^{18}F-FDG PET in Detecting Metastatic Infectious Disease

Chantal P. Bleeker-Rovers, MD[1–3]; Fidel J. Vos, MD [2,3]; Geert J.A. Wanten, PhD[4]; Jos W.M. van der Meer, PhD[2,3]; Frans H.M. Corstens, PhD[1,3]; Bart-Jan Kullberg, PhD[2,3]; and Wim J.G. Oyen, PhD[1,3]

[1]Department of Nuclear Medicine, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; [2]Department of Internal Medicine, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; [3]Nijmegen University Centre for Infectious Diseases, Nijmegen, The Netherlands; and [4]Department of Gastroenterology and Hepatology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

Timely identification of metastatic complications of bloodstream infections due to spreading of the microorganisms to distant sites, although critical, is often difficult. As ^{18}F-FDG accumulates in activated leukocytes in infectious lesions, ^{18}F-FDG PET represents a promising imaging technique in these patients. The aim of this study was to assess the value of ^{18}F-FDG PET in detecting infectious foci in patients at high risk of metastatic complications. **Methods:** The results of all ^{18}F-FDG PET scans ordered because of suspected metastatic infection from October 1998 to September 2004 were analyzed retrospectively. These results were compared with conventional investigation techniques and the final clinical diagnosis. **Results:** The results of 40 ^{18}F-FDG PET scans were evaluated. In 60% of all episodes, Gram-positive bacteria were cultured, in 18% Gram-negative bacteria, in 20% *Candida* spp., and in 3% the infection was polymicrobial. Metastatic complications were diagnosed in 75% of all episodes. A median number of 4 diagnostic procedures to search for metastatic infection had been performed before ^{18}F-FDG PET was ordered. ^{18}F-FDG PET diagnosed a clinically relevant new focus in 45% of cases and confirmed abnormalities already diagnosed in 30% of cases. The positive predictive value of ^{18}F-FDG PET was 91% and the negative predictive value was 100%. **Conclusion:** ^{18}F-FDG PET is a valuable imaging technique in patients at high risk of metastatic infectious disease, even when the results of other diagnostic procedures are normal.

Key Words: ^{18}F-FDG; PET; bloodstream infection; metastatic infection

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One of the main complications of bloodstream infections, especially in case of *Staphylococcus aureus* bacteremia or candidemia, is secondary metastatic infection caused by spreading of the microorganisms to distant sites. The prevalence of metastatic infection in patients with *S. aureus* bacteremia varies from approximately 2% to 30% (*1,2*). In a retrospective study, 29% of patients who were treated for candidemia developed disseminated disease (*3*). The frequency of metastatic complications after bacteremic episodes caused by other microorganisms is not known. Known risk factors for developing metastatic complications of *S. aureus* bacteremia are community acquisition, unknown portal of entry, longer time span between the first symptoms and initiation of antibiotic therapy, the presence of prosthetic devices, persistent fever after 72 h, and positive follow-up blood cultures at 24 to 96 h (*4–8*). An important consequence of metastatic infection is the need for prolonged antimicrobial therapy. Failure to identify metastatic complications may lead to early cessation of therapy and relapse of bloodstream infection and unfavorable outcome. Timely identification of infectious lesions, however, is often difficult, especially in patients without signs pointing to a specific localization.

Focal infectious disease can be detected by CT, MRI, and ultrasonography. These techniques, however, are less suitable as a screening method when clues for specific sites of infection are absent. Scintigraphic imaging allows delineation of the localization of foci in all parts of the body, based on functional changes of tissues. Because activated inflammatory cells take up large amounts of glucose as a result of an increased metabolic rate (*9*), ^{18}F-FDG PET represents a promising imaging technique in these patients. The aim of this study was to assess the value of ^{18}F-FDG PET in detecting metastatic infectious foci in patients with bacteremia or fungemia at high risk of metastatic infection.

