three-phase bone scan, has been evaluate in a pilot study in 65 diabetic patients with suspected osteomyelitis of the foot with very promising results (sensitivity, specificity and accuracy of 100%) [114].

[$^{18}$F]FDG-PET and PET/CT represent an extremely interesting possibility for the evaluation of diabetic foot complications. Initial data on the use of [$^{18}$F]FDG-PET/CT in diabetic foot infection, demonstrate increased [$^{18}$F]FDG with the possibility to differentiate soft tissue from bone uptake by CT imaging with overall accuracy of 70-90% with [$^{18}$F]FDG-PET [115, 116], increasing up to 95% with [$^{18}$F]FDG-PET/CT [117-119]. Few and contractictory data are available on the comparison between [$^{18}$F]FDG-PET and MRI since first experience describing MRI as most accurate than PET (90% versus 70%) [115] have been confuted (MRI 81% versus PET 90%) [116].

A direct comparison between three-phase bone scan and [$^{18}$F]FDG-PET/CT in 79 patients with complicated diabetic foot, showed higher specificity and NPV for [$^{18}$F]FDG-PET/CT than three-phase bone scan in diagnosing pedal osteomyelitis (71% *versus* 28% and 71% *versus* 40%) while three-phase bone scan was found to be more sensitive and useful than [$^{18}$F]FDG-PET/CT in detecting early Charcot's neuropathy as it incrementally diagnosed early neuropathic foot in 8 more patients thereby warning the clinician to bring about more stricter glycemic controls in them and to adopt preventive conservative measures like off-loading of the foot or advising molded foot wear in them so as to help prevent further clinical or symptomatic deterioration [92].

A direct comparison between [$^{18}$F]FDG-PET and $^{99m}$Tc-labeled monoclonal anti-granulocyte antibody scintigraphy in diabetic patients with chronic foot ulcers, showed a clear advantage of [$^{18}$F]FDG-PET (70% versus 65% accuracy) with high negative predictive value. Furthermore, [$^{18}$F]FDG-PET may be used for

differentiating osteomyelitis and soft tissue infection from the uncomplicated neuropathic joint (accuracy of about 94% versus 75% of MRI) [117].

A direct comparison between [$^{18}$F]FDG-PET/CT (three time points images at 10 minutes, 1 and 2 hours after radiopharmaceutical administration) and $^{99m}$Tc-HMPAO-WBC scintigraphy (early and delayed images) has also been performed in diabetic patients with pedal osteomyelitis [120]. Using a time dependent increased target/background ratio > 2.0 at 20 hours images as interpretation criteria for a positive scan $^{99m}$Tc-HMPAO-WBC scintigraphy, sensitivity, specificity, positive predictive value, negative predictive value, and accuracy for osteomyelitis diagnosis were 86%, 100%, 100%, 86%, and 92%, respectively. Similarly, for [$^{18}$F]FDG-PET the better interpretation criteria for the diagnosis of osteomyelitis was a SUVmax value > 2.0 at 2 hours scan with time-increasing fashion (sensitivity = 43%, specificity = 67%, positive predictive value = 60%, negative predictive value = 50%, and accuracy = 54%); combining visual assessment of PET images at 1 hours and CT findings the diagnostic accuracy increased to 62%.

In conclusion, radiolabeled leukocyte imaging is the nuclear medicine procedure of choice for investigation of diabetic foot infections. In presence of low clinical suspicion of osteomyelitis of the forefoot and contemplated medical treatment, a 3-phase bone scan followed by a radiolabeled leukocytes scintigraphy are the studies of choice. For suspected infection of the mid and hind foot, radiolabeled leukocytes imaging is the most accurate test for determining the presence of infection, although, a positive result may requires a complementary study with a marrow agent. SPECT/CT acquisition will improve diagnostic accuracy, especially in the mid and hind foot while for the evaluation of the forefoot it may be useless. Data on [$^{18}$F]FDG-PET and PET/CT are limited, but extremely promising and require further investigation before the introduction into daily clinical practice.

### 2.1.5. Prosthetic Joint Infections

While radiographic technique may be easily diagnosed prosthesis failures caused by heterotopic ossification, fracture, and dislocation differential diagnosis between aseptic loosening (> 25% of all prostheses and associated with inflammation with histiocytes, giant cells, lymphocytes and plasma cells recruitment and generally managed with a single-stage exchange arthroplasty) and infection (about 1-2% for primary implants, 3-5% for revision implants characterized by neutrophils infiltrations, treated with debridement without removal of the prosthesis, one or two-stage replacement + protracted antimicrobial therapy, permanent removal + arthrodesis + suppressive long term antibiotic treatment) is challenging. Clinical signs, biochemical tests may be absent and inconclusive. Joint aspiration with Gram stain and culture (considered the gold standard) presents variable sensitivity ranging from 28% to 92% (specificity 92-100%). Plain radiographs are neither sensitive nor specific and CT and MRI may be limited by hardware induced artifacts. Functional procedures already considered the method of choice for such differential diagnosis, but suffering from the limitation of poor anatomical landmarks, have increased diagnostic accuracy with the availability of hybrid imaging modalities (SPECT/CT and PET/CT, Fig. **4**). The most extensively used radiopharmaceutical for bone infection diagnosis is represented by radiolabeled autologous leukocytes (either with $^{99m}$Tc-HMPAO or $^{111}$In-Oxina associated with bone marrow images) with about, 89% diagnostic accuracy, sensitivity (83-89%) and specificity (84-94%) [9, 10]. The use of standardized acquisition protocol using time-decay corrected images [14, 15] as well as SPECT/TC acquisition further increase the diagnostic accuracy by either decreasing the rate of false positive findings and allowing more accurate anatomical localization and extension of bone and joint infection site [14, 15,19, 121, 122].

