Nuclear medicine practice in the field of infection and inflammation imaging: a pragmatical survey

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During the last decade, the interest in nuclear medicine techniques for diagnosing infections has been growing [1]. There is an increasing body of evidence to support the use of [¹⁸F]-FDG positron emission tomography/computed tomography ([¹⁸F]-FDG-PET/CT) for several indications in this field. Nevertheless, [¹⁸F]-FDG has some important limitations and pitfalls, especially in patients with foreign body material [2]. In these cases, differentiation between reactive inflammation and infection can be challenging and a correct diagnosis is of utmost importance for subsequent treatment. For these cases, white blood cell (WBC) scintigraphy is a highly valuable technique that allows for the visualization of the dynamics of white blood cells, hence differentiation between sterile inflammation and infection with high accuracy [3].

Back in 2013, a first general joint EANM/SNM guideline about the use of [¹⁸F]-FDG-PET/CT for inflammation and infection was published [4]. This guideline was based on limited data available at that time, and the authors claimed that this guideline could not be seen as definitive given the rapidly evolving use of [¹⁸F]-FDG-PET/CT. Now, 9 years

later, we agree with this statement, since not only there is accumulating evidence for existing indications, but also more and more data are available in new indications, and in larger patient populations. Several important EANM guidelines were developed for the correct use of [¹⁸F]-FDG-PET/CT and WBC scintigraphy in infectious diseases [3, 5–11]. These guidelines are evidence-based, and include the correct patient preparation, the correct image acquisition, and the correct analysis and interpretation of the scans. Moreover, NM techniques have been incorporated in several clinical guidelines, written in collaboration with clinical societies, in which the preferred imaging technique, the correct use of the technique, and the time point in the disease course when the technique should be used are described and illustrated by diagnostic flowcharts, e.g. for endocarditis [6, 7], vascular graft infections [8], peripheral bone infection in adults [9], prosthetic joint infection [10], and spondylodiscitis [11].

To evaluate the use of these guidelines in clinical practice, a survey was performed to collect information on the use of [¹⁸F]-FDG-PET/CT and WBC scintigraphy for infectious/inflammatory disorders. The goal of this survey was to provide an answer to the following questions: Are all centres equipped to perform these imaging modalities? Do they use these imaging techniques and if yes, how often and for which

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indications? Do they use these techniques in the correct way, standardized to guidelines? Which guidelines do they use? And which technique do they prefer for which indication and is this in concordance with the guidelines?

A web-questionnaire was prepared by the authors to evaluate concordances and discrepancies in daily NM practice in Europe in the field of infection imaging, in line with recent recommendations and requirements to maximize response rates such as a personal introductory statement; the offer to make results public; the use of simple headers and textual representation of response categories; and the prerequisite of a relatively short deadline including several reminders [12, 13]. The questionnaire was available in a Google Form Document. As of March 1, 2021, an invitation to the survey was sent to the corresponding authors of scientific articles in the field of NM infection imaging indexed in SCOPUS in 2020, using the following query string: (“infection”) AND (“nuclear medicine” or “pet” or “positron” or “scintigraphy” or “spet” or “spect”). Two reminders were sent to all non-responding recipients. To further increase potential responses, the survey weblink was accessible by social media.

Fifty questions in English were prepared for NM professionals dedicated to infection imaging worldwide. Question types were dichotomous, single-choice, multiple-choice, rating scales, or open-ended for number, text comment, or

date [12, 13]. General questions about personal and demographic data were included. Subsequently, specific questions to evaluate concordances and discrepancies in daily NM practice in Europe in the field of infection imaging were prepared to address the following main issues: (1) general demographic, hospital and NM department information; (2) [^{18}F]-FDG-PET/CT protocols; (3) WBC protocols; (4) clinical indications; and (5) reimbursement. All data about demographics, hospital, department, protocols, indications, and reimbursement were analyzed per individual responder.

In total, 101 individual responses were received, 92 from specialists working in Europe and (only) 9 from specialists working in North America. Given the low number of non-European responders, quantitative analysis focused on the 92 individual responses from Europe. Nearly all responders were from NM departments: only a few responders were from Radiology departments. Most of the responders were NM physicians (84/92, 92%) working in an academic hospital (50/92, 54%) (Fig. 1).

