

## Imaging of infectious diseases using [18F]fluorodeoxyglucose PET

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The role of fluorodeoxyglucose positron emission tomography (FDG PET) in the diagnostic localization of infectious diseases has expanded rapidly in recent years. In general, sensitivity of FDG PET in depicting infections compares favorably to other diagnostic modalities. It is shown to be useful in patients with suspected osteomyelitis, especially in chronic low-grade infections and in vertebral osteomyelitis. Although the sensitivity of FDG PET in prosthetic joint infections is very high, reported specificity varies considerably. In experienced centers, FDG uptake localized along the interface between bone and prosthesis can be used to diagnose infection with acceptable specificity. Combined leukocyte scintigraphy and bone scanning, however, remains the standard scintigraphic method for diagnosis of infected joint prostheses. FDG PET has shown promising results in vascular graft infections, in the evaluation of metastatic infectious foci in patients with blood stream infections and in neutropenic patients, but further studies are needed before definitive conclusions can be drawn. In fever of unknown origin (FUO), FDG PET appears to be of great advantage as malignancy, inflammation and infection can be detected. Image fusion combining PET and computed tomography facilitates anatomical localization of increased FDG uptake and better guiding for further diagnostic tests to achieve a final diagnosis. In conclusion, the body of evidence on the utility of FDG PET in infectious diseases and FUO is growing and FDG PET may become one of the preferred diagnostic procedures for many of these diseases, especially when a definite diagnosis cannot easily be achieved.

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Fluorine-18(<sup>18</sup>F)-fluorodeoxyglucose positron emission tomography (FDG PET) has been an established diagnostic tool in oncology since many years and the indications for FDG PET are expanding rapidly. FDG accumulates in all tissues with a high rate of glycolysis, which not exclusively occurs in neoplastic cells. FDG uptake is also present in all activated leukocytes (granulocytes, monocytes as well as lymphocytes) enabling imaging of acute and chronic inflammatory processes. The mechanism of FDG uptake in activated leukocytes is related to the fact that these cells use glucose as an energy source only after activation during the metabolic burst. FDG, like glucose, passes the cell membrane. Phosphorylated FDG is not further metabolized and remains trapped inside the cell, in contrast to phosphorylated glucose that enters the glycolytic pathway. Increased uptake and retention of FDG has been shown in lesions with a high concentration of inflammatory cells, such as granulocytes and activated macrophages. In an experimental rat model of turpentine-induced inflammation, FDG uptake was elevated even more in chronic inflammation than in an acute inflammatory

TABLE I.—References arranged according to organ system or localization.

Type of infection	References
Abdominal infection	7-10
Chest infection	11-13
Osteomyelitis	14-31
Prosthetic joint infection	18, 21, 32-45
Postoperative infections	21, 22, 46
Vascular infections	18, 47-50
Metastatic infectious foci	51
The immunocompromised host	52-63
Miscellaneous infections	17, 33, 64-67
Fever of unknown origin	65, 68-73
Differentiation between infection and malignancy	31, 74

process.<sup>1</sup> In another rat model of *Escherichia coli* infection, the uptake of FDG in the infectious process was higher than that of [<sup>67</sup>Ga]citrate, radiolabeled thymidine, methionine and human serum albumin.<sup>2</sup>

FDG PET has several advantages as compared to conventional scintigraphic techniques. Physiological uptake of FDG is low in most organs (except for the brain, heart, kidneys, and bladder) and provides relatively high target to background ratios. Low normal organ uptake is best assured by injecting FDG during a normoglycemic, hypo-insulinemic state created by a 6 h fasting period.<sup>3, 4</sup> FDG PET provides high-resolution, three-dimensional images of the whole body. Early imaging after 1 h is possible, resulting in early reporting. Furthermore, the dosimetry of FDG compares favorably to conventional radiopharmaceuticals. Although increased glucose metabolism may correlate with structural anatomical damage as depicted by conventional radiological techniques, FDG PET depicts functional changes in tissue, which may often precede anatomical changes. It may be difficult to detect active disease in scar tissue using conventional radiological techniques while one of the strengths of FDG PET is the delineation of disease activity. Co-registration of PET and computed tomography (CT) in combined PET-CT scanners, improves the interpretation of the PET findings by exact localization of lesions.<sup>5</sup>

### Search of the literature

For the period 1980-January 2007, the National Library of Medicine (PubMed) was searched using

the basic search terms for FDG PET studies as proposed by Mijnhout *et al.*<sup>6</sup> Subsequently, the above string was combined with infection, osteomyelitis, fever of unknown origin (FUO), or pyrexia of unknown origin. Additional search terms 'bacteremia', 'bacterial infection' were subsequently used, but did not reveal studies not already retrieved. A search in the Cochrane database only resulted in reviews focussing on the use of PET in various malignant diseases. No studies were found in the current controlled trials database.

After exclusion of publications written in a language other than English, a total number of 237 publications were retrieved. First, all publications addressing topics other than infection and FUO were excluded. The remaining publications (n=174) were divided into reviews, editorials, and case reports or case series including less than 3 patients (n=106). Clinical studies primarily aimed at diagnosing infection or FUO (n=68) were arranged according to organ system or anatomic site(s) of localization<sup>7-74</sup> (Table I).