[$^{18}$F]FDG in vitro radiolabeled leukocytes represent an initial attempt to develop an infection-specific, positron-emitting tracer
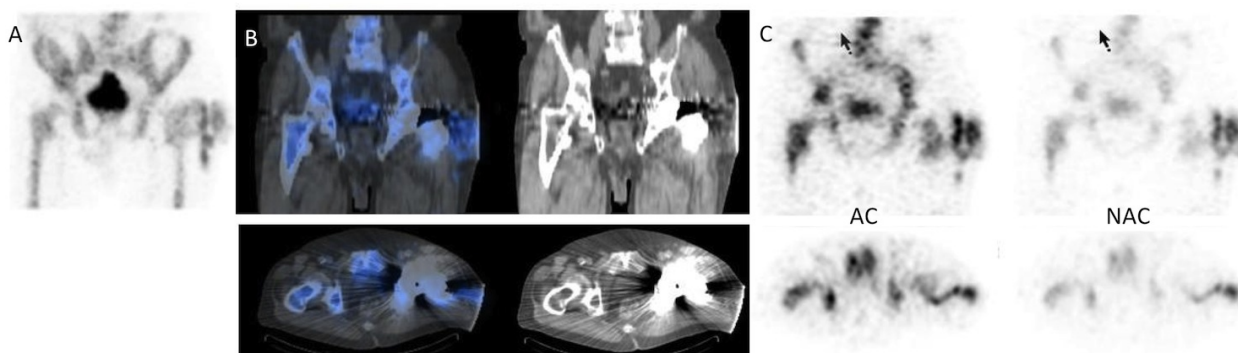
**Fig. (4).** Radiolabeled WBC scintigraphy in a patient with left hip prosthesis infection. MIP imges (A) and SPECT/CT images (B, upper panel coronal and lower panel transaxial, from left to right superimposed SPECT/CT, CT, emission AC and emission NAC) diagnosed the presence of prosthetic infection complicate with a fistula in the soft tissue.

[123, 124]. In patients with infected prosthesis first results (in conjunction to marrow imaging) demonstrated similar diagnostic accuracy to ^{111}In-WBC [8] but with significant low labeling efficiency when [^{18}F]FDG is used.

[99m]Tc-radiolabeled murine anti-granulocyte mAb showed a sensitivity ranging from 75-91% and specificity of 81-86% with a negative predictive value of 66-96% [10, 16, 125, 126]. Increase in specificity (from 71% to 83% and from 78% to 100%) without significant changes in sensitivity (94% and 93%) has been demonstrated in hip and knee prosthesis with dual-time acquisition protocol (4 and 20-24 hours images) [127, 128]. Quantitative evaluation of sulesomab (activity in ROI around the knee prosthesis and the pelvic bone marrow with 10% threshold to differentiate between septic and aseptic abnormalities) increased significantly both sensitivity and specificity compared to visual interpretation, particularly in moderate-low grade infection [129]. A comparative study using ^{99m}Tc-besilesomab and ^{99m}Tc-sulesomab showed similar diagnostic accuracy for the detection of septic total knee arthroplasty [130]. Additionally, ^{99m}Tc-sulesomab scintigraphy combined with ^{99m}Tc-nanocolloid bone marrow scan have demonstrated to improved both specificity and positive predictive value [131].

Attempts to increase scintigraphic specificity, investigation of a number of other radiopharmaceuticals is ongoing. ^{99}Tc-ciprofloxacin at 24 hours images has demonstrated better performances for the diagnosis of knee prosthesis infection in a small series of patients (sensitivity and specificity of 83% and 90%, respectively) as compared to hip prosthesis (sensitivity of 74% and specificity of 90%) [132]. Similarly, based on results in several animal models where radiolabeled Annexin V, a marker of apoptosis and cellular stress or activation, have demonstrated ability to detected acute, subacute, and chronic inflammation, this radiopharmaceutical was tested in patients, suggesting a potential application in the differentiation of infection (uptake more common and intense) from aseptic loosening [133].

