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Review

Molecular Imaging Techniques in the Diagnosis and Monitoring of Infectious Diseases

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Abstract

Purpose of Review Combined positron emission tomography and computer tomography with 2-deoxy-[fluorine-18]-flouro-D-glucose ([^{18}F]FDG-PET/CT) is increasingly used in suspected infection and inflammation. Evidence is mounting within several areas. We believe [^{18}F]FDG-PET/CT is a key modality in infection and inflammation and this overview outlines the diagnostic values in most common uses within this domain.

Recent Findings [^{18}F]FDG-PET/CT is considered helpful in establishing the underlying disease in 50–60% of FUO patients. In patients with complex blood stream infections, [^{18}F]FDG-PET/CT changes treatment and reduces relapse rates and mortality—if scans are negative prognosis is favorable and it may be safe to withhold or de-escalate treatment strategy. In infectious endocarditis, [^{18}F]FDG-PET/CT has an impact in prosthetic valve endocarditis and cardiovascular implantable electronic devices whereas its diagnostic use in NVE is limited. In spondylodiscitis, [^{18}F]FDG-PET/CT and MRI have overall equally and

complementary diagnostic performance with combined sensitivity and specificity of ~ 100%. In vascular graft infections, [^{18}F]F DG-PET/CT is highly sensitive (> 90%) with a high negative predictive value, whereas false positive findings are challenging, especially early post-operative. Leucocyte scintigraphy combined with bone marrow scintigraphy has a better overall accuracy compared to [^{18}F]FDG-PET/CT in suspected hip and knee prosthetic joint infections, but several practical issues favor [^{18}F]FDG-PET/CT. Future developments of more specific tracers and novel scanner technology holds potential.

Summary Evidence for [^{18}F]FDG-PET/CT in infectious and inflammatory disease supports the use in fever of unknown origin, bloodstream infections, spondylodiscitis, infective endocarditis, vascular graft infections, and prosthetic joint infections. However, the literature is generally heterogeneous and several issues remain unclarified, e.g., patient selection and interpretation criteria. [^{18}F]FDG-PET/CT has a definite role in infectious and inflammatory imaging, but firm evidence is still lacking on its precise place in the diagnostic pathways.

Introduction

Imaging of infection and inflammation has been part of nuclear medicine since the 1970s beginning with now-obsolete [^{67}Ga]gallium-citrate scintigraphy and labeled leucocyte scintigraphy. The latter still has a few select indications, but it requires technical skills, is time-consuming, and requires direct contact with patient blood. Today it is generally less available than positron emission tomography combined with computer tomography (PET/CT) which has largely overtaken as the nuclear medicine mainstay for infection and inflammation [1].

Routine PET/CT is based on imaging the distribution and uptake patterns of 2-deoxy-[fluorine-18]-flouro-D-glucose ([^{18}F]FDG), a glucose analogue with great versatility that is taken up by every cell proportional to their energy consumption. Increased uptake is present in hypermetabolic cells, e.g., activated cells in inflamed tissue, due to upregulation of glucose transporters and intracellular metabolic trapping of the molecule to provide high target-to-background ratio [2]. In the first decades of [^{18}F]FDG and PET, the incidentally encountered [^{18}F]FDG-uptake in infectious or inflammatory foci in cancer patients was considered a false-positive nuisance. However, from the 1990s onward, this shifted towards a greater understanding and appreciation of [^{18}F]FDG outside the initial indications of neurology and oncology, especially with increased availability of [^{18}F]FDG PET/CT-scanners [3].

In our opinion, [^{18}F]FDG-PET/CT is a key modality in infection and inflammation and this overview outlines the diagnostic values in most common uses within this domain.

Fever of unknown origin

Fever of unknown origin (FUO) represents a complex diagnostic challenge, the cause remain undiagnosed in up to 50% of cases. The diverse clinical symptoms and many possible causes of FUO add to the intricacy of its evaluation, making it a time-consuming and expensive process. The definition of fever of unknown origin (FUO) has changed over time; a broad definition is a fever lasting longer than usually seen in self-limiting conditions (e.g., viral infections) without a known cause despite thorough assessment by an

experienced physician. The latest expert recommendations revised the temperature criterion for FUO to > 38.0 °C (100.4 °F), a slight reduction from the previous threshold of > 38.3 °C (100.9 °F) [4].

Currently, there is no specific diagnostic algorithm for FUO, and with > 200 differential diagnoses, it is quite challenging to pinpoint a specific diagnosis. In simple terms, the potential underlying causes of FUO can be grouped into five main categories: infections, neoplasms, non-infectious inflammatory conditions, miscellaneous diseases, and idiopathic or unexplained [5]. The factors influencing the etiology of FUO vary significantly, but a recent 2023 study encompassing participants from 21 countries with varying levels of economic development revealed that the causes of FUO were primarily infections (51.6%), followed by neoplasms (11.4%), collagen vascular diseases (9.3%), a variety of other conditions (7.7%), and cases that remained undiagnosed (20.1%) [6].

With no standardized workup for FUO, examinations may vary according to the individual patient's characteristics and clinical features, but usually include basic laboratory examinations like complete blood count and urinalysis, and first-line radiological examinations, where contrast-enhanced computed tomography of the abdomen and pelvis seems to be replacing chest X-ray and abdominal ultrasound. In many cases, second-line investigations, including specialized imaging techniques, are required when the first-line tests yield no diagnostic information [5].

Based on a meta-analysis, [^{18}F]FDG-PET/CT has been found to be helpful in diagnosing many of the different diseases and categories (infectious, inflammatory, and malignancy) that may lead to FUO [7]. In infectious diseases, [^{18}F]FDG-PET/CT showed a diagnostic yield of 77.2%, with tuberculosis (15.4%), pneumonia (9.5%), bone and joint infections (5.4%), and intra-abdominal abscesses (5.0%) being the main conditions identified. In non-infectious inflammatory diseases (NIID), the diagnostic yield was 64.9%, with vasculitis (22.8%), sarcoidosis (7.0%), adult-onset Still's Disease (AOSD) (5.8%), and thyroiditis (4.7%) as the main diagnoses. In malignancies, the diagnostic yield was impressive 96% with lymphoma being the significant portion at 62% [7]. Thus, [^{18}F]FDG-PET/CT is most effective for identifying fevers caused by neoplasms or infections. A recent study conducted in India demonstrated similar results in developing countries [8], which highlights the importance of increasing the accessibility to PET in the developing world.