MATERIALS AND METHODS

Patients

The results of all ^{18}F-FDG PET scans ordered because of suspected metastatic infectious disease from October 1998 to September 2004 at the Radboud University Nijmegen Medical Centre were analyzed retrospectively. The suspicion of metastatic complications was based on positive blood cultures and one or more of the following symptoms and signs: persistent fever or positive blood cultures for >48 h after initiation of antibiotic therapy, clinical deterioration after initial improvement of symp-

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For correspondence or reprints contact: Chantal P. Bleeker-Rovers, MD, Department of Internal Medicine, 541, Radboud University Nijmegen Medical Centre, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands.

E-mail: c.bleeker-rovers@AIG.umcn.nl

toms, or metastatic infectious foci elsewhere. All patients were evaluated with other imaging modalities and laboratory tests as was considered clinically appropriate.

^{18}F-FDG PET

A full-ring PET scanner (ECAT-EXACT; Siemens/CTI) was used for data acquisition. Patients had fasted for at least 6 h before ^{18}F-FDG injection. Immediately before the procedure, the patients were hydrated with 500 mL of water. One hour after intravenous injection of 200–220 MBq ^{18}F-FDG (Tyco Healthcare/Mallinckrodt Medical) and 10–15 mg furosemide, emission and transmission images of the area between the proximal femora and the base of the skull were acquired (10 min per bed position). The images were corrected for attenuation and were reconstructed using the ordered-subsets expectation maximization (OSEM) algorithm. Reconstructed images were displayed in coronal, transverse, and sagittal planes. ^{18}F-FDG PET results were judged to be abnormal if focal accumulation of the tracer was detected outside areas of physiologic uptake.

Clinical Features

The portal of entry was defined as a localized focus of infection preceding bacteremia or fungemia. Primary infection of the respiratory or urinary tract was diagnosed only when symptoms and signs typically associated with bacterial infections of those systems were present in addition to appropriate culture results. Other foci were considered to be secondary metastatic infection. Endocarditis, defined according to the Duke criteria (*10*), and spondylitis were always considered as secondary metastatic infection. An intravascular catheter was considered to be the portal of entry if there was evidence of inflammation at the insertion site or culture of the vascular catheter tip was positive for the same microorganism without clinical evidence of another source for infection. The infection was considered to be nosocomial if cultures obtained after >48 h of hospitalization were positive and clinical signs of infection were absent at the time of admission. The infection was considered to be community acquired if cultures were positive within 48 h after admission or signs of bloodstream infection were present before admission.

Clinical Assessment of Test Results and Diagnosis

The results of ^{18}F-FDG PET were evaluated for their diagnostic contribution. A normal ^{18}F-FDG PET scan was termed true-negative when no metastatic complications or relapse of infection was diagnosed during clinical follow-up of at least 3 mo. A normal ^{18}F-FDG PET scan was considered false-negative when a focal infection was diagnosed except for infection in the brain, heart, kidneys, or bladder (sites known for low sensitivity of ^{18}F-FDG PET due to physiologic uptake of ^{18}F-FDG) or the legs (not routinely imaged). Results were considered to be true-positive when abnormal ^{18}F-FDG uptake pointed to the organ or tissue where the cause of the symptoms was eventually found. ^{18}F-FDG uptake in the source of the infection as well as in metastatic infectious foci was considered as a true-positive result. True-positive ^{18}F-FDG PET results were further categorized as a "clinically relevant new finding" when the abnormality caused a change of treatment (longer duration of antibiotic therapy, switching to another antibiotic or combination of antibiotics, drainage of abscesses, or surgical intervention), as a "clinically irrelevant new finding" when the abnormality did not change treatment, or as "already known" when ^{18}F-FDG PET showed only metastatic foci already diagnosed by other diagnostic techniques. Abnormal results were categorized as false-positive when the abnormality could not be confirmed. The final or probable clinical diagnosis served as a standard of reference and was used for the assessment of the ^{18}F-FDG PET results.