### Abdominal infection

In 1989, Tahara *et al.* were the first to report increased FDG uptake in 2 patients with abdominal abscesses.<sup>7</sup> Numerous reports regarding FDG uptake in infectious and inflammatory diseases followed. In patients with polycystic kidney disease, FDG PET proved to be very helpful in 7 episodes of suspected renal or hepatic cyst infection by correctly pointing to the infected cysts.<sup>8</sup> A follow-up PET scan showed complete normalization after 6 weeks of treatment in one patient and ruled out re-infection in a subsequent episode of fever in another patient. In 12 inoperable patients with alveolar echinococcosis of the liver, Reuter *et al.* evaluated the glucose metabolism of lesions by use of FDG PET.<sup>9</sup> Necrotic parasitic lesions and areas of enhanced metabolic activity could be clearly discriminated. Most notably, 3 of 8 patients with metabolically active lesions, who were re-examined after chemotherapeutic treatment clearly showed improvement. In another study, PET showed increased FDG uptake in 21/26 patients with newly diagnosed alveolar echinococcosis and in only 1 of 12 patients with newly diagnosed cystic echinococcosis.<sup>10</sup> In 5 of 10 patients with non-resectable disease and increased baseline FDG uptake, the intensity of uptake decreased (or disappeared) during benzimidazole

therapy. It is concluded that FDG PET is a sensitive and specific adjunct in the diagnosis of suspected alveolar echinococcosis and can help in differentiating alveolar from cystic echinococcosis in the liver. FDG PET also appears to be valuable in assessing the efficacy of chemotherapy by showing the disappearance of metabolic activity.

### Chest infection

There have been numerous reports about FDG uptake in pulmonary infection and inflammation, most arising from false positive results in studies on the use of FDG PET in oncology. Bakheet *et al.* reviewed 650 FDG PET scans performed in patients suspected of lung cancer. In 10 patients pulmonary FDG uptake mimicked pulmonary metastases, but proved to be caused by benign disease.<sup>11</sup> In another study in a region with a high incidence of pulmonary histoplasmosis, sensitivity of FDG PET, as assessed in 84 patients with solitary pulmonary nodules, was 93% for diagnosing non-small cell lung cancer, but specificity was only 40%.<sup>12</sup> In 97 patients with untreated lung cancer, 14 patients with untreated pulmonary tuberculosis, and 5 patients with untreated atypical mycobacterial infection, standardized uptake values (SUV) of FDG and of [<sup>11</sup>C]choline were compared using PET.<sup>13</sup> SUV of FDG was highest in patients with lung cancer, lower in patients with tuberculosis and lowest in patients with atypical mycobacterial infection, but there was considerable overlap in SUV of both FDG and [<sup>11</sup>C]choline. This underlines the conclusion that FDG PET is not able to make a definite differentiation between malignancy and infection on an individual patient basis.

### Osteomyelitis

FDG PET has been used successfully in diagnosing acute osteomyelitis,<sup>14</sup> but it has no added value to physical examination, laboratory results, three-phase bone scanning and MRI in the absence of complicating factors. The diagnosis of chronic osteomyelitis is more complex. In patients with chronic osteomyelitis, excellent accuracy was found for FDG PET comparable to scintigraphy with antigranulocyte antibodies and <sup>111</sup>In-labeled leukocytes.<sup>14-19</sup> In the central skele-

ton, accuracy of FDG PET was even higher than for <sup>111</sup>In-labeled leukocytes and antigranulocyte antibody scintigraphy.<sup>15, 16</sup> In a prospective study including 31 patients suspected of osteomyelitis (peripheral skeleton: n=21 and central skeleton: n=10), overall accuracy of FDG PET was 97% with a high degree of interobserver concordance.<sup>20</sup> In another study, sensitivity, specificity, and accuracy of FDG PET were 100%, 88%, and 93% in 60 patients with a suspected chronic musculoskeletal infection involving the central skeleton (n=33) or the peripheral skeleton (n=27).<sup>21</sup> Hartmann *et al.* studied the use of FDG PET-CT in 33 trauma patients suspected of chronic osteomyelitis (23 peripheral skeleton, 10 central skeleton).<sup>22</sup> Sensitivity, specificity and accuracy for the whole group were 94%, 87% and 91%.

In 42 patients suspected of chronic osteomyelitis of the mandible, sensitivity of FDG PET (64%) was lower than sensitivity of bone scintigraphy (84%), but specificity of FDG PET proved to be higher (78% *vs* 33%).<sup>23</sup> During follow-up, specificity of FDG PET was still 63% while specificity of bone scintigraphy decreased to <10%. In 14 patients with diabetic foot infections, suspected of underlying osteomyelitis, PET-CT correctly localized the infectious foci in 4 patients to bone.<sup>24</sup> PET-CT correctly excluded osteomyelitis in 5 patients, with the abnormal FDG uptake limited to infected soft tissues only. One site of mildly increased focal FDG uptake was localized by PET-CT to diabetic osteoarthropathy changes demonstrated on CT. Four patients showed no abnormally increased FDG uptake and no further evidence of an infectious process on clinical and imaging follow-up.

It is well known that acute fractures can result in increased FDG accumulation and, therefore, cause difficulties when patients are evaluated for other indications by FDG PET. Zhuang *et al.* retrospectively assessed the pattern and time course of abnormal FDG uptake following traumatic or surgical fracture in 1 517 consecutive patients, who underwent whole-body FDG PET imaging.<sup>25</sup> Thirty-seven patients with a known date of traumatic or surgical fracture were identified. In 14 patients with fractures, less than 3 months old, only 6 had abnormally increased FDG uptake. In 23 patients with fractures, more than 3 months old, only one patient showed increased FDG uptake, which was shown to be a result of complicating osteomyelitis. It is concluded that FDG uptake is expected to be normal within 3 months following traumatic or surgical fractures.