Meta-analyses of patients with classic FUO have demonstrated sensitivities of 84–86%, specificities of 52–63%, and diagnostic efficacy of at least 50% for identifying the underlying cause of FUO [5]. In contrast, now obsolete [^{67} Ga]-citrate and labeled leukocyte tests had pooled sensitivities of 60% and 33%, specificities of 63% and 83%, and diagnostic efficacy of 35% and 20%, respectively [9]. The higher yield of FDG PET/CT compared to [^{67} Ga]-citrate and white blood cell scintigraphy in FUO was recently confirmed by a paper that analyzed 63 articles including 5094 patients [10•]. In lieu of the growing evidence in favor of [^{18}F]FDG-PET/CT in FUO, the United States Center for Medicare and Medicaid Services decided to counter their previous decision to not reimburse infection and inflammation and the use in this setting is now increasing [11]. The number of studies on pediatric patients is limited, and

FUO in children is not completely equivalent to FUO in adults, but generally speaking, [^{18}F]FDG-PET/CT has shown the same positive outcomes in children with FUO. A recent meta-analysis including six studies found that children with abnormal [^{18}F]FDG-PET/CT scans were approximately 17 times more likely to be diagnosed definitively [12].

Whole-body imaging is a crucial component and an advantage of radionuclide FUO assessments with [^{18}F]FDG-PET/CT, and newly introduced total-body scanners may offer additional advantages (see further below). A meta-analysis also compared stand-alone PET with PET/CT. [^{18}F]FDG-PET/CT demonstrated higher sensitivity (98% vs. 83%) and specificity (86% vs. 58%) [13]. Regarding the CT-component, contrast-enhanced CT improve the diagnostic yield of [^{18}F]FDG-PET/CT in FUO [14]. Although CT is first-line modality and [^{18}F]FDG-PET/CT the second-line investigation, recent evidence suggests to reverse this order: A meta-analysis that reported on the outcomes of CT scans conducted prior to [^{18}F]FDG-PET/CT in the evaluation of FUO found additional diagnostic yield of [^{18}F]FDG-PET/CT of 32% [7]. Expert consensus currently suggests using [^{18}F]FDG-PET/CT relatively earlier in FUO evaluation when conventional work-up is unsuccessful, especially in patients with suspected serious diagnoses such as malignancy. Furthermore, [^{18}F]FDG-PET/CT scan within the weeks of FUO workup may secure earlier diagnosis and save costs by avoiding unnecessary and invasive investigations and reducing the duration of hospitalization [15].

It is also important to note that a negative [^{18}F]FDG-PET/CT may be equally useful by ruling out focal diseases as the cause of fever and predict a favorable prognosis of patients with FUO, i.e., spontaneous resolution of the fever. In a 2018 meta-analysis, patients with negative test results were more likely to experience spontaneous fever remission compared to those with positive results [16]. In addition, patients with negative [^{18}F]FDG-PET/CT scans were not diagnosed with a focal disease during a follow-up period of up to 2 years [17].

Bloodstream infections

Bacteremia or bloodstream infections (BSI) are systemic infections in a continuum from asymptomatic to life threatening. They may be clinically challenging with non-specific symptoms and few localizing signs. BSI may be simple (positive blood culture only) or complex (metastatic foci outside the bloodstream). Complex BSI has a significantly poorer prognosis than simple BSI and requires more aggressive treatment to reduce mortality. The same goes for patients at high risk for complex BSI to prevent progression, but many patients never progress to complex BSI and as many as 50% are over-treated [5, 18•].

[^{18}F]FDG-PET/CT is helpful in BSI when it directly influences patient management by directing the diagnostic process or modify the treatment strategy, e.g., escalation/de-escalation or more specific antibiotics or invasive drainage. However, literature on [^{18}F]FDG-PET/CT in BSI remains relatively sparse and challenging; studies are mostly retrospective and relatively small with

heterogeneous populations. This hampers comparison and overall conclusions, and several knowledge gaps remain, e.g., the timing of [^{18}F]FDG-PET/CT (upfront or following a number of potentially futile examinations). Also, very little is known about the impact of the clinical courses, e.g., if long-term antibiotics, the duration of symptoms, or underlying malignancies affect the diagnostic performance [5, 18•].

Several studies found [^{18}F]FDG-PET/CT had high impact (i.e., scan identified foci as the first modality or led to treatment modifications) in ~40–50% of patients. PET-positive foci are often endovascular or located in the spine that often show no symptoms, but do require prolonged antibiotic regimen. The value of a negative scan (or a scan with no suspicion of metastatic foci) is controversial but it may be safe to withhold therapy, de-escalate or switch from resource demanding intravenous to more patient friendly oral regimens if disease is limited. A negative [^{18}F]FDG-PET/CT may also reduce the need for further imaging [19–22].

Spondylodiscitis

Infectious spondylodiscitis (SD) comprises osteomyelitis of the spine and the intervertebral discs (Fig. 1); left untreated, it leads to progressive destruction of the infected vertebral segment with increased morbidity and mortality. SD incidence is increasing in developed countries due to aging demographics, increased BSI, and infected instrumentation; SD is often caused by secondary hematogenous spread. Early diagnosis is important to ensure timely treatment and avoid irreversible damage, but early diagnosis may be challenging due to non-specific symptoms and significant timespan from symptom debut to morphologic changes become apparent [23•, 24].

MRI is still considered the modality of choice with superior soft tissue characterization and generally speaking sensitivities and specificities > 90%. But it has certain limitations; in the earlier stages with few morphologic changes and in the post-operative setting, post-surgical structural changes may hamper correct interpretation of MRI, and metal implants from back surgery may contraindicate MRI [24, 25].

In recent years, [^{18}F]FDG-PET/CT has emerged as viable alternative with comparable sensitivity but reportedly slightly lower and variable specificity—much data is, however, based on stand-alone PET and more recent studies find sensitivities and specificities in the 85–95% range (Fig. 1). [^{18}F]FDG-PET/CT is a reasonable alternative in patients with contraindications to MRI and in patients with suspected post-operative spine infections. Each modality has advantages over the other; MRI visualizes the epidural space including the presence of epidural abscesses, whereas whole-body [^{18}F]FDG-PET/CT coverage also detect (unsuspected) distant foci of infection including paravertebral and psoas abscesses often not included in the MRI field-of-view [24, 26]. In addition, [^{18}F]FDG-PET/CT is probably better in early diagnosis within the