Follow-up

Medical charts were reviewed for follow-up data. After a minimum follow-up of 3 mo, the patient was considered to be cured when no symptoms or signs of infection were present after discontinuation of antibiotic therapy. Attributable mortality included all patients who died with persistent signs or symptoms of systemic infection, positive blood culture results, or a persistent focus of infection in the absence of another explanation for death. Relapse was defined as a second episode of bacteremia or fungemia with the same microorganism within 12 wk of the initial episode.

Statistical Analysis

Descriptive statistics for continuous variables are represented as median ± SD. Categoric variables are reported in terms of the number and percentage of patients affected. Differences between the group of patients eventually diagnosed with metastatic infection and the group of patients without metastatic infection were tested with unpaired Student *t* tests for continuous variables and with the Fisher exact tests for categoric variables. Differences were considered to be statistically significant at $P < 0.05$.

RESULTS

From October 1998 to September 2004, 40 ^{18}F-FDG PET scans were performed because of suspected metastatic infection. In 2 patients, ^{18}F-FDG PET was performed during 2 separate episodes of central venous catheter (CVC)-related bloodstream infection. Patient characteristics for the total number of infectious episodes and subdivided for patients eventually diagnosed with metastatic disease and patients without metastatic foci are shown in Table 1. Three-quarters of infections were community acquired with a short duration of symptoms before presentation (median, 1 d). All patients had at least one risk factor for developing complicated disease. None of the patients had neutropenia. The total number of positive blood cultures and the number of days for which blood cultures remained positive were significantly higher in patients with metastatic disease.

Culture results are shown in Table 2. *S. aureus* was the most common cause of bacteremia (14 episodes; 35%). All patients with Gram-negative bacteremia for whom an ^{18}F-FDG PET scan was ordered were eventually diagnosed with metastatic complications. Metastatic infection was also found in 16 episodes of Gram-positive bacteremia (64%) and 7 episodes of candidemia (78%). The portal of entry was known in 28 episodes (70%; Table 3). In all patients with CVC-related bloodstream infections, the CVC was removed before ^{18}F-FDG PET was requested. In 30 cases (75%), metastatic infectious foci were eventually diagnosed by conventional diagnostic techniques, ^{18}F-FDG PET, or both. Metastatic infection was most often diagnosed in the cardiovascular system, lungs, and bones or joints (Table 4). Of those with metastatic infection, 11 (37%) were diagnosed with metastatic foci in >1 organ system.

TABLE 1
Characteristics of 40 Patients with Suspected Metastatic Infectious Disease on Whom ^{18}F-FDG PET Was Performed

Characteristic	Total (n = 40)	Metastatic foci	
		Yes (n = 30)	No (n = 10)
Male (%)	23 (58)	17 (57)	6 (60)
Female (%)	17 (42)	13 (43)	4 (40)
Age (y)*	60 ± 17	60 ± 17	60 ± 18
Community-acquired infection (%)	30 (75)	23 (77)	7 (70)
Duration of symptoms until presentation (d)*†	1 ± 8	1 ± 7	1 ± 9
Duration of symptoms until adequate therapy (d)*†	2 ± 8	3 ± 8	2 ± 9
CVC present (%)	13 (33)	10 (33)	3 (30)
Duration of CVC present (wk)*	12 ± 62	14 ± 69	1 ± 9
Total parenteral nutrition (%)	9 (23)	7 (23)	2 (20)
Diabetes mellitus (%)	4 (10)	3 (10)	1 (10)
Peritoneal dialysis (%)	2 (5)	1 (3)	1 (10)
Hemodialysis (%)	1 (3)	0	1 (10)
Pacemaker (%)	3 (8)	3 (10)	0
Congenital heart disease (%)	3 (8)	3 (10)	0
Mechanical heart valve (%)	2 (5)	2 (7)	0
Malignancy (%)	1 (3)	1 (3)	0
Immunosuppressive drugs (%)	8 (20)	7 (23)	1 (10)
Intravenous drug use	0	0	0
Positive blood cultures (no. per patient)*	3 ± 3	4 ± 3‡	2 ± 1‡
Duration of positive blood cultures (d)*	2 ± 8	3 ± 8‡	1 ± 1‡