PET using either [^{18}F]-fluoride and [^{18}F]FDG has been proposed as alternative imaging modality to leukocyte scintigraphy during the last years. [^{18}F]-fluoride has been used to guide tissue sampling to confirm infection of hip prosthesis (sensitivity of the combined histopathology, microbiological culture, real-time PCR of 96% when sampling only major [^{18}F]-fluoride uptake sites) [134]. Results for [^{18}F]FDG-PET have demonstrated about 73-95% accuracy for bone prosthesis infection diagnosis with 81-95% of sensitivity, and specificity of 66-95% considering both periprosthetic or bone-prosthesis interface [^{18}F]FDG uptake as interpretation criteria [10, 135-140]. Many interpretative criteria have been introduce to improve diagnostic performances of [^{18}F]FDG-PET and PET/CT in prosthetic joint infections. Stumpe *et al.* [141] dif-

ferentiated aseptic loosening from infection deemed positive for infection only cases presenting similar or higher [^{18}F]FDG uptake than bladder (grade 3 or 4) according to a 5-point scale (accuracy=69%). Reinartz *et al.* [142] based their evaluation on [^{18}F]FDG pattern of uptake considering suggestive for hip prosthesis infection only cases presenting periprosthetic involvement (sensitivity=94%, specificity=95%, accuracy=95%). Chacko *et al.* [143] considered positive for infection increased [^{18}F]FDG uptake at the prosthesis-bone interface (sensitivity=92%, specificity=97%) while for Wenter *et al.* [135] a higher bone [^{18}F]FDG uptake compared to adipose tissue or inactive muscles (considered as background) was considered positive for infection. Love *et al.* [144] proposed and compared different criterion to evaluate prosthesis infection. According to the first one the presence of any [^{18}F]FDG uptake adjacent to the prosthesis (prosthesis-bone interface, tip of prosthesis and/or soft tissues surrounding prosthesis) was indicative for infection (sensitivity=100%, specificity=9%, accuracy=47%); the second one was the same proposed by Chacko *et al.* [143] (sensitivity=96%, specificity=35%, accuracy=61%); the third one took into account the prosthesis-bone interface activity, regardless of intensity (sensitivity=52%, specificity=44%, accuracy=47%), and the fourth criterion used a semi-quantitative analysis calculating a target-to-background ratio between the most intense activity at the bone interface and the uptake of the soft tissue of the corresponding controlateral side (sensitivity=36%, specificity=97%, accuracy=71%) [144].

Wenter *et al.* [135] compared their method to others in patients with orthopaedic implant confirming a very high sensitivity for the criterion 1 suggested by Love *et al.* (100%) compared to others (Familiari=83%, Stumpe=84%, Reinartz=87%, Chacko=77%, Love criterion 4=61%, and their ones=86%) despite the highest specificity and accuracy were reached using the method proposed by themselves (67% and 76%, respectively) compared to other (Familiari=54% and =68%, Stumpe=37% and =61%, Reinarzt=29% and =56%, Chacko=46% and =61%, Love criterion 1=20% and =58%, Love criterion 4=63% and =62%).

Specificity of the technique may be improved used PET/CT evaluation of both NAC images and AC as demonstrated in patients with painful primary hip prostheses (from 62% to 87%) and in patients with an interim hip spacer (from 50% to 62%) [145]. Despite encouraging results, clinical comparative study have demonstrated that leukocyte/bone [31] as well leukocyte/marrow imaging are more accurate than [^{18}F]FDG-PET and PET/CT (any interpretation criteria: any periprosthetic activity, regardless of location or intensity; periprosthetic activity, without corresponding activity on the marrow image; only bone-prosthesis interface activity, regardless of intensity; semiquantitative analysis-a lesion-to-background ratio)

for differential diagnosis between aseptic and septic loosening [144, 146]. Nevertheless better performances of [$^{18}$F]FDG-PET compared to $^{111}$In-oxina leukocytes/marrow imaging for the diagnosis of periprosthetic infection of the hip has also been reported (95% and 93% *versus* 50% and 95%) [137]. The main argument in the use of [$^{18}$F]FDG for the differential diagnosis of prosthesis infection is due to the finding of increased [$^{18}$F]FDG uptake in case of inflammatory arthritis, fractures, normally healing bone, degenerative changes [147, 148], synovial proliferation [149], muscle activity due to malalignment of knee replacement and soft tissue imbalance, heterotopic ossification, granuloma and neuroma [150]. However, in contrast to $^{99m}$Tc-diposfonates, [$^{18}$F]FDG rapidly normalizes after traumatic or surgical fractures [151, 152] as consequence of fibroblasts predomination in normally healing bone, subsiding 4 months after surgery [153]. Therefore, specificity increases if recently (less than 4 months) traumatized or operated bone is excluded and if when all possible sources of false positive findings are ruled out.

The monitoring of antimicrobial treatment response in patients with infected joint prosthesis by nuclear medicine procedure is currently clinically applied, despite validated clinical trials supporting this use of PET and scintigraphy are still lacking. In fact, few data are available to support such use of either radiolabeled leukocytes and [$^{18}$F]FDG in this clinical setting. The combination of gallium-67 and technetium-99m MDP using as positivity criteria gallium uptake > $^{99m}$Tc MDP have demonstrated the ability of non-arbitrary determine the moment of reimplantation of the prosthesis (no clear consensus regarding the interval before reinsertion is present in the literature) with extremely low rate of infection recurrence [154]. Additionally, $^{99m}$Tc-ciprofloxacin results at the end of therapy had the highest sensitivity (83%), accuracy (70%) and negative predictive value (95%) in predicting infection resolution or recurrence as compared to ESR assessment and clinical examinations [155]. UBI$_{29-41}$ was also employed to differentiate infection from aseptic loosening of prostheses [156] as well as to assess response to antibiotic therapy with reduction in radiopharmaceutical uptake after treatment as compared to baseline scan in the responder group [157].