Most departments were equipped with both PET/CT and SPECT/CT (73/92, 80%), mostly using both [^{18}F]-FDG and HMPAO-labelled WBCs for infection imaging, respectively. Many responders (39/92, 42%) performed less than five PET scans weekly and the vast majority (72/92, 78%) performed less than five SPECT scans weekly for infectious indications. The three main indications for infection imaging were

Fig. 1 General demographic and hospital information, such as age (a), department (b), healthcare profession (c), and hospital type (d)

FUO, sepsis/bacteraemia, and endocarditis/CIED, followed by vascular graft infection and prosthetic joint infection. For infection imaging, most of the responders had their own institutional protocols (74/92, 80%), and followed EANM guidelines in most centres (70/92, 76%), either stand-alone EANM in 53%, or in combination with clinical guidelines in 23% (Fig. 2).

Most responders used 3 MBq/kg (41/92, 45%) for [^{18}F]-FDG-PET and 6-h fasting duration for infection imaging (60/92, 65%). A significant part of the responders (26/92, 28%) used a 12-h fasting duration for infection PET scans. A specific diet was in most centres suggested only for endocarditis and CIED (65/92, 71%), mostly consisting of a high-fat low carbohydrate diet with or without prolonged fasting or heparin administration. Fifteen responders (16%) used a specific diet for all infectious indications; twelve responders (13%) used no specific diet at all. A glycaemia cut-off of 200 mg/dl (68/92, 74%) and scan time point at 60 min after injection (80/92, 87%) were largely used (Fig. 3).

In total, 69 of the 92 responders used WBC imaging. $^{99\text{m}}\text{Tc}$ -HMPAO alone was the most used tracer for WBC imaging in our cohort (40/69, 58%), with an injected activity ranging between 185 and 550 MBq. The remaining centres used $^{99\text{m}}\text{Tc}$ -antigranulocyte monoclonal antibodies (14/62, 23%), a combination of $^{99\text{m}}\text{Tc}$ -HMPAO and $^{99\text{m}}\text{Tc}$ -antigranulocyte monoclonal antibodies (9/62, 15%), a combination of $^{99\text{m}}\text{Tc}$ -HMPAO and ^{111}In -oxine labelled WBC (2/62, 3%),

or a combination of all three possibilities (3/62, 5%). Only one centre used only ^{111}In -oxine for WBC labelling. The number of scans performed for $^{99\text{m}}\text{Tc}$ -HMPAO WBC imaging differed. Most of them used two imaging time points (at 2–4 h and 20–24 h) in 32 out of 60 responses (53%), or three imaging time points (including a scan at 30 min (18/60, 30%). Other centres used only 1 imaging time point (3/60, 5%) or more than 3 imaging time points (7/60, 12%). Regarding the time points of these scan sessions, there was a lot of difference, with scans performed after 30 min, between 2 and 4 h, between 4–8 h, and between 20 and 24 h. Both planar and SPECT imaging are mostly considered (53/67, 79%), with just in 34 out of 67 (51%) using an acquisition time corrected for $^{99\text{m}}\text{Tc}$ decay. Most of the responders used EANM procedural guidelines for WBC infection imaging (alone or with other ones), but not all centres applied the recommended scan time points, and used decay-corrected acquisition times (Fig. 4).

Participants were asked about which imaging modality they performed first for the main clinical infectious conditions. [^{18}F]-FDG-PET/low-dose CT was largely used as first imaging modality in adults (57/92, 62%) and children (74/92, 81%) with FUO, prosthetic (54/92, 59%) and native (48/92, 52%) valve endocarditis, myocardial inflammation (60/92, 65%), vascular graft infection (47/92, 51%), and spondylodiscitis (50/92, 54%). For these indications, $^{99\text{m}}\text{Tc}$ -HMPAO-labelled WBC was rarely used, except for vascular

Fig. 2 Data about general NM department information on infection imaging, such as equipment (a), number of PET (b) and SPECT scans (c), and guidelines used (d)

Fig. 3 Data about [^{18}F]-FDG-PET protocols, in terms of administered activity (a), fasting duration (b), specific diet (c), and diet for endocarditis (d)

Fig. 4 Data about WBC protocols, such as tracers used (a), activity for HMPAO (b), planar/SPECT imaging (c), and WBC procedure guidelines (d)

graft infection (16/92, 17%). In some centres, ^{67}Ga or ^{68}Ga -citrate was used as first imaging modality. $^{99\text{m}}\text{Tc}$ -HMPAO WBC scintigraphy was mainly used as first imaging modality in suspected prosthetic joint infections and in fracture-related infections (with and without implants), which is in accordance with EANM diagnostic flowcharts (Fig. 5).

Hospital and physician reimbursement for infection imaging did not differ amongst responders, with a prevalent absence of specific infection imaging costs. Prevalent reimbursement schemes were between 200 and 500 euros for $^{99\text{m}}\text{Tc}$ -HMPAO WBC scintigraphy and between 500 and 1000 euros for FDG-PET/low-dose CT, respectively.