*Median ± SD.
†One patient was excluded from these calculations because she had lower back pain, periodic low-grade fever, and fatigue for almost 3 y before she was diagnosed with a *S. aureus* psoas abscess and before ^{18}F-FDG PET was performed.
‡$P < 0.05$.

A median number of 4 diagnostic procedures to search for metastatic complications was performed before ^{18}F-FDG PET was requested (range, 1–10). Chest x-ray was performed on 34 patients (85%), chest CT on 7 patients (18%), abdominal ultrasound on 25 patients (63%), abdominal CT on 18 patients (45%), Doppler ultrasonography of the subclavian and internal jugular veins on 6 patients (50% of all patients with CVC-related infection), and echocardiography on 21 patients (53%).

TABLE 2
Culture Results

Category	Total (n = 40)	Metastatic foci	
		Yes (n = 30)	No (n = 10)
Gram-positive bacteria			
Staphylococcus aureus	14	7	7
Staphylococcus epidermidis	1	1	0
Streptococcus pneumoniae	3	3	0
Other *Streptococcus* spp.	5	4	1
Enterococcus spp.*	2	1	1
Gram-negative bacteria			
Escherichia coli	3	3	0
Proteus mirabilis	1	1	0
Enterobacter cloacae	1	1	0
Salmonella group D	1	1	0
Serratia marcescens	1	1	0
Yeasts			
Candida albicans	6	6	0
Candida parapsilosis	2	1	1
*Candida tropicalis**	1	0	1

*In 1 patient, blood cultures were positive for *Enterococcus faecium* as well as *Candida tropicalis*.

TABLE 3
Portal of Entry: Source of Bacteremia or Fungemia

Diagnosis	Total (n = 40)	Metastatic foci	
		Yes (n = 30)	No (n = 10)
CVC-related bloodstream infection	12	9	3
Soft-tissue or skin infection	5	1	4
Pneumonia	1	1	0
Urinary tract infection	4	4	0
CAPD-peritonitis	2	1	1
Wound infection	1	0	1
Cholangitis	2	1	1
Meningitis	1	1	0
Unknown	12	12	0

CAPD = continuous ambulatory peritoneal dialysis.

TABLE 4
Localization of Metastatic Infectious Foci in 30 Patients Eventually Diagnosed with Metastatic Disease

Organ system	Patients (n = 30)
Endocarditis	5
Endovascular	10
Lungs	7
Liver or biliary tract	2
Spleen	2
Arthritis	4
Nonvertebral osteomyelitis	1
Vertebral osteomyelitis	3
Psoas abscess	1
Skin or soft tissue	5
Brain	2
Eye	1

In 11 patients, metastatic infectious foci were found in >1 organ system.