In conclusion radiolabeled leukocytes eventually combined with marrow imaging remains the technique of choice for diagnosing prosthetic joint infection with significant advantage in spatial resolution and differential diagnosis of bone/prosthesis from soft tissue involvement with SPECT/CT acquisitions. The value of [$^{18}$F]FDG-PET and PET/CT in this setting is still debatable and need further investigation. Despite the routine use of nuclear medicine procedure to evaluate and monitoring response to antimicrobial treatment, prospective studies to support such application are warrant.

## 2.2. Cardiovascular System

### 2.2.1. Infective Endocarditis

Infective endocarditis (IE), has dramatically changed over the last years both the etiology (from Streptococcus to Staphilococcus), predisponing conditions (rheumatic and congenital disease or syphilis are less frequent the underlying disease while mitral valve prolapsed, mitral and aortic valve calcifications, prosthetic valve and device, intravenous drug abuse are more frequently observed) and patients' population (younger patients). Diagnosis of IE is essentially clinical. Microbiological tests for germ characterization along with echocardiography (transthoracic, TTE and transesophageal, TEE) for the visualization of vegetation and local complications are needed to define the diagnosis according to the modified Dukes criteria (diagnosis categorized as definite, possible and rejected). In the New European Society of Cardiology 2015 modified criteria for the diagnosis of infective endocarditis molecular imaging techniques and computed tomography were also included to increase the likelihood to reach a diagnosis [158]. Nuclear medicine has been demonstrated valuable in cases of undetermined echo findings (i.e.

marantic vegetations, artifacts deriving from mechanical prosthesis or device's catheter) as well as for embolism detections. Furthermore, nuclear medicine might play a role for treatment management, since antimicrobial therapy discontinuation is empirically determined [159, 160].

Gallium-67 scintigraphy has been described by several authors for the detection of IE and myocardial abscess with a quite low specificity [161] while discordant results have been reported using radiolabeled WBC scintigraphy [162-167].

A meta-analysis of the literature from 1976 to 2005, (12 articles, referring to 378 patients, 380 lesions) defines $^{99m}$Tc-labeled anti-granulocyte mAbs alone or in association with echocardiography the most accurate procedure for the detection of infective endocarditis (sensitivity = 100%, specificity = 86% and accuracy = 92% with 89% positive predictive value) [168]. The real breakthrough for nuclear medicine procedure in IE and device related infection has reached with the introduction of SPECT/CT and PET/CT equipment: an exhaustive evaluation of the heart region is impossible without the possibility to acquire 3D images of the thorax. With such technology $^{99m}$Tc-HMPAO labeled autologous leukocytes demonstrated the ability to accurately diagnosed cardiac and additional unsuspected extra-cardiac sites of infection up to 41% of the patients with IE [169, 170]. No data are available for $^{67}$Ga-SPECT/CT in IE, with the exception of a single case report [171]. More recently (all reports are published from 2010 underling the renewed interest in the field) favorable results with the use of PET/CT with both in vitro [$^{18}$F]FDG-WBC (the first published series of patients included two IE and the same concerns described in the paragraph of FUO are true also for IE) and [$^{18}$F]FDG were reported for the visualization of valve vegetation and the detection of distant embolism and metastatic site of infection (24-57%) [123, 172-183] with high diagnostic performances (87% sensitivity, 97% specificity and 52% PPV) [174].

Particularly, in prosthetic valve endocarditis [$^{18}$F]FDG uptake around a prosthetic valve has been introduced as new major criterion, increasing the sensitivity of the modified Duke criteria from 70 to 97% trought the reduction of "possible" IE [176]. Very recently, Rouzet *et al.* [182] compared [$^{18}$F]FDG-PET/CT to $^{99m}$Tc-HMPAO WBC (planar + SPECT/CT images) in 39 patients with suspected prosthetic valve endocarditis. [$^{18}$F]FDG-PET/CT resulted in a higher sensitivity (93% *versus* 65%) but a lower specificy (71% *versus* 100%) and accuracy (80% *versus* 86%) compared to WBC imaging.

An additional promising role of [$^{18}$F]FDG-PET/CT may be seen in patients with established IE, in whom it could be used to monitor response to antimicrobial treatment [184].

In order to avoid potential sources of false-positive findings in PET or PET/CT studies some considerations should be take into account in the imaging interpretation [185]. Variable focal of diffuse physiological [$^{18}$F]FDG uptake is often observed in the normal myocardium (mainly in the left ventricle) of fasting non-diabetic patients (6-12 hours to overnight) with normal glucose levels [185, 186]. Many factors such as patients' age, fasting time, blood glucose levels, and a low-carbohydrate diet may influence myocardial [$^{18}$F]FDG uptake [185, 187,188]. Some approaches might be used to decrease myocardial [$^{18}$F]FDG uptake including low-carbohydrate diet [189] and very high-fat, low-carbohydrate, protein-permitted meal followed by fasting for 3-6 hours [190] before tracer injection [185, 187]. Alternatively, unfractionated heparin (50 IU/kg iv) which acts activating lipoprotein lipase and hepatic lipase, enhances plasma lipolytic activity and elevates plasma levels of FFA, could be administered before [$^{18}$F]FDG injection [185, 191, 192]. According to the SNMMI/ASNC/SCCT Guidelines [193] patients should be prepared with a fat-enriched diet lacking carbohydrates for 12–24 h prior to the scan, a 12–18-h fast, and/or the

use of intravenous heparin approximately 15 min prior to [18F]FDG injection [187].