The usefulness of antigranulocyte antibody or radiolabeled leukocyte scintigraphy is low in the central skeleton due to physiological uptake in normal bone marrow. In several studies, FDG PET enabled correct visualization of vertebral osteomyelitis.<sup>26-28</sup> FDG PET proved to be superior to MRI, [<sup>67</sup>Ga]citrate scintigraphy and 3 phase bone scan in these patients, especially in patients with low-grade vertebral osteomyelitis (as compared with magnetic resonance imaging (MRI), adjacent soft tissue infections (as compared with [<sup>67</sup>Ga]citrate) and advanced bone degeneration (as compared with [<sup>99m</sup>Tc]MDP).<sup>26, 27</sup> FDG PET was also able to differentiate between mild infection and degenerative changes.<sup>27</sup> In another study including 56 patients suspected of having spinal infection after previous surgery of the spine, sensitivity, specificity and accuracy of FDG PET were 100%, 81%, and 86%, respectively.<sup>29</sup> In the group without metallic implants (n=27), false positives (n=2) only occurred in the first 6 months after surgery. In the group with metallic implants (n=30), false positives (n=6) were not confined to recently operated patients. It is concluded that FDG PET holds promise to become the standard imaging technique in this difficult patient population, especially after previous surgery, as it is straightforward and provides a rapid result. PET images are not disturbed by the presence of metallic implants, which is a major advantage when compared to CT and MRI. In addition, FDG PET is a very sensitive tool even for chronic and low-grade infections.

De Winter *et al.* evaluated the feasibility of dual-head  $\gamma$ -camera coincidence (DHC) imaging in 24 patients, referred for the confirmation or exclusion of orthopedic infection.<sup>30</sup> Despite lower image quality for FDG DHC imaging, results in this limited series were comparable with the results of FDG dedicated PET. In conclusion, FDG PET is very useful in cases of suspected osteomyelitis of the central skeleton or chronic low-grade infections of the peripheral skeleton.

### Prosthetic joint infection

The most frequent complications of joint arthroplasty are infection or aseptic loosening of the prosthesis. Preoperative differentiation is essential, since optimal surgical treatment depends on the correct diagnosis. Diagnosing prosthetic joint infection is very difficult, because radiographic methods and three-

phase bone scanning cannot differentiate adequately between septic and aseptic loosening. FDG PET is very sensitive in detecting infected joint prostheses, but specificity varies from approximately 50% to 95% in literature.<sup>21, 32-37, 46, 75</sup> When compared to three-phase bone scanning, both sensitivity and specificity of FDG PET proved to be higher in patients with suspected infection of total hip prostheses.<sup>36, 38</sup> In a prospective study in 35 patients with painful hip prostheses by Stumpe *et al.*, however, FDG PET was more specific, but less sensitive than conventional radiography for the diagnosis of infection.<sup>39</sup> In this study, sensitivity and specificity of FDG PET was comparable to three-phase bone scanning.

In a retrospective study including 97 patients suspected of infection of orthopedic hardware, accuracy of FDG PET was 96% for hip prosthesis, 81% for knee prosthesis and 100% in 15 patients with other orthopedic devices.<sup>18</sup> Among the 23 patients, who had recent orthopedic procedures, FDG PET imaging was accurate in 87% of cases. In a study by Zhuang *et al.*, accuracy of FDG PET was also higher in patients suspected of infected hip prostheses than in patients suspected of infected knee prostheses (90% *vs* 78%).<sup>37</sup> In a prospective study comparing FDG PET to <sup>99m</sup>Tc-labeled leukocytes in combination with bone scintigraphy in patients suspected of infected hip prostheses and in controls with asymptomatic hip prostheses, the combined analysis of bone scintigraphy and leukocyte scintigraphy resulted in a comparable sensitivity, but a lower specificity for FDG PET.<sup>40</sup> Pill *et al.* compared the accuracy of FDG PET with <sup>99m</sup>Tc-colloid-<sup>111</sup>In-labeled leukocytes in 89 patients with 92 painful hip prostheses.<sup>41</sup> Sensitivity of FDG PET was considerably higher (95% *vs* 50%) while specificity was comparable to scintigraphy with <sup>99m</sup>Tc-colloid-<sup>111</sup>In-labeled leukocytes (93% *vs* 95%). In a study by Van Acker *et al.* comparing combined three-phase bone scanning and <sup>99m</sup>Tc-labeled leukocyte scintigraphy with FDG PET in 21 patients with painful knee arthroplasties, sensitivity of both techniques was 100% while specificity of FDG PET proved to be lower (80% *vs* 93%).<sup>42</sup>