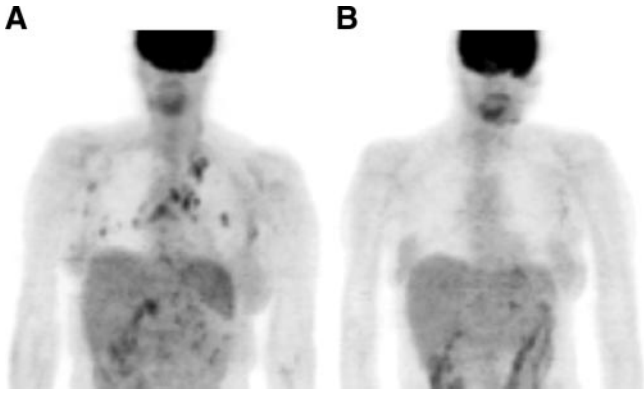

FIGURE 1. (A) In 45-y-old woman with *S. aureus* septicemia and persistent fever during therapy, PET showed increased ^{18}F-FDG uptake in multiple lesions in both lungs, mediastinum, and upper abdomen. Subsequently, chest CT also showed multiple lesions in both lungs and mediastinum. Cholangitis caused by gallstones was confirmed by abdominal ultrasound and endoscopic retrograde cholangiopancreatography (ERCP). Fever disappeared within 2 d after ERCP. (B) After 3 mo, ^{18}F-FDG PET was normal and antibiotic therapy was discontinued.

Results of ^{18}F-FDG PET were negative in 6 patients (Table 5). None of these patients was diagnosed with metastatic complications or relapse after a follow-up period of at least 3 mo; therefore, these results were considered true-negative. ^{18}F-FDG PET results were true-positive in 31 cases (78%). ^{18}F-FDG PET diagnosed a clinically relevant new focus (Fig. 1) in 18 cases (45%), diagnosed a clinically irrelevant new focus in 1 patient, and confirmed already diagnosed abnormalities in 12 cases (30%). In 27 of these 31 episodes, ^{18}F-FDG PET results were fully confirmed by conventional diagnostic techniques. Results were partially confirmed in 3 cases. In the first patient, PET demonstrated increased ^{18}F-FDG uptake in the right wrist and the left hip. Infection of the wrist was confirmed by ultrasound showing a small fluid collection and an infiltrate surrounding the ulnar artery, but no diagnostic procedure was performed to confirm arthritis of the left hip. In the second patient, PET showed increased ^{18}F-FDG uptake in the liver and both total hip prostheses. Abdominal CT and culture confirmed liver abscesses, but ultrasound only partially confirmed infection of both total hip prostheses by demonstrating a large fluid collection around the left hip prosthesis. In the third patient, PET demonstrated abnormal ^{18}F-FDG uptake in multiple foci in both lungs and the liver hilus and irregular uptake in the spleen. Pulmonary abscesses and cholangitis were confirmed by other diagnostic procedures, but abdominal CT did not show any abnormalities of the spleen. In 1 patient with endocarditis, PET showed increased ^{18}F-FDG uptake around a vascular prosthesis of the abdominal aorta. Infection of his vascular prosthesis was supported by clinical signs and favorable reaction to antibiotic therapy but was not confirmed otherwise. In this case, surgery was not possible because of his deteriorating cardiovascular condition. The histories of 3 patients with *Candida* lung abscesses diagnosed with ^{18}F-FDG PET have been described in a research note (*11*). In 3 patients, ^{18}F-FDG PET results were false-positive. The first patient was diagnosed with a urinary tract infection and abdominal CT showed extensive thrombosis of both femoral veins, iliac veins, and the inferior caval vein extending from a caval filter, which was suspected to be infected. PET showed increased ^{18}F-FDG uptake in the thrombosed blood vessels but also in several mediastinal lymph nodes. However, on chest CT, no pathologically enlarged lymph nodes were found. In the second patient, PET demonstrated increased ^{18}F-FDG uptake in the right hip and the left femur. Arthritis of the right hip was confirmed by ^{111}In-labeled polyclonal IgG scintigraphy, but no abnormal IgG uptake in the left femur was found. In the third patient who was treated with azathioprine and pred-

TABLE 5
^{18}F-FDG PET Results on 40 Patients with Suspected Metastatic Infectious Disease

^{18}F-FDG PET results	Patients (n = 40)	Confirmation		
		Total	Partial	Not
Negative				
True-negative	6			
False-negative	0			
Positive				
True-positive	31*	27	3	1
Clinically relevant	18	15	2	1
Clinically irrelevant	1	0	1	0
Already known	12*	12	0	0
False-positive	3	0	0	3

*In 1 patient with *S. aureus* bacteremia without metastatic infection, ^{18}F-FDG uptake was seen in an abscess of his right arm, which was the source of his bacteremia. ^{18}F-FDG PET was otherwise normal.