The increased metabolic activity along the posterior aspect of the heart, where lipomatous hypertrophy of the interatrial septum may appear as a fat-containing mass with increased [18F]FDG uptake, could be another potential counfonding factor in the interpretation of PET/CT results [185, 194]. Several different pathologic conditions such as active thrombi [186], soft atherosclerotic plaques [190], vasculitis [195], primary cardiac tumors [196], cardiac metastasis from a noncardiac tumor [197], postsurgical inflammation [198], and foreign body reactions [199] can mimic the pattern of focally increased [18F]FDG uptake that is typically observed in IE [185, 187]. Therefore they should be considered in the differential diagnosis and excluded before diagnosis IE [185, 187]. A precise time-line after surgery has not been jet identified, at least 3 months from surgical procedure are suggested to minimize the risk of [18F]FDG-PET/CT false positive results [182, 185, 200]. The patterns of [18F]FDG uptake and the anatomic changes observed at [18F]FDG-PET/CT angiography in the early post-operative setting (i.e., after prosthetic valve or valve-tube graft surgery) have been recently reported [201] in order to help imagers to differentiate inflammation from infection [187]. Indeed, only an accurate patients selection and specfic inclusion criteria allow to achieve a high specificity for IE diagnosis using [18F]FDG. Conversely, [18F]FDG-PET/CT in patients with lower pretest probability would rely on the high negative predictive value of this imaging procedure [185, 187].

All together these data suggest a role of nuclear medicine imaging procedures for diagnosis confirmation of endocarditis particularly in presence of uncertainly echo findings, and for the exclusion of heart valve involvement during febrile episodes/sepsis in high risk patients, expecially in patients with prosthetic valve IE, as recently pointed out by the inclusion of nuclear medicine procedures in diagnostic flowcharts and clinical guidelines [158, 161]. The choice between a high specificity test as radiolabeled WBC (with SPECT/CT acquisition mandatory) or a high sensitive test as [18F]FDG-PET/CT is on the pre-test probability, patient clinical conditions and the elapsed time between the latest surgical event and the moleculr imaging test. For the detection of distant embolism and metastatic site of infections (with some costrains in the case of CNS embolisms if constrast medium is not applied) as well as for the monitoring of the antibiotic treatment response both radiolabeled WBC and [18F]FDG-PET/CT might be indicated, with some potential advantage of the latter due to higher spatial resolution and extremely high negative predictive value.

### 2.1.2. Cardiovascular Implantable Electronic Devices

Cardiac devices (CIED) infection occurs in 1% and 7% [202, 203]. CIED infection is associated with significant morbidity and mortality [204-207]. The main ethiological agents are Staphylococci (60-80%); Gram-negative bacilli causes CIED infection in 5-10% of the cases, while cultures are negative in another 10% [5]. Fungeal or or mycobacteria infection is rare [5]. CIED-related infection may occur either as a surgical site infection within 1 year after implantation or as late-onset leading to endocarditis [5, 208, 209]. The contamination with cutaneous microorganisms when the pacemaker is implanted or the generator is revised results in early CIED infections [5, 210]. The majority of infections begin in the surgical pocket. Infection extention may be underestimated in localized pocket infections. Local manifestations at the site of PM implantation are associated with infection of the intravascular part of the leads in up to 79% of cases [5, 211]. Therefore, the extention of infection shoul alwayas be quantified. Systemic infection may be a consequence of a persistent infection that progress through the catheter leads involving the bloodstream and/or the endocardium or of a bacteremia originated in other foci, that then colonizes the leads, as occurs in healthcare related procedures [5, 207, 212]. Bacteriemia is almost unavoidably in CIED-related infection resulting often in metastatic foci [5]. Murdoc *et al.* [213] rerpoted that 10%