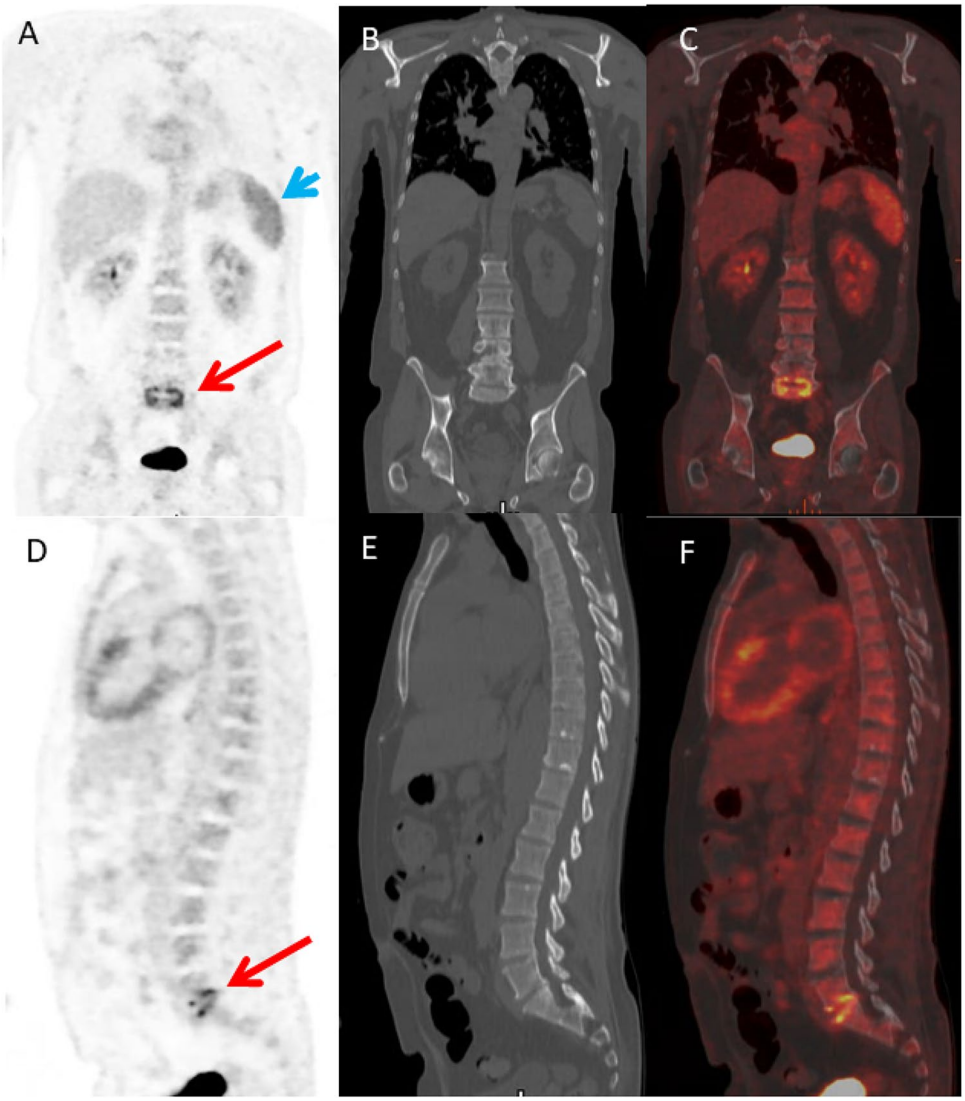

Fig. 1 Diffusely and intensely increased uptake around the discus consistent with spondylodiscitis at the L5/S1 level (red arrow). The patient has concurrent endocarditis (not shown) and *Enterococcus faecalis* bacteremia. Note diffuse uptake in the spleen (blue arrowhead), a non-specific sign of systemic inflammation

first 14 days of disease onset as sensitivity and specificity is > 90% compared to 76% and 84%, respectively, for MRI [26].

SD is also an indications where [^{18}F]FDG-PET/CT has shown some promise with regard to predicting patient outcome and monitoring response to treatment [24]. Righi et al. retrospectively assessed serial [^{18}F]FDG-PET/CT and MRI before and after at least 2 weeks antibiotics and found sensitivities and specificities for predicting clinical response of 89% and 100%, respectively, for FDG-PET/CT, and 37% and 50%, respectively, for MRI. Several studies found similar results, but others were more

inconsistent and equivocal and based on current available data no firm conclusions are possible [23•, 24].

Infective endocarditis

Infective endocarditis (IE) (Fig. 2) is a potentially life-threatening disease that comprise infection of the inside surface of the heart that may involve heart valves and leads, mural endocardium, native (NVE) or prosthetic valves (PVE), and cardiac implantable electronic device (CIEDs) and its leads (CIED IE). The clinical diagnosis of IE remains a diagnostic challenge and has for years been based on the probabilistic Duke Criteria. These include blood cultures and echocardiography (EC), but blood cultures may be negative in up to one-third of patients with verified IE, and EC has high specificity, but artefacts from prostheses and leads may hamper sensitivity [27].

Over the past decades, the use of [^{18}F]FDG-PET/CT has increased, and since 2015, the European Society of Cardiology (ESC) has recommended the ESC diagnostic criteria, supporting the implementation of abnormal [^{18}F]FDG-uptake around prosthetic valves as a novel major criterion for IE [27, 28]. Early diagnosis, identification of the causative pathogen, and assessment of extra-cardiac metastatic, embolic infection are crucial for patient outcome

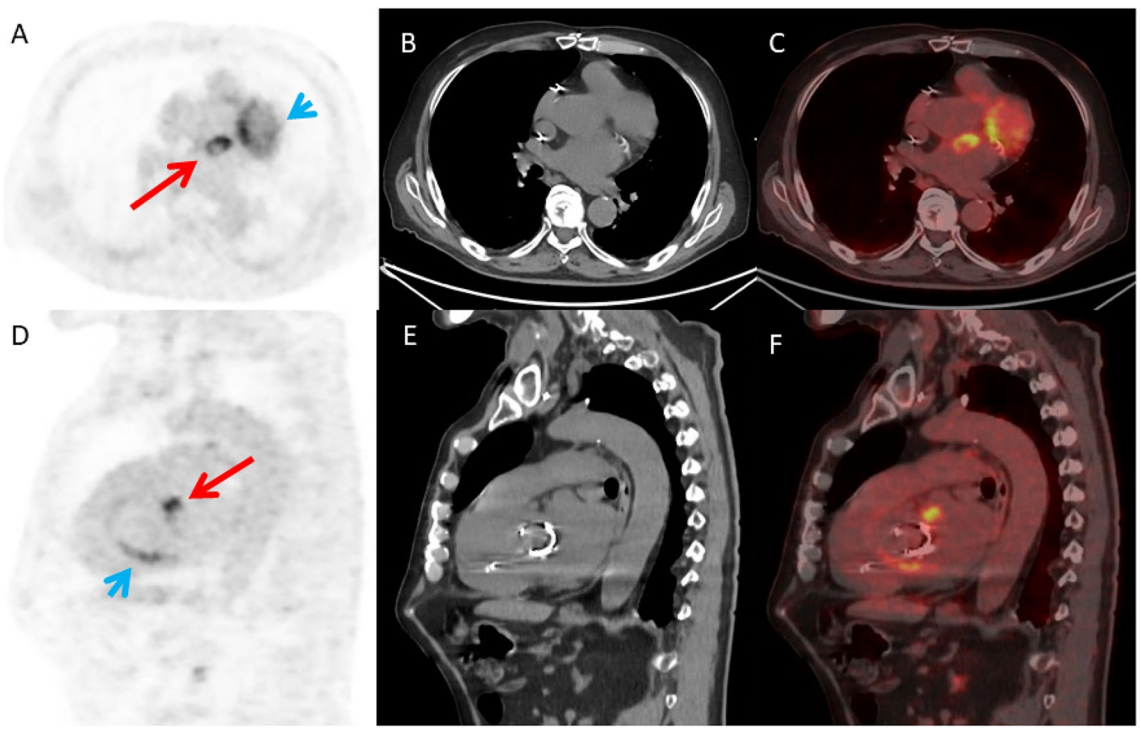

Fig. 2 Focal FDG-uptake in an infective abscess in the root of the aorta (red arrow) in close proximity of the TAVI (transcatheter aortic valve implantation)-prosthesis. No positive blood culture. Note diffuse uptake around the TAVI-prosthesis (blue arrowhead), consistent with physiologic, reactive activity

in order to secure timely and sufficient treatment—simple, uncomplicated IE is treatable with a 2-week course of antibiotics, whereas more complicated cases, e.g., bacteremic patients with metastatic spread requires longer treatment regimens. The guidelines underline the benefit of whole-body PET/CT for detection of extra-cardiac infection [27, 28].