TABLE 6
Outcome of 40 Patients with Suspected Metastatic Infectious Disease

Characteristic	Total (n = 40)	Metastatic foci: Yes (n = 30)	Metastatic foci: No (n = 10)
Duration of fever (d)*	18 ± 27	25 ± 30	7 ± 14
Duration of hospitalization (d)*	45 ± 25	47 ± 25†	23 ± 18†
Duration of antibiotic therapy (d)*	50 ± 266	75 ± 299†	35 ± 16†
Admission to ICU (%)	7 (18)	6 (20)	1 (10)
Duration of ICU stay (d)*	2 ± 6	2 ± 6	2
Cure (%)	30 (75)	20 (67)†	10 (100)†
Persistent infection (%)	4 (10)	4 (13)	0
Relapse (%)	1 (3)	1 (3)	0
Death (%)	5 (13)	5 (17)	0

*Median ± SD.
†$P < 0.05$.
ICU = intensive care unit.

nisone because of a renal transplant, PET showed right-sided retroperitoneal ^{18}F-FDG uptake, but abdominal ultrasound was normal. In the remaining 7 patients treated with immunosuppressive drugs, ^{18}F-FDG PET was true-positive. In the 40 cases studied, the positive predictive value of ^{18}F-FDG PET was 91% and the negative predictive value was 100%.

The median duration of follow-up was 12 mo (range, 3–51 mo). The duration of hospitalization was significantly longer in the patients with metastatic complications (median, 47 vs. 23 d; Table 6). The patients with metastatic complications were also treated with antibiotics for a longer time period (median, 75 vs. 35 d). However, the duration of fever, the percentage of patients admitted to the intensive care unit (ICU), and the duration of ICU stay did not differ significantly between patients with and without metastatic complications. In the group with metastatic infection, 5 patients died of complications of infection and 4 patients had persistent infection (1 patient with a mycotic aortic aneurysm with a follow-up of 36 mo and 3 patients with infected vascular prostheses, who could not be treated surgically, with a follow-up of 3, 6, and 23 mo, respectively). One patient, who had been treated for a *S. aureus* psoas abscess, was diagnosed with a relapse after discontinuation of antibiotic therapy. The cure rate was significantly lower in the group with metastatic infection than in patients without metastatic complications (67% vs. 100%).

DISCUSSION

In this study, the utility of ^{18}F-FDG PET in patients with suspected metastatic infectious disease was evaluated. Even after a median number of 4 conventional diagnostic tests, ^{18}F-FDG PET revealed clinically relevant new infectious foci in 45% of all patients. In these cases, the results of ^{18}F-FDG PET led to a change of treatment. To our knowledge, this study represents the largest patient population screened for metastatic infectious foci by ^{18}F-FDG PET. No comparable studies are available at this time. In several previous studies, the accuracy of ^{18}F-FDG PET for diagnosing primary—mostly orthopedic—infections ranged from 80% to 100% (*12–14*). Although ^{18}F-FDG PET is able to detect infection of joint prostheses, it is less accurate than, and is not a suitable replacement for, leukocyte imaging or labeled IgG for this indication (*15,16*). In 3 prospective studies, ^{18}F-FDG PET enabled correct visualization of spondylodiscitis and proved to be superior to MRI, ^{67}Ga-citrate scintigraphy, and bone scanning (*17–19*). In 2 studies, ^{18}F-FDG PET reliably identified septic thrombophlebitis in cancer patients with CVCs suspected of infection and was able to distinguish septic thrombophlebitis from deep venous thrombosis, leading to significant therapeutic changes (*20,21*). PET revealed increased ^{18}F-FDG uptake at the site of the CVC even in patients without signs of infection and in several patients with severe neutropenia. It is obviously impossible to compare these studies because of different study designs and different patient characteristics, but the results of these studies and our results suggest that ^{18}F-FDG PET is a sensitive method to detect various infectious foci in different organ systems with a reasonable specificity.