Stumpe *et al.* evaluated FDG uptake in 28 patients with painful knee prostheses.<sup>43</sup> Diffuse synovial and focal extra-synovial FDG uptake was found in patients with malrotation of the femoral component and was not related to pain location. In this study, the information provided by FDG PET did not contribute to the diagnosis and management of individual patients with

persistent pain after total knee replacement. Zhuang *et al.* have shown in a small prospective study of 9 patients with uncomplicated hip prostheses that increased FDG uptake around the femoral head or neck portion of the prosthesis with extension to the soft tissues surrounding the femur persisted up until 1 year after surgery.<sup>44</sup> In a larger retrospective study, increased FDG uptake around the femoral head or neck portion was found in 81% of 21 uncomplicated hip prostheses with an average time interval between surgery and FDG PET of 71 months.<sup>44</sup> In a study of 41 total hip arthroplasties from 32 patients by Chacko *et al.*, increased FDG uptake was found along the interface between bone and the intensity of the FDG uptake varied from mild to moderate in patients with infection.<sup>45</sup> In contrast, images from uninfected, loose hip prostheses revealed very intense uptake around the head or neck of the prosthesis with SUV as high as 7. It is concluded that the intensity of increased FDG uptake is less important than the location of increased FDG uptake when FDG PET is used to diagnose periprosthetic infection in patients with hip arthroplasty.

It is concluded that FDG PET has a high sensitivity in diagnosing infected joint prostheses. Specificity, however, is lower than specificity of combined leukocyte scintigraphy and bone scanning. This limited specificity probably results from persisting FDG uptake around the prosthesis for many years after arthroplasty, even in uncomplicated cases.<sup>44, 75</sup> Location of FDG uptake is probably important since FDG uptake along the interface between bone and prosthesis appears to be a more specific pattern of imaging for infection.

### Postoperative infections

In the study by Hartmann *et al.*, showing an accuracy of FDG PET-CT of 91% in 33 trauma patients suspected of chronic osteomyelitis, 18 patients with metallic implants were included.<sup>22</sup> PET results were not affected by attenuation correction artefacts due to the metallic implants (n=15) used in trauma surgery, but no information was provided about the time between insertion of these implants and FDG PET. In patients with prosthetic devices (n=3), the non attenuation-corrected scans showed no FDG uptake at sites where the attenuation-corrected images were FDG positive. The authors speculate that this can be explained by the

lower photon absorption of the slender metallic instrumentation used in trauma surgery, in contrast to the joint arthroplasties with a high photon absorption used in orthopedic surgery. De Winter *et al.* studied the value of FDG PET in 35 patients with surgery in the previous 2 years who were suspected of harboring a chronic musculoskeletal infection.<sup>21</sup> Accuracy was 94%, which was comparable to patients without recent surgery in the same study. In a prospective study by Schiesser *et al.*, 29 partial-body FDG PET scans in 22 patients suspected of having metallic implant-associated infections were obtained.<sup>46</sup> The interval between the last surgical intervention and the time of PET scanning ranged between 6 weeks and 14 months. Sensitivity, specificity, and accuracy were 100%, 93%, and 97%, respectively. FDG PET appears to be a sensitive and specific method for the detection of infectious foci due to metallic implants in patients with trauma, even in patients within 1 year after surgery.

FDG uptake in physiological wound healing is expected to diminish over time. In a German study exploring the value of FDG PET in 18 patients with suspected postoperative infections, sensitivity and specificity of infection imaging in areas outside the region of surgical trauma were 86% and 100%. Sensitivity of infection imaging in the area of the surgical wound was 100%, while specificity was only 56%.<sup>76</sup> The interval between surgery and FDG PET was significantly shorter in patients with false positive results. Further studies on the degree, pattern and duration of physiological FDG uptake after surgery are warranted.

### Vascular infections

Aortic prosthetic graft infection is associated with high morbidity and mortality in the absence of immediate, definitive antibiotic therapy and surgical intervention. CT has been used as a complementary imaging approach for the assessment of graft infection. However, hematomas and seromas in the vicinity of a vascular graft appear anatomically similar to an abscess, thus making it sometimes difficult to distinguish between non-infected and infected prosthetic grafts on CT images. Chacko *et al.* showed that FDG PET was useful in 3 patients suspected of blood vessel graft infection. In 2 patients, increased FDG uptake corresponded with infection. Around the blood vessel graft of the other patient, believed to be non-

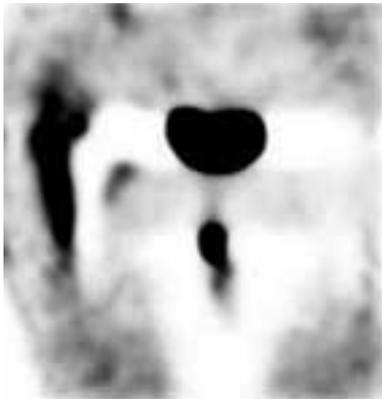


Figure 1.—A 85-year old female patient with MSRA-infected right hip replacement. Image courtesy of Dr. Christofer Palestro, Long Island Jewish Medical Center, New York.

infected, no abnormal FDG uptake was seen.<sup>18</sup> In a recent study systematically comparing CT and FDG uptake on PET in patients suspected of vascular graft infection, the sensitivity of FDG PET (91%) was significantly higher than that of CT (64%;  $P < 0.05$ ). However, the specificity of FDG PET (64%) was lower than that of CT (86%; not significant). When the PET criterion for infection was defined as focal abnormal uptake, all the false-positive cases were categorized as negative. With this alteration of the diagnostic criteria, the specificity of FDG PET improved significantly from 64% to 95% ( $P < 0.05$ ).<sup>47</sup> In conclusion, FDG PET seems to be a promising modality for the evaluation of infected aortic grafts and may serve as a useful tool for non-invasive diagnosis of this clinical problem (Figures 1, 2). Moreover, FDG PET shows a diagnostic performance superior to that of CT when specific uptake patterns of FDG are included in the diagnostic criteria. Because many of the false positive PET results occurred in patients with recent graft implantation, it is to be expected that specificity and positive predictive value are even better after a certain period after surgery. In addition, combined PET-CT-scans are suspected to further increase the usefulness of this imaging modality.