Since the first small study by Yen et al. [29] in the beginning of the aughts, several works has followed. A recent systematic review [30] including 26 studies found pooled overall sensitivity and specificity of 74% and 88%, respectively. Dividing results according to subtype yielded sensitivities and specificities of 31% and 98%, respectively, for NVE, 86% and 84%, respectively, for PVE, and 72% and 83%, respectively, for CIED. Thus, specificity is relatively high in all scenarios, but sensitivity was considerably lower in native valve IE than in prosthetic valve IE; [^{18}F]FDG-uptake in the small moving excrescences on native valves are often too limited to be detectable, whereas uptake in the struts and surroundings of prosthetic valves is much more pronounced. Some studies also point towards different composition of vegetations, i.e., higher degrees of fibrosis and biofilm in native valve IE compared to prosthetic valve IE may hamper [^{18}F]FDG-uptake [31•].

However, the risk of false positive findings is also higher, i.e., from the general post-operative reactive physiologic uptake and related to surgical adhesive, a well-known confounder. Thus, [^{18}F]FDG should be interpreted with caution especially within the initial 3–4 months. Newer studies generally show better diagnostic performance than older studies [30], probably due to more stringent interpretation criteria and better understanding of the importance of sufficient patient preparation. Regarding the latter, it is crucial to reduce the physiologic uptake in the myocardial musculature through prolonged fasting and dietary constraints [32].

Some studies also address the potential of [^{18}F]FDG-PET/CT for monitoring treatment response and guide the rather complex treatment regimen towards a more personalized approach, and an important prerequisite is local endocarditis teams, i.e., a multidisciplinary team with regular conferences equivalent to the well-established tumor boards [27].

Vascular prostheses

Vascular graft infections (VGI) are rare but have high morbidity and mortality. Clinical diagnosis of VGI is complicated; symptoms vary and are non-specific. Clinically suspected VGI are confirmed with bacterial culture of explant graft or tissue surrounding the graft, but retrieving material for culture is often not possible. Thus, accurate non-invasive diagnostic tools are of great importance; false negative workup may be fatal, and false positive workup may lead to overtreatment. Ultrasonography and CT are usual first choices and detect morphologic changes, e.g., edema, bleeding or pseudoaneurysms, but tests may be false negative, especially in low-grade infections [33]. To alleviate this, [^{18}F]FDG-PET/CT is an alternative or complementary modality. However, results have been variable for various reasons; first, the literature is highly variable with regard to methodology, scan technique, and interpretation criteria which

hamper comparison. Second, [^{18}F]FDG-PET/CT has inherent limitations due to its difficulties in differentiation infection from the physiological immune response after graft implantation, which produces reactive FDG uptake. This reduces specificity, especially in the early post-operative stages [34].

Several systematic reviews/meta-analyses from the past 5 years identified a limited number of studies [35–40]. The overall conclusion was that [^{18}F]FDG-PET/CT is mostly quite sensitive for detecting infection with varying specificity with differences mostly related to interpretation methods with [^{18}F]FDG uptake pattern (focal vs. diffuse) and quantitative measures providing most favorable results, i.e., pooled sensitivities of 91–95% and pooled specificities of 76–81%. This should be compared to the values for CT presented by one of the studies, i.e. sensitivity and specificity of 67% and 63%, respectively [36]. Some studies also questioned the value of [^{18}F]FDG-PET/CT compared to the classic leucocyte scintigraphy which is suggested to have better specificity than [^{18}F]FDG-PET/CT, especially in the early post-operative period. The timing issue remains controversial; [^{18}F]FDG-uptake may reach its peak in the first few weeks after surgery and tends towards normal values around 4 weeks post-operatively [35], while others found lingering reactive activity several years after surgery [37]. However, due to the aforementioned drawbacks of leucocyte scintigraphy, [^{18}F]FDG-PET/CT is generally recommended as the first choice with the exception of the first post-operative months [34].

[^{18}F]FDG-PET/CT has been proposed for guiding treatment decisions in VGI [34]; in one prospective study, FDG-uptake was used along with biochemical and clinical information to guide treatment, i.e., whether to start, escalate, continue, or stop, and they concluded that consecutive PET/CTs could influence the clinical decision-making [41••]. However, as with SD, data remain too limited for firm conclusions.

Prosthetic joint infections

Prosthetic joint infections (PJI) are relatively rare, but incidence in rising with steadily increasing number of arthroplasties and elder demographics, currently 2.0–2.4% in primary interventions, up to 20% in revision prosthesis, and it accounts for 20% of revision procedures [42, 43].

As with other prosthesis-related infections, symptoms can be relatively non-specific with pain as the most frequent symptom. Prompt identification of the infection is necessary to ensure early and successful treatment with the aim of preserving joint functionality [44]. PJI can be categorized as early (<3 months three months from surgery), delayed (3 months–2 years), and late (>2 years post-surgery). Early and delayed infections are typically the result of bacteria introduced during surgery while hematogenous spread from other foci or secondary to bacteremia is a risk regardless of time from surgery [45].

No single routine test can diagnose PJI with sufficient accuracy. Clinical evaluation, microbiological and laboratory examinations, and imaging are all important diagnostic tools. Joint fluid aspiration has traditionally been used to rule out PJI, but there is often not enough to aspirate [45]. Conventional

plain radiographs are neither sensitive nor specific, whereas diagnostic accuracy of CT and MRI are less validated, more variable, and impacted by hardware-induced artifacts [46, 47].

Many consider leukocyte scintigraphy with SPECT/CT combined with bone marrow scintigraphy the reference standard with the highest accuracy in diagnosing PJI. However, leukocyte scintigraphy is limited by the spatial resolution of the gamma camera and the procedure is complex and time consuming and requires direct handling of patient blood. [^{18}F]FDG-PET/CT has advantages, e.g., higher spatial resolution, faster and single-day imaging protocols, and whole-body imaging that aids in establishing other foci of infection. On the other hand, [^{18}F]FDG-uptake is non-specific, and in the case of PJI, this hampers specificity due to reactive, inflammation around the prosthesis, especially in the first months after surgery [44–46].