of 2,781 episodes of IE were device-related endocarditis. Rarely conservative treatments with antimicrobial drugs are effective in CIED infection [214-216] which generally requires a complete removal of the hardware [217]. Nonetheless, device replacement for battery depletion or upgrades may become necessary some years after the first implantation [5]. Infection rates are higher in replacements compared to initial implantation [5, 202, 218, 219]. CIED infection diagnosis is generally based on microbiological assessment (blood cultures and culture of exudates from the pocket) and TEE, which may also be used to define patients' likelihood to have infection according to the Duke criteria/New European Society of Cardiology 2015 modified criteria [5, 158, 207]. However, it should be considered that such criteria have been originally developed for IE, therefore some appropriate implementations should be applied in suspected CIED infections. Nevertheless, underestimation of the extent of CIED infection it is possible even when introducing these corrections. In fact, the lead portion between pocket and superior cava debouchment may not be accurately explored by TEE [4]. Some radiological findings such as the presence of fluid density between the heart and the device, although not specific since they can be observed also in the postoperative or inflammatory noninfectious changes, may be suggestive for CIED infection [5, 207, 220]. Additonally, CIED infection cannot be rule out in case of the absence of crumpling of patches in plain X-ray, or fluid around the heart in the CT scan [5]. Nuclear medicine imaging techniques have been applied to evaluate suspected or ascertained CIED infection altought the level of evidence of the published remains relatively low (Level II, class C) [151]. 67Ga-citrate scan has been successfully employed in CIED infection [5, 221, 222]. Radiolabaled WBC scintigraphy helps to define the presence and the extent of CIED infection [5, 223-226]. The anatomic location and extent of a suspected infection has been precisely identified and detected by WBC SPECT/CT, improving patients' management [5, 170, 226]. Additionally WBC SPECT/CT has bee reported to be useful to detected additional unsuspected extracardiac sites of infection in device-related sepsis, although with some limitations in case of small CNS embolism [5, 170]. Similar results have been published in lead-associated infection using 99mTc-sulesomab SPECT/CT [5, 227]. [18F]FDG-PET/CT has been also used to identify CIED infection with promising results [228, 229] particularly when it is performed to rule out device involvement during infection [5, 230] and to define the embolic burden [5, 230-233]. Ad-hoc diagnostic criteria have been proposed by Serrazin *et al.* [234] to improve the diagnostic performances of [18F]FDG-PET/CT in CIED infections. Dual-point PET/CT (standard plus 3 hours images) seems to be promising particularly in case of lead infection [235]. A dual-point approach with standard plus delayed (3 hours) images has been evalauted also in this specific clinical field with promising results particularly in case of lead infection [235]. However, as for IE, a positive [18F]FDG-PET/CT scan should be carefully interpreted [5, 185]. Additionally, postsurgical changes and inflammatory reaction to foreign material (as in a Dacron pouch) [234] should always be considered in the differential diagnosis of CIED infection, especially in early infection [5]. Furthermore, when used to guide discontinuation of antibiotic treatment [18F]FDG-PET/CT relies on extremely high negative predictive value, thus a negative scan is mandatory. False negative cases due to antimicrobial treatment can occur [5]. The great potential of radionuclide imaging is mostly to be seen in the differential diagnosis between pocket hematoma and purulent collection, fibrous casts or thrombus and active vegetations detected by TEE on leads, and in the definition of disease extent when in the presence of ascertained pocket infection [5].

### 2.1.3. Vascular Graft Infection

Vascular prosthesis infection (VPI) occurs in 0.5-5% of implantations [5]. Staphylococcus aureus, Escherichia coli and S. epidermidis are responsible of the majority of cases whereas, Klebsiella,

Pseudomonas, Enterobacter and Proteus accounts for most of the remaining cases [1, 236]. Surgery associated to antimicrobial therapy is the treatment of choice if there are no contraindication for surgery, while antimicrobial therapy alone may be the only option in high-risk patients [1]. An early diagnosis is closely associated to the success of the treatment. CT angiography is the technique of choice for both infection confirmation and complication detection (sensitivity 85-100%) [1]. Nuclear medicine and MRI are used in unclear situation when CT sensitivity decrease (as in low-grade infection or in early infection) [1]. $^{67}$Ga-citrate, radiolabeled HIG, radiolabeled WBC (either with $^{99m}$Tc or $^{111}$In), and labeled anti-granulocyte antibodies have been used in VPI. $^{99m}$Tc-labeled autologous leukocytes resulted better than other diagnostic methods including CT (sensitivity 82-100% versus 75%, specificity 85-100% versus 57%, respectively) in prosthetic graft infection [237]. This superiority over other methods has been heightened by SPECT/CT that allows to characterize pathological site of infection and to define its extension, to exclude false positive results such as bowel aspecific tracer accumulation, and to confirm or reject graft involvement even in presence of post-surgical distortions and complex anatomical sites [1, 18, 121, 238, 239] (Fig. 5). High specificity is maintained even when scintigraphy is performed during the first month after surgery [1,239, 240]. When the abdominal region is included in the study and $^{99m}$Tc-HMPAO WBC used, methodological efforts (i.e., adequate image acquisition time) are necessary to decrease false positive findings [1]. $^{111}$In-WBC scintigraphy has been reported to perform similar to MRI (positive and negative predictive value of 80% and 82% for $^{111}$In-WBC and 95% and 80% for MRI) [241]. WBC scintigraphy may be used to determine the response to treatment, preventing the risk of adverse drug reactions related to long-lasting regimens as well as the acquisition of resistance in patients treated with long-term suppressive antibiotic treatment [1, 239, 242].

$^{99m}$Tc-Fanolesomab (approved in the United States for equivocal presentation of appendicitis, but withdrawn from the market in late 2005 following postmarketing reports of serious adverse events, including two fatalities) was shown to diagnose prosthetic vascular graft infection with an accuracy of 95% [243].