Other endovascular foci, such as septic thrombophlebitis or septic arteritis, can also be successfully diagnosed by FDG PET, as has been shown in several case reports and series.<sup>48, 77</sup> In a retrospective study, FDG PET correctly identified 9 patients with septic thrombophlebitis due to central venous catheters, while acute thrombosis did not lead to increased FDG uptake in the remaining 27 patients with proven acute

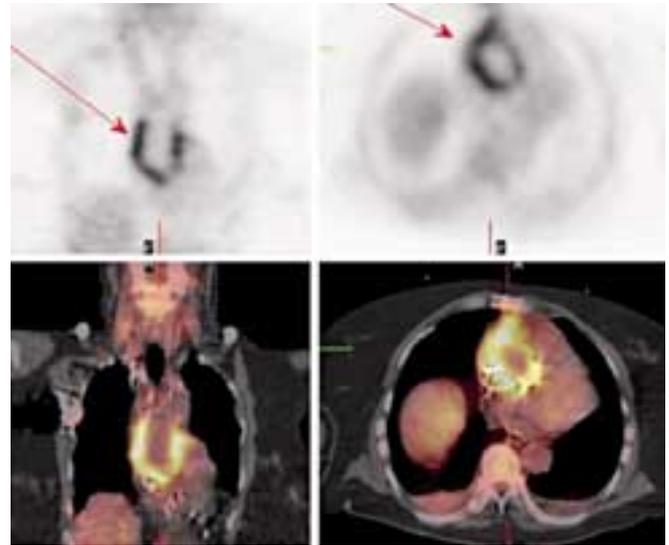


Figure 2.—A-D) This 61-year-old woman presented with a one day history of fever and chills. Since 5 years, she had an aortic arch prosthesis (Bentall). Blood cultures repeatedly grew *Staphylococcus aureus*. Thoracic computed tomography (CT) on day 2 was completely normal (not shown). Positron emission tomography-CT showed markedly increased fluorodeoxyglucose uptake surrounding the aortic arch prosthesis on day 5 after admission. During surgical replacement of the aortic arch prosthesis and the aortic valve endocarditis and infection of the prosthesis was confirmed.

or chronic thrombosis.<sup>78</sup> FDG PET diagnosis of septic thrombophlebitis resulted in therapeutic changes in all patients. In a small case series, however, increased FDG uptake was found in 4 patients at the distal end of a central venous catheter.<sup>49</sup> Catheter-related thrombosis was identified as the cause of FDG activity in 3 patients, whereas catheter-related infection was diagnosed in one patient. Further prospective studies are necessary to decide whether FDG PET is useful in diagnosing catheter-related infection.

Myocardial FDG uptake shows variable intra- and inter-individual uptake patterns among other things depending on blood glucose levels. FDG PET, therefore, is not likely to become the preferred diagnostic technique to identify infectious endocarditis due to limited specificity. Focal myocardial FDG uptake, however, corresponded with echocardiographic localization of infection in 6 patients with proven endocarditis.<sup>50</sup> In our clinical experience, however, the diagnostic usefulness of FDG PET in diagnosing endocarditis appears to be limited and the results of larger prospective studies will be necessary to confirm these early reports.

### Metastatic infectious foci

Secondary metastatic infection is a well-known complication of blood stream infections. Timely identification of metastatic complications, although critical, is often difficult. In a retrospective study in 40 patients with a high suspicion of metastatic complications after blood stream infection, FDG PET diagnosed a clinically relevant new focus in 45% of cases while on average, 4 conventional diagnostic tests had been performed before FDG PET.<sup>51</sup> It is concluded that FDG PET appears to have a promising role in detecting metastatic infectious foci in patients with a high level of clinical suspicion (Figure 3). A prospective study further evaluating this subject is ongoing.

### The immunocompromised host

In children with chronic granulomatous disease, a primary immunodeficiency leading to granuloma formation and numerous infections, FDG PET was compared with CT in detecting active infective foci.<sup>52</sup> PET excluded 59 lesions suspicious for active infection on CT and revealed 49 infective lesions not seen on CT. All active infective lesions were identified by PET, allowing targeted biopsy and identification of the infective agent followed by specific antimicrobial treatment or surgery.

Fever frequently complicates the management of pediatric patients with terminal chronic liver failure during the pretransplantation period. Non-hepatic origins of systemic infections may render a patient unsuitable for transplantation, whereas infections within the liver may require organ resection for cure. In 11 children with biliary cirrhosis presenting with fever during the waiting period for liver transplantation, positive intrahepatic FDG uptake was shown to correlate with infection (proven after liver transplantation) in 5 children.<sup>53</sup> In 6 children, no abnormal hepatic FDG PET foci were found and no infections could be detected in the liver. Standard imaging techniques did not reveal abnormalities compatible with infection in any of these children. In conclusion, in children presenting with fever who are on waiting lists for liver transplantation, information obtained by FDG PET may be useful for decision-making on therapy and suitability for liver transplantation. Jones *et al.* performed FDG PET scans in 15 lung transplant recipients suspected of infection or rejection.<sup>54</sup> Rejection alone