Recent meta-analyses generally find comparable results for combined leucocyte scintigraphy/bone marrow scintigraphy (including SPECT/CT) and [^{18}F]FDG-PET/CT when it comes to hip replacements with sensitivity and specificity > 90%, while [^{18}F]FDG-PET/CT is probably slightly inferior when it comes to knee prostheses [45, 48]. Two Danish studies found poor results for both leukocyte scintigraphy and FDG-PET/CT in chronic, low-grade shoulder PJI, i.e., sensitivities, specificities, PPV, and NPV of 18%, 100%, 100%, and 67%, and 14%, 91%, 40%, and 71%, respectively, and neither is recommended in this setting [49, 50]. Generally, for hips and knees, sensitivity and negative predictive value are higher for FDG-PET/CT, while specificity is superior for leukocyte scintigraphy, especially in the early post-operative period. However, considerable controversy remains and papers are heterogeneous in methodology, which hampers direct comparison. Furthermore, the disadvantages of leucocyte scintigraphy should be kept in mind when deciding on the modality of choice, e.g., local availability, time efficiency, patient comfort, and cost.

Different interpretation regimes have been proposed to increase the specificity. The most important differential diagnosis to PJI is aseptic loosening which also shows some degree of peri-prosthetic inflammatory reactions. In general, [^{18}F]FDG-uptake patterns are better than the intensity of [^{18}F]FDG-uptake when it comes to PJI. Focal [^{18}F]FDG-uptake or heterogeneous activity with focal hotspots is more suspicious for infection than diffuse, and moderate-strong [^{18}F]FDG-uptake along the femoral component of the prosthetic stem should also raise suspicion of infection. Conversely, focal [^{18}F]FDG uptake at the tip of the stem or at the bone-prosthetic junction in the proximal femur and diffuse [^{18}F]FDG uptake around the bone and in the soft tissues is a frequent finding without infection and is considered an expression of reactive physiological activity [45, 48].

Potential novel developments

Bacteria-specific tracers

Both structural imaging and nuclear medicine can detect inflammatory changes, but have difficulties distinguishing bacterial infection from sterile inflammation.

Although radioisotopes may identify biochemical and pathophysiologic changes at various stages of inflammation, it also lacks specificity. The most commonly used tracer [^{18}F]FDG can identify and image inflammation due to the presence of hypermetabolic cells, but cannot per se determine if the hypermetabolic cells are bacteria, cellular response to bacteria or non-infectious inflammation in a particular case [51]. Thus, development of more targeted radiopharmaceuticals that are aimed directly at receptors or enzymes specific to bacteria to differentiate between infectious and non-infectious inflammation has been ongoing for more than three decades now, but controversy remains regarding their validity [52–55].

A multitude of different radiopharmaceuticals has been studied: glucose analogs, antimicrobial and chemotactic peptides, antibiotics, white blood cells, cytokines, immunoglobulins, bacteriophages, and siderophores that can be labeled with radioisotopes such as ^{18}F, ^{99m}Tc, ^{111}In, and ^{67} Ga. Important examples include 6-[^{18}F]-fluoromaltose and [^{18}F]-FDS (glucose analogs); ubiquicidin, D-[methyl-^{11}C]methionine ([^{11}C]D-Met) and [^{68} Ga]Ga-NOTA/DOTA-UBI-29–41) (peptides or amino acids); and [^{68} Ga]Ga-desferrioxamine-B ([^{68} Ga]Ga-DFO-B) and [^{68} Ga]Ga-pyoverdine PAO1 ([.^{68} Ga]Ga-PVD-PAO1) (radiolabeled siderophores). While numerous in vitro and in vivo studies have been performed with these compounds, the results have not been encouraging. Despite a number of candidates being introduced every year and tested preclinically, unfortunately, only a few have made it to human studies, and that is too with limited success [52, 56, 57•]

Several systematic reviews from the same group is available on various aspects of radiopharmaceuticals for direct bacteria imaging, including radiolabeled antibiotics. A key observation from the many studies included was that only a few of these radiopharmaceuticals was ever translated into human subjects and only with limited impact. There was significant heterogeneity in the selected animal models, index tests, and particularly the bacterial concentrations used to induce infections across these studies making direct comparison between studies challenging. The meta-analyses also highlighted the lack of standardized infection models and experimental settings in this area of research and highlighted the risk of developing antibiotic resistance with radiolabeled antibiotics [56, 57•].

Finally, it is worth mentioning other important aspects contributing to the repeatedly unsuccessful attempts with these so-called bacteria-specific radiotracers, e.g., the biology of bacterial infections and the relative low-resolution imaging procedure [52, 54]. For successful PET imaging of bacteria, a certain volume is necessary at the site of infection (~8–10 cubic mm). In addition, the concentration of radiotracer within them must be substantially greater than the background [54, 58, 59]. However, bacteria are usually rapidly phagocytosed by WBCs attracted by cytokines to the site as a dynamic immunological response to a foreign bacterial agent. It is unlikely that such a huge volume of bacteria will accumulate and be exposed to radiotracers.

Large axial field of view PET/CT scanners

Large axial field of view (LAFOV) PET/CT scanners have recently been introduced with additional advantages over standard PET/CT scanners [60, 61]. LAFOV PET/CT has been described as a game-changer due to significantly higher sensitivity, rapid acquisition, reduced required activity of radiotracer, and lower radiation exposure [60–62]. Increased sensitivity may enable us to identify infectious processes usually missed on standard PET/CT systems, e.g. early and low-grade infections. While a standard PET/CT scan takes 15–20 min for acquisition, acquisition time for LAFOV scanners may be reduced to 2–3 min. This may be highly beneficial for patients who are seriously ill, e.g., ICU patients and patients with discomfort, pain, or disability [62].

In a recently published case report, Rijsewijk et al. demonstrated its tremendous capability to image infection in a newborn with subcutaneous abscess of the foot and possible endocarditis by giving ultra-low-dose FDG and without requiring sedation [10•]. The advantage of lower radiation exposure with this modality cannot be overemphasized in the case of children. Finally, the potential to do dynamic imaging by including all the main organs in a single field of view may enable exploration of tracer kinetics in infection vs. inflammation with a potential to differentiate. This will largely offset the limitations of FDG as a radiotracer due to its inability to differentiate infection vs. inflammation [62].

However, LAFOV PET/CT scanners are currently only available in limited centers with relatively large nuclear medicine departments, limiting their accessibility.

Conclusion

Evidence for whole-body [^{18}F]FDG-PET/CT in infectious and inflammatory disease supports the use in the abovementioned settings, i.e., FUO, BSI, SD, IE, VGI, and PJI. The literature is generally heterogeneous and several issues remain unclarified, e.g., impact of antibiotics on [^{18}F]FDG-uptake and a lack of consensus on parameters used for interpretation.

In FUO, [^{18}F]FDG-PET/CT is considered helpful in establishing the underlying disease in 50–60%. In patients with high-risk complex BSI with risk of metastatic disease, [^{18}F]FDG-PET/CT changes treatment in a significant proportion of patients resulting in reduced relapse rates and mortality; if scans are negative it may be safe to withhold or de-escalate treatment strategy. In IE, [^{18}F]FDG-PET/CT has largest impact in PVE and CIED IE whereas its diagnostic use in NVE is limited. Patient preparation and local endocarditis teams are key.