[$^{18}$F]FDG-PET/CT may be considered a valuable method to evaluate suspected VPI [1, 244, 245]. Good diagnostic performances have been reported for [$^{18}$F]FDG images (sensitivity 91% and specificity 64% versus 64% and 86% for CT scan), significantly improved adopting appropriate interpretation criteria (focal [$^{18}$F]FDG uptake) [1, 246]. In fact, inhomogeneous [$^{18}$F]FDG uptake is an unspecific finding that may be related either to very low grade infection, weak immune reaction, inflammatory conditions such as vasculitis and atherosclerosis, chronic aseptic inflammation, and post-surgical changes that may persist for years after the prosthesis implantation [1, 247]. Potential pitfalls related to [$^{18}$F]FDG uptake over time in noninfected implants have been described in relationship to the prosthetic material and the location [1]. Gore-Tex graft rae characterized by homogeneous pattern whereas the inhomogeneous uptake has been reported more in Dacron ones (none of the grafts demonstrated focal uptake). Uptake intensity was significantly higher in Dacron than in Gore-Tex and native vein grafts. Native vein grafts showed a significant decrease in [$^{18}$F]FDG uptake over time whereas synthetic grafts showed no change in intensity for during follow-up (up to 16 years) [1, 248]. The use of PET/CT increased sensitivity to 93%, specificity to 70-91% (positive and negative predictive values of 82-88% and 88-96%) [249], mainly as a consequence of the better anatomical localization [1]. Dual-time-point images seems to be useful to detect aortic graft infection, improving image quality, and enhancing delineation of the infected aortic grafts [1, 250]. A high rate of false positive results has been reported using both patterns of [$^{18}$F]FDG uptake (SUVmax, tissue to background ratio, visual grading scale, and focality of [$^{18}$F]FDG uptake) and CT features (graft wall thickening, oedema, gas surrounding the graft or any other sights) [251] due to the fact that they may largely overlap either in infected or uninfected vascular grafts [1, 252, 253]. More recently a new five point visual grading [$^{18}$F]FDG score which resulted in a very high accuracy has been proposed [254]. Nevertheless, Spacek *et al.* [255] identified focal [$^{18}$F]FDG uptake and irregular graft boundary at CT images as independent significant predictors of low-grade VPI (erroneous classification occurring in < 5% in the majority of patients).

[$^{18}$F]FDG-PET/CT may also be used to monitor antimicrobial treatment as shown by Husmann *et al.* [256]. They prospectively evaluated 25 patients with proven VPI performing baseline and follow-up (89-249 day after the baseline) PET/CT examinations. [$^{18}$F]FDG-PET/CT had an impact on management in all patients: antibiotic treatment was continued in 76% of cases (persistent
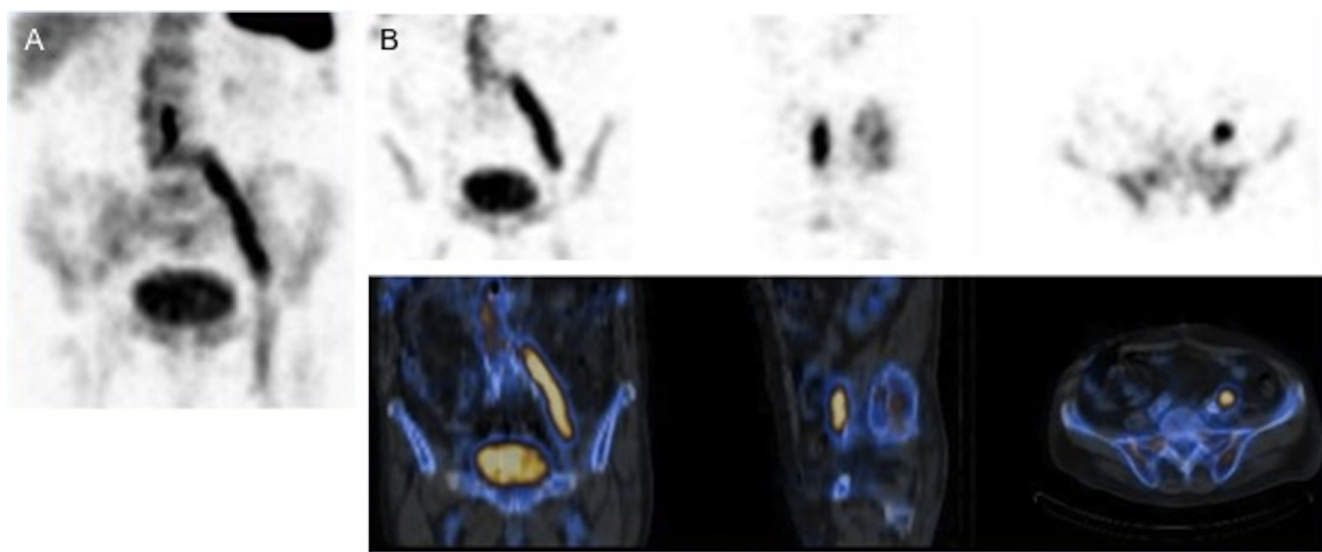


**Fig. (5).** $^{99m}$Tc-HMPAO WBC in a patient with aorto-bisiliac vascular graft. MIP images (A) and SPECT/CT images (B upper panel emission, lower panel fused SPECT-CT, from left to right coronal, sagittal and transaxial images, respectively) show the presence of intense and diffuse radiolabeled leukocyte uptake all along the distal aortic and the left bisiliac branches of the vascular graft.