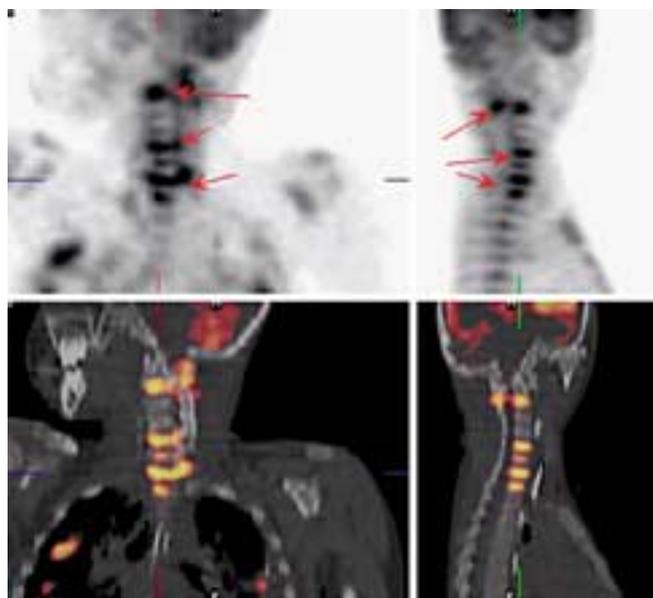


Figure 3.—A-D) Fluorodeoxyglucose (FDG) positron emission tomography-computed tomography-scan in a 10-year-old child with *Streptococcus milleri* bacteremia showing increased uptake of FDG in the cervical spine and the lungs due to metastatic infectious lesions.

did not increase FDG uptake possibly due to the absence of neutrophil activation in acute rejection. It is concluded that increased FDG uptake in these patients is indicative of infection and not of rejection, rendering FDG PET a useful diagnostic method that could reduce the number of transbronchial biopsies required during episodes of breathlessness after lung transplantation.

In infectious diseases, abnormal FDG uptake is caused by increased glucose uptake in activated leukocytes. In case of severe neutropenia, it is questionable whether FDG PET can be used for diagnosing infectious diseases due to the markedly decreased number of activated leukocytes at the site of infection. In 3 severely immunocompromised patients (chemotherapy because of acute myeloid leukemia, bone marrow transplant because of myelodysplastic syndrome and high-dose salvage chemotherapy because of relapsed high-grade non-Hodgkin's lymphoma), however, increased FDG uptake revealed foci of *Candida* and *Aspergillus* abscesses, respectively.<sup>55</sup> Mahfouz *et al.* retrospectively studied 248 PET scans ordered in patients with multiple myeloma either for staging disease progression or infection work-up.<sup>56</sup> FDG PET identified 165 infectious foci even in patients with

severe neutropenia (in 30 cases). In 46 patients, infection was not identified by a regular diagnostic work-up. In this study, FDG PET contributed to patient care in 46% of all patients. It is concluded that FDG PET is a useful tool for diagnosing and managing infections in patients with multiple myeloma, even in the setting of severe immunosuppression.

As early as 1995, FDG PET was described as a possible diagnostic technique for differentiation between infectious central nervous system (CNS) foci and lymphoma in human immunodeficiency virus (HIV) infected patients.<sup>57</sup> In a prospective case series of 18 patients with HIV infection and focal CNS lesions, FDG PET could accurately differentiate lymphoma from infections in 16 of 18 cases. Two cases of progressive multifocal leukoencephalopathy had high metabolic activity and could not be differentiated from lymphoma.<sup>58</sup> In three other studies, FDG PET was also able to accurately differentiate between a malignant (lymphoma) and nonmalignant etiology in HIV infected patients with CNS lesions.<sup>57, 59, 60</sup> Biopsy, however, is often still necessary to confirm the diagnosis of lymphoma or to perform cultures to determine the exact etiology of infectious foci, which limits the usefulness of FDG PET in clinical practice. O'Doherty *et al.* studied the use of FDG PET in 57 HIV-infected patients with FUO and/or weight loss.<sup>59</sup> FDG PET had a sensitivity of 92% and a specificity of 94% for localization of focal pathology that needed treatment. High uptake of FDG (greater than liver) had a positive predictive value of 95% for pathology needing treatment. In these patients, FDG PET appears to be a potentially useful diagnostic technique.

Various patterns of FDG accumulation in HIV-positive patients have been described previously and hypothesized to potentially represent regions of active HIV replication or nodal activation. Brust *et al.* evaluated FDG biodistribution visually and quantitatively in HIV-negative individuals and various groups of HIV-infected patients to determine the impact on the pattern of nodal activation of HIV infection, the stage of HIV infection and degree of viremia, and highly active antiretroviral therapy (HAART).<sup>61</sup> Abnormal FDG accumulation occurred in the nodes of individuals with detectable viral loads. Interruption of effective HAART resulted in the activation of previously quiescent nodal areas. Iyengar *et al.* investigated the ability of PET to detect and measure magnitude of lymph-node involvement in 8 HIV-1-uninfected individuals who had received licensed killed influenza vaccine, 12

patients recently infected with HIV-1, and 11 chronic long-term HIV-1 patients who had stable viremia (non-progressors).<sup>62</sup> Node activation was more localized after vaccination than after HIV-1 infection. In early and chronic HIV-1 disease, node activation was greater in cervical and axillary than in inguinal and iliac chains. Non-progressors had small numbers of persistently active nodes, most of which were surgically accessible, which may reflect microenvironmental niche selection. In a study by Scharko *et al.*, FDG PET images from 15 patients with HIV-1 showed distinct lymphoid tissue activation in the head and neck during acute disease, a generalized pattern of peripheral lymph-node activation at mid-stages, and involvement of abdominal lymph nodes during late disease.<sup>63</sup> It is suggested that the anatomy of HIV-1 infection could encourage use of surgical or radiological interventions to supplement chemotherapy in the future.