For SD, [^{18}F]FDG-PET/CT and MRI has overall equally diagnostic performance, and many consider them complementary with combined sensitivity and specificity of ~ 100%. [^{18}F]FDG-PET/CT may be useful—and superior to MRI—for monitoring treatment and predict response, but data remains too sparse for firm conclusion.

In VGI, [^{18}F]FDG-PET/CT is highly sensitive (>90%) with a high negative predictive value, whereas specificity is more moderate with false positive findings, especially early post-operative. Leucocyte scintigraphy SPECT/CT combined with bone marrow scintigraphy has a better overall accuracy compared to [^{18}F]FDG-PET/CT in suspected hip and knee PJI, but several practical issues favor [^{18}F]FDG-PET/CT.

Author Contributions

All authors contributed to conceptualizing this work and contributed individual sections of the main text. K.R. prepared figures 1 & 2. All authors reviewed the manuscript and approved the final version.

Declarations

Competing Interests
The authors declare no competing interests.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Palestro CJ. A brief history of nuclear medicine imaging of infection. J Infect Dis. 2023;228(Suppl 4):S237–40. https://doi.org/10.1093/infdis/jiac466.
2. Basu S, Hess S, Nielsen Braad PE, Olsen BB, Inglev S, Hoilund-Carlsen PF. The basic principles of FDG-PET/CT imaging. PET Clin. 2014;9(4):355–70. https://doi.org/10.1016/j.cpet.2014.07.006.
3. Gormsen LC, Hess S. Challenging but clinically useful: fluorodeoxyglucose PET/computed tomography in inflammatory and infectious diseases. PET Clin. 2020;15(2):xi–xii. https://doi.org/10.1016/j.cpet.2020.01.002.
4. Wright WF, Mulders-Manders CM, Auwaerter PG, Bleeker-Rovers CP. Fever of unknown origin (FUO) - a call for new research standards and updated clinical management. Am J Med. 2022;135(2):173–8. https://doi.org/10.1016/j.amjmed.2021.07.038.
5. Hess S. FDG-PET/CT in fever of unknown origin, bacteremia, and febrile neutropenia. PET Clin. 2020;15(2):175–85. https://doi.org/10.1016/j.cpet.2019.11.002.
6. Erdem H, Baymakova M, Alkan S, Letaief A, Yahia WB, Dayyab F, et al. Classical fever of unknown origin in 21 countries with different economic development: an international ID-IRI study. Eur J Clin Microbiol Infect Dis: Off Publ Eur Soc Clin Microbiol. 2023;42(4):387–98. https://doi.org/10.1007/s10096-023-04561-5.
7. Bharucha T, Rutherford A, Skeoch S, Alavi A, Brown M, Galloway J. Diagnostic yield of FDG-PET/CT in fever of unknown origin: a systematic review, meta-analysis, and Delphi exercise. Clin Radiol. 2017;72(9):764–71. https://doi.org/10.1016/j.crad.2017.04.014.

8. Yadav BK, Pannu AK, Kumar R, Rohilla M, Kumari S. Fever of unknown origin in older adults: a prospective observational study from North India. J Assoc Phys India. 2021;69(10):11–2.
9. Betrains A, Boeckxstaens L, Moreel L, Wright WF, Blockmans D, Van Laere K, et al. Higher diagnostic yield of 18F-FDG PET in inflammation of unknown origin compared to fever of unknown origin. Eur J Intern Med. 2023;110:71–6. https://doi.org/10.1016/j.ejim.2023.01.025.
10• van Rijsewijk ND, Ffa IJ, Wouthuyzen-Bakker M, Glaudemans A. Molecular imaging of fever of unknown origin: an update. Sem Nucl Med. 2023;53(1):4–17. https://doi.org/10.1053/j.semnuclmed.2022.07.002.
An excellent overview of the clinical value of molecular imaging in FUO based on a systematic literature review.
11. Wahl RL, Dilsizian V, Palestro CJ. At Last, (18)F-FDG for inflammation and infection! J Nucl Med: Off Publ Soc Nucl Med. 2021;62(8):1048–9. https://doi.org/10.2967/jnumed.121.262446.
12. Li Q, Tian R, Wang H, Li L, Wu T, Ren Y, et al. Quantifying the contribution of (18)F-FDG PET to the diagnostic assessment of pediatric patients with fever of unknown origin: a systematic review and meta-analysis. Pediatr Radiol. 2022;52(8):1500–11. https://doi.org/10.1007/s00247-022-05333-7.
13. Dong MJ, Zhao K, Liu ZF, Wang GL, Yang SY, Zhou GJ. A meta-analysis of the value of fluorodeoxyglucose-PET/PET-CT in the evaluation of fever of unknown origin. Eur J Radiol. 2011;80(3):834–44. https://doi.org/10.1016/j.ejrad.2010.11.018.
14. Gafter-Gvili A, Raibman S, Grossman A, Avni T, Paul M, Leibovici L, et al. [18F]FDG-PET/CT for the diagnosis of patients with fever of unknown origin. QJM : Monthly J Assoc Phys. 2015;108(4):289–98. https://doi.org/10.1093/qjmed/hcu193.
15. Palestro CJ, Brandon DC, Dibble EH, Keidar Z, Kwak JJ. FDG PET in evaluation of patients with fever of unknown origin: AJR expert panel narrative review. AJR Am J Roentgenol. 2023;221(2):151–62. https://doi.org/10.2214/ajr.22.28726.
16. Takeuchi M, Nihashi T, Gafter-Gvili A, Garcia-Gomez FJ, Andres E, Blockmans D, et al. Association of 18F-FDG PET or PET/CT results with spontaneous remission in classic fever of unknown origin: a systematic review and meta-analysis. Medicine. 2018;97(43):e12909. https://doi.org/10.1097/md.0000000000012909.
17. Keidar Z, Gurman-Balbir A, Gaitini D, Israel O. Fever of unknown origin: the role of 18F-FDG PET/CT. J Nucl Med. 2008;49(12):1980–5. https://doi.org/10.2967/jnumed.108.054692.
18• Hess S. [18F]FDG-PET/CT in patients with bacteremia: clinical impact on patient management and outcome. Front Med. 2023;10. https://doi.org/10.3389/fmed.2023.1157692.
A comprehensive overview of the role of [18F]FDG-PET/CT in bloodstream infections.
19. Brondserud MB, Pedersen C, Rosenvinge FS, Hoilund-Carlsen PF, Hess S. Clinical value of FDG-PET/CT in bacteremia of unknown origin with catalase-negative Gram-positive cocci or Staphylococcus aureus. Eur J Nucl Med Mol Imaging. 2019;46(6):1351–8. https://doi.org/10.1007/s00259-019-04289-5.
20. Tsai HY, Lee MH, Wan CH, Yang LY, Yen TC, Tseng JR. C-reactive protein levels can predict positive (18)F-FDG PET/CT findings that lead to management changes in patients with bacteremia. J Microbiol Immunol Infect = Wei Mian Yu Gan Ran Za Zhi. 2018;51(6):839–46. https://doi.org/10.1016/j.jmii.2018.08.003.
21. Vos FJ, Bleeker-Rovers CP, Sturm PD, Krabbe PF, van Dijk AP, Cuijpers ML, et al. 18F-FDG PET/CT for detection of metastatic infection in gram-positive bacteremia. J Nucl Med: Off Publ Soc Nucl Med. 2010;51(8):1234–40. https://doi.org/10.2967/jnumed.109.072371.
22. Berrevoets MAH, Kouijzer IJE, Aarntzen E, Janssen MJR, De Geus-Oei LF, Wertheim HFL, et al. (18)F-FDG PET/CT optimizes treatment in Staphylococcus aureus bacteremia and is associated with reduced mortality. J Nucl Med: Off Publ Soc Nucl Med. 2017;58(9):1504–10. https://doi.org/10.2967/jnumed.117.191981.
23.• Lapa C, Rischpler C, Bundschuh RA, Dierks A, Lang S, Wassilew G, et al. Value of [18F]FDG PET/CT in diagnosis and management of spondylodiscitis. Z Orthop Unfall. 2023;161(5):544–51. https://doi.org/10.1055/a-2075-8873.
A good contemporary review on the value of [18F]FDG-PET/CT in spondylodiscitis.
24. Lazzeri E, Bozzao A, Cataldo MA, Petrosillo N, Manfrè L, Trampuz A, et al. Joint EANM/ESNR and ESCMID-endorsed consensus document for the diagnosis of spine infection (spondylodiscitis) in adults. Eur J Nucl Med Mol Imaging. 2019;46(12):2464–87. https://doi.org/10.1007/s00259-019-04393-6.
25. Paez D, Sathekge MM, Douis H, Giammarile F, Fatima S, Dhal A, et al. Comparison of MRI, [(18)F]FDG PET/CT, and (99m)Tc-UBI 29–41 scintigraphy for postoperative spondylodiscitis-a prospective multicenter study. Eur J Nucl Med Mol Imaging. 2021;48(6):1864–75. https://doi.org/10.1007/s00259-020-05109-x.
26. Smids C, Kouijzer IJ, Vos FJ, Sprong T, Hosman AJ, de Rooy JW, et al. A comparison of the diagnostic value of MRI and (18)F-FDG-PET/CT in suspected spondylodiscitis. Infection. 2017;45(1):41–9. https://doi.org/10.1007/s15010-016-0914-y.
27. Delgado V, Ajmone Marsan N, de Waha S, Bonaros N, Brida M, Burri H, et al. 2023 ESC guidelines for the management of endocarditis. Eur Heart J. 2023;44(39):3948–4042. https://doi.org/10.1093/eurheartj/ehad193.