We were happy to learn that the majority used institutional protocols and followed existing guidelines. However, the protocols were not always implemented according to the recommendations, especially not in WBC scintigraphy. The three main indications for infection imaging were FUO, sepsis/bacteraemia, and endocarditis/CIED. ^{18}F -FDG-PET/low-dose CT was largely used as first imaging modality in adults and children with FUO, prosthetic and native valve endocarditis, myocardial inflammation, vascular graft infection, and spondylodiscitis. In contrast, $^{99\text{m}}\text{Tc}$ -HMPAO WBC scan was mainly used as first imaging modality in fracture-related infections with and without implants and in prosthetic joint infections.

In general, the overall number of PET and SPECT scans performed for infections was quite low, in 77% less than ten scans per week. Only a limited number of departments perform 10–20 PET scans for infection per week (11%), and in only 5% of the departments more than 20 PET scans were performed weekly. For SPECT scans, the results are less than 10 scans per week in 78% of the responses, in 1% 10–20 scans per week, and in 3% more than 20 scans per week. Remarkably, 18% and 7% of the responders do not perform or has no access to SPECT or PET scans, respectively. These differences could be explained by the variable availability and reimbursement and to the fact that not all referring clinicians do request a nuclear medicine scan, despite the existing evidence. Therefore, it is important to have joint clinical guidelines and diagnostic algorithms, to widely adopt NM techniques in every centre based on existing evidence and not only by clinicians who believe in and/or are familiar with NM techniques.

Looking particular into the protocols used for ^{18}F -FDG-PET/CT, the majority used an administered ^{18}F -FDG activity of 3 MBq/kg (45%), but 26% administer 4 or 5 MBq/kg which should be decreased for the benefit of both the technologists and patients, for radiation protection issues. On the contrary, in 18% of cases, 2 MBq/kg is injected into the patients. This is most likely

Fig. 5 Data about clinical indications, in terms of which imaging modality performed first in the following scenarios: adults with FUO (a), vascular graft infection (b), prosthetic joint infection (c), and spondylodiscitis (d)

attributed to the newer (digital) PET/CT camera systems that are used more frequently and administered activities should be adapted to the existing equipment. We also observed differences in the specific diet used, not only between the indications (only for endocarditis or for all indications), but also between the diets used (no diet at all, high-fat low carbohydrate with or without prolonged fasting and with or without heparin). This could be more standardized between users according to a recently published recommendation paper [5].

For WBC scintigraphy, marked differences were found in the tracers used (^{99m}Tc -HMPAO, ^{111}In -oxine, or ^{99m}Tc -antigranulocyte monoclonal antibodies), in administered activity, in scanning time points, and in scan acquisition with or without decay correction. In a recent EANM guideline (3), and in several studies including homogenous and large patient populations [14, 15], it was demonstrated that scanning times corrected for decay yielded a better diagnostic accuracy. However, this was only used in 51% of the respondents using WBC scintigraphy. This leaves room for optimization and standardization amongst centres, to avoid misinterpretation, and, as a consequence, a lower diagnostic accuracy compared to scanning times corrected for decay.

Despite several efforts, only nine responses outside Europe were received. The reason for this limited response rate remains unclear, but one of the explanations could be the lack of reimbursement by the CNS of [^{18}F]-FDG-PET for infectious indications until recently, so probably only a few centres use [^{18}F]-FDG-PET/CT for these indications. Finally, the time has come for the USA to embrace [^{18}F]-FDG as the molecular imaging test of choice for many inflammatory and infectious indications [16]. Further research should focus on standardization and harmonization worldwide in order to achieve the same and optimal clinical practice for patients with infections complications everywhere.

In summary, this survey showed that there is a large consensus on the preferred nuclear medicine imaging technique for specific infectious indications and the adherence to the existing EANM/joint clinical guidelines to correctly use [^{18}F]-FDG-PET/CT and WBC scintigraphy. Nevertheless, efforts should be made to have the techniques available everywhere, to adhere to the guidelines in every centre, and to interact with the clinicians to adopt our techniques based on the available evidence and existing guidelines. Furthermore, a revision of the 2013 evidence-based guideline for the use of [^{18}F]-FDG-PET/CT in infection and inflammation is highly needed, since new indications, new patient data, and new guidelines have become available.

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Declarations

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent to anonymously collect and publish personal and opinion data of this survey was obtained in the presentation page of the web questionnaire.

Conflict of interest The authors declare no competing interests.

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