### Miscellaneous infectious diseases

FDG PET has been studied in patients with various infectious and inflammatory diseases. In a small study by Sugawara *et al.*, FDG PET correctly identified the infectious foci in 10 of 11 patients.<sup>64</sup> In a retrospective study, 55 FDG PET scans were performed in 48 patients with suspected focal infection or inflammation.<sup>65</sup> A final diagnosis was established in 38 patients (32 patients with an infectious disease). Of the total number of scans, 65% were clinically helpful. The positive predictive value of FDG PET in these 55 episodes of suspected infection or inflammation was 95% and the negative predictive value was 100%. Ichiya *et al.* studied the usefulness of FDG PET in the detection of various infectious foci in 24 patients with lesions of bacterial, tuberculous and fungal origin.<sup>66</sup> High FDG uptake was observed in 23 of 25 lesions (92%). Two lesions, in which no abnormal uptake was noted included one in the healing stage and the other consisting of a thin-walled cavity. In a retrospective study by Jaruskova *et al.*, either FDG PET or FDG PET-CT was performed in 118 patients with prolonged fever.<sup>33</sup> Infection was diagnosed in 21 patients, systemic connective tissue disease in 17 patients, lymphoma in 3 patients, and inflammatory bowel disease in 2 patients. FDG PET or PET-CT contributed to establishing a final diagnosis in 36% of all 118 patients. Stumpe *et al.* studied FDG PET in 27 patients sus-

TABLE II.—Studies evaluating the value of fluorodeoxyglucose positron emission tomography in patients with fever of unknown origin.

First author	Study design	FDG PET technique	Conclusions
Meller <i>et al.</i> <sup>69</sup>	Prospective (n=20): comparison FDG PET and [ <sup>67</sup> Ga]citrate (n=18)	Dual-headed coincidence camera	FDG PET helpful in 55%, PPV 92%, NPV 75%, FDG PET superior to [ <sup>67</sup> Ga]citrate
Blockmans <i>et al.</i> <sup>68</sup>	Prospective (n=58): comparison to [ <sup>67</sup> Ga]citrate (n=40)	Full ring PET scanner	FDG PET helpful in 41%, FDG PET superior to [ <sup>67</sup> Ga]citrate
Lorenzen <i>et al.</i> <sup>70</sup>	Retrospective (n=16)	Full ring PET scanner	FDG PET helpful in 69%, PPV 92%, NPV 100%
Bleeker-Rovers <i>et al.</i> <sup>65</sup>	Retrospective (n=35)	Full ring PET scanner	FDG PET helpful in 37%, PPV 87%, NPV 95%
Kjaer <i>et al.</i> <sup>71</sup>	Prospective (n=19): comparison to [ <sup>111</sup> In]granulocyte	Full ring PET scanner	FDG PET helpful in 16%, PPV 30%, NPV 67%, [ <sup>111</sup> In]granulocyte scintigraphy helpful in 26%
Buysschaert <i>et al.</i> <sup>72</sup>	Prospective (n=74)	Full ring PET scanner	FDG PET helpful in 26%
Bleeker-Rovers <i>et al.</i> <sup>73</sup>	Prospective, multicenter (n=70)	Full ring PET scanner	FDG PET helpful in 33%, PPV 70%, NPV 92%

FDG PET: fluorodeoxyglucose positron emission tomography; PPV: positive predictive value; NPV: negative predictive value.

pected of soft tissue infections.<sup>17</sup> Sensitivity was 96% on a per body region basis (dividing the body into 22 regions) and specificity was 99%. One false-negative result was found in a patient with cholangitis. In a small case series, increased FDG uptake is also found in patients with brain abscesses.<sup>67</sup> It is concluded that FDG PET appears to be a highly sensitive method to detect various infectious foci in many parts of the body. Specificity is more difficult to estimate, but is probably in the range from 70% to above 90%.

### Fever of unknown origin

The value of FDG PET has been studied in several studies in 292 patients with FUO<sup>65, 68-73</sup> (Table II), showing an overall helpfulness of FDG PET corrected for study population of 36%, which is very high compared to radiological techniques and [<sup>67</sup>Ga]citrate scintigraphy. Comparing these studies, however, is difficult. First of all, the definition of FUO was different in each study. Second, the FDG PET technique in the study by Meller *et al.*<sup>69</sup> is inferior to the FDG PET technique in the other studies. Furthermore, FDG PET was performed at different stages of the diagnostic process. The use of a structured diagnostic protocol including FDG PET has reduced the chance of selec-

tion bias in the last FUO study.<sup>73</sup> In this study, it was also shown that FDG PET did not contribute in any of the patients with normal C-reactive protein and erythrocyte sedimentation rate, so FDG PET is not indicated in these patients.