28 Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, et al. ESC guidelines for the management of infective endocarditis: the task force for the management of infective endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J. 2015;36(44):3075–128. https://doi.org/10.1093/eurheartj/ehv319.

29. Yen R-F, Chen Y-C, Wu Y-W, Pan M-H, Chang S-C. Using 18-fluoro-2-deoxyglucose positron emission tomography in detecting infectious endocarditis/endoarteritis. Acad Radiol. 2004;11(3):316–21. https://doi.org/10.1016/s1076-6332(03)00715-3.

30. Wang TKM, Sánchez-Nadales A, Igbinomwanhia E, Cremer P, Griffin B, Xu B. Diagnosis of infective endocarditis by subtype using (18)F-fluorodeoxyglucose positron emission tomography/computed tomography: a contemporary meta-analysis. Circ Cardiovasc Imaging. 2020;13(6):e010600. https://doi.org/10.1161/circimaging.120.010600.

31.• Boczar KE, Lau L, Hejji N, Wiefels C. Infective endocarditis: the role of PET imaging in diagnosis and management. J Med Imaging Radiat Sci. 2024. https://doi.org/10.1016/j.jmir.2023.12.012.

A very good contemporary review on the value of [18F] FDG-PET/CT in spondylodiscitis.

32. Hess S, Scholtens AM, Gormsen LC. Patient preparation and patient-related challenges with FDG-PET/CT in infectious and inflammatory disease. PET Clin. 2020;15(2):125–34. https://doi.org/10.1016/j.cpet.2019.11.001.

33. Chakfé N, Diener H, Lejay A, Assadian O, Berard X, Caillon J, et al. Editor's Choice - European Society for Vascular Surgery (ESVS) 2020 clinical practice guidelines on the management of vascular graft and endograft infections. Eur J Vasc Endovasc Surg: Off J Eur Soc Vasc Surg. 2020;59(3):339–84. https://doi.org/10.1016/j.ejvs.2019.10.016.

34. Lauri C, Signore A, Glaudemans A, Treglia G, Gheysens O, Slart R, et al. Evidence-based guideline of the European Association of Nuclear Medicine (EANM) on imaging infection in vascular grafts. Eur J Nucl Med Mol Imaging. 2022;49(10):3430–51. https://doi.org/10.1007/s00259-022-05769-x.

35. Rojoa D, Kontopodis N, Antoniou SA, Ioannou CV, Antoniou GA. 18F-FDG PET in the diagnosis of vascular prosthetic graft infection: a diagnostic test accuracy meta-analysis. Eur J Vasc Endovasc Sur: Off J Eur Soc Vasc Surg. 2019;57(2):292–301. https://doi.org/10.1016/j.ejvs.2018.08.040.

36. Reinders Folmer EI, Von Meijenfeldt GCI, Van der Laan MJ, Glaudemans A, Slart R, Saleem BR, et al. Diagnostic imaging in vascular graft infection: a systematic review and meta-analysis. Eur J Vasc Endovasc Surg: Off J Eur Soc Vasc Surg. 2018;56(5):719–29. https://doi.org/10.1016/j.ejvs.2018.07.010.

37. Sunde SK, Beske T, Gerke O, Clausen LL, Hess S. FDG-PET/CT as a diagnostic tool in vascular graft infection: a systematic review and meta-analysis. Clin Trans Imaging. 2019;7(4):255–65. https://doi.org/10.1007/s40336-019-00336-1.

38. Kim SJ, Lee SW, Jeong SY, Pak K, Kim K. A systematic review and meta-analysis of (18)F-fluorodeoxyglucose positron emission tomography or positron emission tomography/computed tomography for detection of infected prosthetic vascular grafts. J Vasc Surg. 2019;70(1):307–13. https://doi.org/10.1016/j.jvs.2019.01.051.

39. ReindersFolmer EI, von Meijenfeldt GCI, Te Riet OokGenaamdScholten RS, van der Laan MJ, Glaudemans A, Slart R, et al. A systematic review and meta-analysis of (18)F-fluoro-d-deoxyglucose positron emission tomography interpretation methods in vascular graft and endograft infection. J Vasc Surg. 2022;72(6):2174–85. https://doi.org/10.1016/j.jvs.2020.05.065.

40. Mahmoodi Z, Salarzaei M, Sheikh M. Prosthetic vascular graft infection: a systematic review and meta-analysis on diagnostic accuracy of 18FDG PET/CT. Gen Thorac Cardiovasc Surg. 2022;70(3):219–29. https://doi.org/10.1007/s11748-021-01682-6.