[$^{18}$F]FDG uptake) while was stopped or changed in 8% and 16% of patients, respectively. In 32% of patients, Additional incidental findings were detected in 32% of cases by follow-up [$^{18}$F]FDG-PET/CT further impacting on patient management.

In conclusion, radiolabeled autologous leukocyte scintigraphy is the 'gold standard' for vascular graft infection diagnosis and treatment monitoring since the high sensitivity and specificity; SPECT/CT acquisition should be mandatory since it increases the diagnostic accuracy reducing the possibility of false positive results [1]. [$^{18}$F]FDG-PET/CT may provide a valid alternative to WBC scan when adopting appropriate criteria for imaging interpretation. Still, no data on its the use in the early phase of post-surgical setting are currently available [1].

## 2.3. Abdominal Infection

### 2.3.1. Abdominal Abscess

Abdominal abscess, a pocket of inflamed tissue filled with pus or infected fluid, that can occur as consequence of a number of different causes, rapresents a serious problem in surgical practice [4]. The appropriate treatment of abdominal abscess is often delayed due to the obscure nature of many conditions resulting in abscess formation, which can make diagnosis and localization difficult [4]. Ultrasound, in experienced hands, has an accuracy rate greater than 90% [257] except in case of retroperitoneal or mid-abdominal abscess. CT scan is the best diagnostic method since its high accuracy (> 95%) [5, 258]. Gallium scan has been compared to CT in the detection of intra-abdominal abscess after colorectal surgery (sensitivity, specificity and accuracy of 100%, 78% and 91%, respectively versus 93%, 100%, and 96%) [223, 259]. Leukocyte scintigraphy is sensitive in detecting abdominal abscess in different locations (76-100% sensitivity, 85-100% specificity, 88-100% accuracy) [260] except for the liver and spleen due to physiological localization of labeled cells in these organs [261]. The addition of $^{99m}$Tc-sulfur colloid liver-spleen scan to the WBC increases the sensitivity of the WBC scan in the detection of hepatosplenic infections [260, 262]. Furthermore, WBC scintigraphy can reveal unsuspected extra-abdominal sites of infection [260, 263]. WBC scan has been reported to be helpful in intra-abdominal infection patient management in 76% of cases [260, 264]. False positive results have been described in the early postoperative period due to non-specific postsurgical inflammatory uptake [198, 260].

Synthetic mesh is used commonly in the repair of abdominal wall herniopathy, one of the most common operation. Infection at the surgical site where mesh is present, is an important clinical problem (1-2% cases/years). For late mesh infection following incisional hernia repair, particularly for silent abdominal wall infections after surgery radiolabeled antigranulocyte antibodies represented a useful method for the detection of infection and subsequent appropriate therapy [116, 265].

[$^{18}$F]FDG PET/CT has been used in the diagnosis of cyst infection in patients with autosomal dominant polycystic kidney disease, proving the ability to define cyst infection in 84.6% of patients and revealing other source of infection in 64% [266]. Intense [$^{18}$F]FDG uptake have been also reported in mendelian and complex inflammatory disorders. At the time of relapse, it can be used to differentiate between a sequela of previous flares and a new localization [267].

### 2.3.2. Appendicitis

Inflammation in the appendix requires immediate medical attention. Many nuclear medicine techniques including $^{99m}$Tc-HMPAO or $^{111}$In oxine autologous leukocytes, $^{99m}$Tc-HIG, $^{99m}$Tc mAbs ($^{99m}$Tc-anti-CD15, LeuTech®; $^{99m}$Tc-BW 250/183, Granuloscint®; $^{99m}$Tc sulesomab, Leukoscan®) can be indistinctly used since their high accuracy. Annovazzi *et al*. [237], evaluated articles published between 1987 to 2004 (24 papers for a total of 1548 patients) demonstrating radiolabeled mAbs as the radiopharmaceutical

of choice for the diagnosis of appendicitis since with this radiopharmaceutical prevent time waste. $^{99m}$Tc-Fanolesomab, was approved in the United States for use in patients with equivocal presentation of appendicitis in 2004, but soon withdrawn from the market since serious adverse events occurrence, including two fatalities [268].

More recently, Reavey *et al*. [269] described the patterns of normal pediatric bowel [$^{18}$F]FDG activity with specific regard within the appendix in order to avoid misinterpretation of images. They concluded that [$^{18}$F]FDG uptake in the appendix is typically similar to that of background activity, however, since children have more active lymphoid tissue than adults, slight variations in appendiceal [$^{18}$F]FDG uptake do occur which should not be misinterpreted as pathological.

## CONCLUSION

Nuclear Medicine imaging has diagnostic, prognostic and therapeutic impacts on infectious diseases. Different techniques and radiotracers may be used based on the diseases' patho-biochemical features and the clinical need. Technological improvements result in innovative equipment that has increased spatial resolution of nuclear medicine modalities. The appropriate definition of the role of each procedure in diagnostic/therapeutic clinical algorithms is the next challenge. This process is on-going by the European Association of Nuclear Medicine (EANM) in collaboration with several other European societies and, as a result, several procedural and joint guidelines have been already published [261-266].

## CONSENT FOR PUBLICATION

Not applicable.

## CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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