When compared to conventional radiopharmaceuticals routinely used in clinical practice, such as <sup>67</sup>Ga and <sup>111</sup>In-labelled or <sup>99m</sup>Tc-labeled leukocytes, advantages of FDG PET are higher resolution, sensitivity in chronic low-grade infections, and high accuracy in the central skeleton. Another major advantage of FDG PET in the work-up of FUO is the vascular FDG uptake in patients with vasculitis.<sup>69, 79</sup> A theoretical disadvantage is the impossibility to differentiate between malignancy and infectious diseases or inflammation. In patients with FUO, however, this appears to be an advantage rather than a drawback since all of these disorders are represented in this patient group and additional diagnostic tests are needed in most cases. An obvious disadvantage is the relatively high cost and the lesser availability of PET. However, as the number of PET systems further increases, the high diagnostic yield of FDG PET may very well become a cost-effective modality, since adequate, early diagnosis limits the number of other non-contributing (invasive) tests required and the time to diagnosis and thus decreases

es the duration of hospitalization necessary for diagnostic purposes.

From two prospective studies comparing FDG PET with [<sup>67</sup>Ga]citrate scintigraphy in a total of 58 patients with FUO, it was concluded that FDG PET was superior to [<sup>67</sup>Ga]citrate scintigraphy, because the diagnostic yield is at least similar to that of [<sup>67</sup>Ga]citrate scintigraphy and the results are available within hours instead of days.<sup>68, 69</sup> Kjaer *et al.*<sup>71</sup> conclude in their prospective study comparing FDG PET with <sup>111</sup>In-granulocyte scintigraphy in 19 patients with FUO that <sup>111</sup>In-granulocyte scintigraphy is superior to FDG PET, because of the high percentage of false positive FDG PET scans (37%). Although unnecessary tests should, of course, be prevented if possible, it is very questionable whether a relatively high percentage of false positive results is sufficient justification to reject FDG PET as a valuable diagnostic method in patients with FUO. In a recently published study, false positive FDG PET results were responsible for less than 1% of all diagnostic studies performed in patients with FUO despite the fact that FDG PET was purposely over-interpreted to provide high sensitivity. On the other hand, an abnormal FDG PET scan leading to the underlying cause of fever, deters the use of tests that are considered in most diagnostic protocols as second level screening investigations. Furthermore, FDG PET has very high sensitivity for most malignant tumors while <sup>111</sup>In-granulocyte scintigraphy does not. In addition, the therapeutic and prognostic consequences of a delay in diagnosing a malignancy responsible for FUO may occur in up to 25% of cases. Therefore, we believe that high accuracy in diagnosing malignant disease should be an important operational characteristic for recommended nuclear medicine techniques in FUO patients. Based on the results of prior studies that are a consequence of the favorable characteristics of FDG PET, conventional scintigraphic techniques may in the future be replaced by FDG PET in the investigation of patients with FUO in institutions where this technique is available.

### **Differentiation between infection and malignancy**

In malignant diseases, generally higher SUV of FDG are expected to be found when compared to

FDG accumulation in infectious or inflammatory disorders. Bryant *et al.* studied the usefulness of SUV for differentiation of infection and malignancy in solitary pulmonary nodules in 585 patients.<sup>74</sup> Although higher SUV were related to a higher likelihood of malignancy, many false positives and negatives were found. For example, there was a 24% chance a suspicious nodule that had a maximal SUV of 0 to 2.5 was cancer. Sahlmann *et al.* investigated glucose metabolism in chronic bacterial osteomyelitis by using FDG PET and a dual time protocol.<sup>31</sup> In patients with chronic osteomyelitis, the median SUV did not change significantly between 30 and 90 min, while the median SUV increased in patients with malignant bone lesions. Although the authors speculate that this could be useful for differentiation between infection and malignancy, median and maximal SUV values and changes in SUV over time showed considerable overlap in some patients with infection and patients with malignant disease. In most patients, biopsy or microbiology results will still be needed to confirm the diagnosis.

### **Conclusions and future directives**

FDG PET has a lot to offer in visualization of various infectious foci in many organ systems. It is shown to be useful in FUO and in patients suspected of osteomyelitis, especially in cases of chronic low-grade infections and in vertebral osteomyelitis. The usefulness of FDG PET in suspected joint prosthesis infection has been previously addressed. Although sensitivity is very high, some authors reject the use of FDG PET in favor of combined leukocyte scintigraphy and bone scanning in patients with suspected prosthesis infections due to low specificity while others advocate its use noting that specificity for the identification of infection markedly increases when FDG accumulation is seen along the bone-prosthesis interface.

FDG PET has shown promising results in vascular graft infections and the evaluation of metastatic infectious foci in patients with blood stream infections. Since FDG uptake surrounding the graft or implant can still be physiological in the early postoperative period, further studies are needed to determine the normal time course of FDG distribution between surgery and FDG PET scanning so, in patients with suspected infected vascular grafts or metallic implants

scans can be interpreted with high specificity. The usefulness of FDG PET in neutropenic patients should also be further evaluated in larger clinical studies before widespread use of this technique can be advised.

Although FDG PET does not directly provide a definitive diagnosis, *i.e.* a histological or a microbiological diagnosis, it often provides anatomic localization where a particular metabolic process is ongoing and with the help of other techniques, such as biopsy and culture facilitates timely definitive diagnosis and therapy. Since combined PET-CT scanners assist the interpretation of the PET findings by exact localization of lesions, the accuracy of FDG PET in diagnosing infectious diseases will most likely improve further with the availability of hybrid PET-CT and demonstrate its usefulness much in the same manner as it has in oncology.

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