41.•• Husmann L, Ledergerber B, Anagnostopoulos A, Stolzmann P, Sah BR, Burger IA, et al. The role of FDG PET/CT in therapy control of aortic graft infection. Eur J Nucl Med Mol Imaging. 2018;45(11):1987–97. https://doi.org/10.1007/s00259-018-4069-1.

This prospective clinical study described the value of FDG PET/CT in therapy control of aortic graft infection.

42. Premkumar A, Kolin DA, Farley KX, Wilson JM, McLawhorn AS, Cross MB, et al. Projected economic burden of periprosthetic joint infection of the hip and knee in the United States. J Arthroplasty. 2021;36(5):1484-9.e3. https://doi.org/10.1016/j.arth.2020.12.005.

43. Signore A, Sconfienza LM, Borens O, Glaudemans A, Cassar-Pullicino V, Trampuz A, et al. Consensus document for the diagnosis of prosthetic joint infections: a joint paper by the EANM, EBJIS, and ESR (with ESCMID endorsement). Eur J Nucl Med Mol Imaging. 2019;46(4):971–88. https://doi.org/10.1007/s00259-019-4263-9.

44. Glaudemans AW, Prandini N, Girolamo MD, Argento G, Lauri C, Lazzeri E, et al. Hybrid imaging of musculoskeletal infections. Quart J Nucl Med Mol Imag: off Publ Ital Assoc Nucl Med (AIMN) Int Assoc Radiopharmacol (IAR) Sect So. 2018;62(1):3–13. https://doi.org/10.23736/s1824-4785.17.03045-x.

45. Sconfienza LM, Signore A, Cassar-Pullicino V, Cataldo MA, Gheysens O, Borens O, et al. Diagnosis of peripheral bone and prosthetic joint infections: overview on the consensus documents by the EANM, EBJIS, and ESR (with ESCMID endorsement). Eur Radiol. 2019;29(12):6425–38. https://doi.org/10.1007/s00330-019-06326-1.

46. Romanò CL, Petrosillo N, Argento G, Sconfienza LM, Treglia G, Alavi A et al. The role of imaging

techniques to define a peri-prosthetic hip and knee joint infection: multidisciplinary consensus statements. J Clin Med 2020;9(8). https://doi.org/10.3390/jcm9082548.
47. Sollini M, Lauri C, Boni R, Lazzeri E, Erba PA, Signore A. Current status of molecular imaging in infections. Curr Pharm Des. 2018;24(7):754–71. https://doi.org/10.2174/1381612824666180110103348.
48. Loharkar S, Basu S. PET-computed tomography in bone and joint infections. PET Clin. 2023;18(1):49–69. https://doi.org/10.1016/j.cpet.2022.08.002.
49. Falstie-Jensen T, Daugaard H, Søballe K, Ovesen J, Arveschoug AK, Lange J. Labeled white blood cell/bone marrow single-photon emission computed tomography with computed tomography fails in diagnosing chronic periprosthetic shoulder joint infection. J Shoulder Elbow Surg. 2019;28(6):1040–8. https://doi.org/10.1016/j.jse.2018.10.024.
50. Falstie-Jensen T, Lange J, Daugaard H, Vendelbo MH, Sørensen AK, Zerahn B, et al. 18F FDG-PET/CT has poor diagnostic accuracy in diagnosing shoulder PJI. Eur J Nucl Med Mol Imaging. 2019;46(10):2013–22. https://doi.org/10.1007/s00259-019-04381-w.
51. Signore A. The need of shared diagnostic protocols. Quart J Nucl Med Mol Imag Off Publ Ital Assoc Nucl Med (AIMN) Int Assoc Radiopharmacol (IAR) Sect So. 2014;58(1):1.
52. Singh SB, Bhandari S, Siwakoti S, Bhatta R, Raynor WY, Werner TJ et al. Is imaging bacteria with PET a realistic option or an illusion? Diagnostics (Basel, Switzerland). 2023;13(7). https://doi.org/10.3390/diagnostics13071231.
53. Signore A, Artiko V, Conserva M, Ferro-Flores G, Welling MM, Jain SK et al. Imaging bacteria with radiolabelled probes: is it feasible? J Clin Med. 2020;9(8). https://doi.org/10.3390/jcm9082372.
54. Hess S, Alavi A, Werner T, Høilund-Carlsen PF. Molecular imaging of bacteria in patients is an attractive Fata Morgana, not a realistic option. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2018;59(4):716–7. https://doi.org/10.2967/jnumed.117.207001.
55. Marjanovic-Painter B, Kleynhans J, Zeevaart JR, Rohwer E, Ebenhan T. A decade of ubiquicidin development for PET imaging of infection: a systematic review. Nucl Med Biol. 2023;116–117:108307. https://doi.org/10.1016/j.nucmedbio.2022.11.001.
56. Auletta S, Galli F, Lauri C, Martinelli D, Santino I, Signore A. Imaging bacteria with radiolabelled quinolones, cephalosporins and siderophores for imaging infection: a systematic review. Clin Transl Imaging. 2016;4:229–52. https://doi.org/10.1007/s40336-016-0185-8.
57.• Auletta S, Varani M, Horvat R, Galli F, Signore A, Hess S. PET radiopharmaceuticals for specific bacteria imaging: a systematic review. Journal of clinical medicine. 2019;8(2). https://doi.org/10.3390/jcm8020197.
A comprehensive overview of potential novel bacteria-specific PET-tracers based in a systematic review of the literature.
58. Rousset O, Rahmim A, Alavi A, Zaidi H. Partial volume correction strategies in PET. PET Clin. 2007;2(2):235–49. https://doi.org/10.1016/j.cpet.2007.10.005.
59. Alavi A, Werner TJ, Høilund-Carlsen PF. What can be and what cannot be accomplished with PET to detect and characterize atherosclerotic plaques. J Nucl Cardiol: Off Publ Am Soc Nucl Cardiol. 2018;25(6):2012–5. https://doi.org/10.1007/s12350-017-0977-x.
60. Slart R, Tsoumpas C, Glaudemans A, Noordzij W, Willemsen ATM, Borra RJH, et al. Long axial field of view PET scanners: a road map to implementation and new possibilities. Eur J Nucl Med Mol Imaging. 2021;48(13):4236–45. https://doi.org/10.1007/s00259-021-05461-6.
61. van Sluis J, Borra R, Tsoumpas C, van Snick JH, Roya M, Ten Hove D, et al. Extending the clinical capabilities of short- and long-lived positron-emitting radionuclides through high sensitivity PET/CT. Cancer Imag: Off Publ Int Cancer Imag Soc. 2022;22(1):69. https://doi.org/10.1186/s40644-022-00507-w.
62. Glaudemans A, Gheysens O. Expert opinions in nuclear medicine: finding the "holy grail" in infection imaging. Front Med (Lausanne). 2023;10:1149925. https://doi.org/10.3389/fmed.2023.1149925.

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