A weakness of this study is its retrospective nature. A high percentage of patients had metastatic disease, underscoring that this group of patients had been selected on the basis of their high risk of metastatic complications. Therefore, the results of this study should not be applied to all patients with bloodstream infection. Furthermore, because a rigid investigation protocol for the diagnostic work-up of these patients was not applied, the number and the kind of diagnostic tests performed differed considerably between individual patients. For a period of at least 3 mo after admission, follow-up data were available from the medical charts of all patients. However, it cannot be excluded that relapses have occurred, which remained unnoticed by the attending physicians.

Calculation of sensitivity and specificity of ^{18}F-FDG PET in patients with suspected focal infection is difficult for several reasons. First, the interpretation of this procedure is hampered because of a lack of a gold standard, especially in the case of a normal ^{18}F-FDG PET scan. When additional diagnostic procedures were negative and a follow-up of at least 3 mo did not reveal new infectious foci or a relapse after discontinuation of therapy, it was considered appropriate to presume that other infectious foci were indeed absent. Second, ^{18}F-FDG PET cannot exclude cerebral disease or meningitis, because physiologic uptake in the cerebral cortex in most cases obscures any pathologic uptake. Besides physiologic uptake of ^{18}F-FDG in the brain, normal activity in the heart, kidneys, and bladder severely hampers the delineation of disease in these organs. Variable physiologic ^{18}F-FDG uptake in the bowel is possible (*22*) and, thus, can lead to a false-positive interpretation, although this problem was not encountered in our group of patients.

Detection of infectious foci by CT, MRI, and ultrasonography is difficult in an early phase because of the absence of substantial anatomic change at that time. Also, discrimination of active infectious lesions from residual changes due to cured processes or surgery remains difficult. ^{18}F-FDG PET shows functional changes caused by activation of inflammatory cells and does not depend on anatomic changes. In addition, the advantages of ^{18}F-FDG PET in suspected metastatic infection, compared with CT and MRI, are whole-body screening, high contrast resolution, absence of disturbance by metallic implants, and absence of contrast-related side effects (CT). Conventional radiopharmaceuticals routinely used in clinical practice (^{67}Ga-citrate and ^{111}In-labeled or ^{99m}Tc-labeled leukocytes or IgG) have several disadvantages, such as normal accumulation in liver and spleen, handling of potentially infected blood products, and high radiation burden (^{67}Ga) (*23*). The advantages of ^{18}F-FDG PET are early imaging (1 h vs. up to 48 h); higher resolution; high target-to-background ratio (*24*); sensitivity in chronic low-grade infections (*25–27*); high accuracy in the central skeleton, liver, spleen, and vascular system; and high interobserver agreement (*25*). Obvious disadvantages are the relatively high cost and the currently limited availability. However, when ^{18}F-FDG PET performance for this indication is confirmed in larger prospective studies and the number of PET systems further increases, the high diagnostic yield of ^{18}F-FDG PET may well become a clinically significant and also cost-effective modality, because adequate early diagnosis limits the number of noncontributing (invasive) tests required and the time to diagnosis and, thus, facilitates adequate antibiotic or local (surgical) therapy. A further potential application, which needs to be investigated, is the contribution of ^{18}F-FDG PET in determining the duration of antimicrobial treatment in patients with metastatic infection.

CONCLUSION

^{18}F-FDG PET is a valuable imaging technique in patients at high risk of metastatic infectious disease, even when the results of other diagnostic procedures show no signs of infection. However, for a validation of ^{18}F-FDG PET for this indication and for determination of its exact position in the order of diagnostic tests, prospective studies on a larger number of patients are warranted.

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