Positron emission tomography with ^{18}F-fluorodeoxyglucose in fever of unknown origin and infectious and non-infectious inflammatory diseases

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Positron emission tomography with ^{18}F-fluorodeoxyglucose in fever of unknown origin and infectious and non-infectious inflammatory diseases

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Outline of the thesis

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Despite recent advances in diagnostic techniques, fever of unknown origin (FUO) and suspected focal infection or inflammation remain challenging diagnostic problems. Timely identification and localization of infectious and inflammatory lesions is critical in appropriate treatment of these patients. Early diagnosis, however, is often difficult, especially in patients without signs pointing to a specific localization. Conventional imaging techniques, such as computed tomography (CT), magnetic resonance imaging (MRI) and ultrasonography are less suitable as a screening method when clues for specific sites of disease are absent. Furthermore, infectious and inflammatory foci cannot be detected by these techniques in an early phase because of the lack of substantial anatomical changes at this time. Also, discrimination of active infectious or inflammatory lesions from residual changes due to cured processes or surgery is difficult in some cases. Scintigraphic imaging allows delineation of the localization of foci in all parts of the body, based on functional changes. Since activated inflammatory cells take up large amounts of glucose as a result of an increased metabolic rate, ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) represents a promising imaging technique in patients suspected of infectious or inflammatory disorders. The aim of this thesis was to investigate the clinical value of FDG-PET in diagnosis of fever of unknown origin and several infectious and inflammatory diseases.

Scintigraphy using autologous leukocytes, labeled with ^{111}In or ^{99m}Tc, is still generally considered the "gold standard" nuclear medicine technique for imaging of infection and inflammation, but this is a cumbersome and potentially hazardous approach. Over the past years, a variety of other radiopharmaceuticals have been used for the visualization of infectious and inflammatory disease. **Chapter 1** presents an overview of both well-established and widely available radiopharmaceuticals and of "new" radiolabeled compounds for the scintigraphic diagnosis of infectious and inflammatory processes. The results of previous clinical studies of FDG-PET in patients with FUO and several infectious and inflammatory disorders are also discussed.

The initial interest in the subject of this thesis further increased after experiencing the value of FDG-PET in individual patients with difficult diagnoses of infectious or inflammatory diseases in daily clinical practice. In these cases, specific signs were absent and extensive investigation by conventional diagnostic tests did not provide a correct diagnosis. In **chapter 2**, several of these patients are described in four case reports.

Previously, FDG-accumulation on PET-scanning had been reported in patients with giant cell arteritis, Takayasu arteritis, and aortitis. To further assess the role of FDG-PET imaging in diagnosis and follow-up of patients with different types of vasculitis, the results of FDG-PET scans, performed either because of suspected vasculitis or because of fever of unknown origin with results suggesting the presence of vasculitis were evaluated in **chapter 3**.

In **chapter 4**, the ability of FDG-PET to visualize lipodystrophy in HIV-infected patients was prospectively studied. Treatment with highly active antiretroviral therapy has dramatically reduced

HIV-associated morbidity and mortality, but has also caused lipodystrophy in many patients. It was hypothesized that FDG-PET would be able to visualize lipodystrophy by showing the increased adipose tissue inflammatory activity together with mitochondrial toxicity of nucleoside reverse transcriptase inhibitors, which induces metabolic stress causing increased glucose-uptake.

One of the main complications of blood stream infections, especially in case of *S. aureus* bacteremia or candidemia, is secondary metastatic infection. Failure to identify metastatic complications increases morbidity and mortality. In **chapter 5**, the value of FDG-PET in detecting metastatic infectious foci in patients with bacteremia or fungemia at high risk of metastatic infection was assessed.

Since the first definition of FUO by Petersdorf and Beeson, this definition has been modified several times. Before starting a prospective study in patients with FUO, establishing a correct definition and a standardized diagnostic protocol was necessary. In **chapter 6**, a review is provided describing the adjusted definition of FUO and possible causes of continuous and periodic FUO. Furthermore, suggestions for a diagnostic and therapeutic approach are presented.

After the introduction of FDG-PET in 1998 and after the first reports on the possible value of FDG-PET in patients with FUO and focal infection or inflammation, FDG-PET was ordered in many patients with FUO and several patients suspected of various infectious or inflammatory diseases. In **chapter 7**, the results of all FDG-PET-scans performed because of FUO or suspected focal infection or inflammation in the Radboud University Nijmegen Medical Centre between January 1999 and December 2002 were reviewed in order to provide information on the possible value of FDG-PET in the specific patient population of this hospital.

Comparing the results of previous studies and our retrospective study of the value of FDG-PET in patients with FUO is difficult: the definition of FUO differed, FDG-PET was performed at different stages of the diagnostic process, no structured diagnostic protocol was used and the FDG-PET technique differed between the studies, resulting in considerable selection bias. For a validation of FDG-PET in patients with FUO and for determination of its position in the order of diagnostic tests in the work-up of FUO, we designed a prospective study of FDG-PET as a part of a structured diagnostic protocol. The standardized diagnostic protocol in this study was based on our recommendations for a diagnostic and therapeutic approach described in chapter 6. The results of this prospective multicenter study with regard to the value of FDG-PET in patients with FUO are presented in **chapter 8**.

In literature, no data are available on patients with FUO diagnosed outside of tertiary care and academic hospitals. From the prospective study described in part in chapter 8, data on the diagnostic yield of the standardized protocol including FDG-PET and other investigations in our tertiary care hospital and in five general hospitals in the same region, as well as the influence of several parameters on the chance of reaching a diagnosis are described in **chapter 9**.

In **chapter 10**, a general discussion and future perspectives are provided.

Chapter 1

Radiolabeled compounds in diagnosis of infectious and inflammatory disease

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Abstract

Nuclear medicine offers powerful noninvasive techniques for visualization of infectious and inflammatory disorders using whole body imaging enabling the determination of both localization and number of inflammatory foci. A wide variety of approaches depicting the different stages of the inflammatory response have been developed. Non-specific radiolabeled compounds, such as ^{67}Ga-citrate and radiolabeled polyclonal human immunoglobulin accumulate in inflammatory foci due to enhanced vascular permeability. Specific accumulation of radiolabeled compounds in inflammatory lesions results from binding to activated endothelium (e.g. radiolabeled anti-E-selectin), the enhanced influx of leukocytes (e.g. radiolabeled autologous leukocytes, anti-granulocyte antibodies or cytokines), the enhanced glucose-uptake by activated leukocytes (^{18}F-fluorodeoxyglucose) or direct binding to micro-organisms (e.g. radiolabeled ciprofloxacin or antimicrobial peptides). Scintigraphy using autologous leukocytes, labeled with ^{111}In or ^{99m}Tc, is still considered the "gold standard" nuclear medicine technique for the imaging of infection and inflammation, but the range of radiolabeled compounds available for this indication is still expanding. Recently, positron emission tomography with ^{18}F-fluorodeoxyglucose has been shown to delineate various infectious and inflammatory disorders with high sensitivity. New developments in peptide chemistry and in radiochemistry will result in specific agents with high specific activity. A gradual shift from non-specific, cumbersome or even hazardous approaches to more sophisticated, specific approaches is ongoing. In this review, the different approaches to scintigraphic imaging of infection and inflammation, already in use or under investigation, are discussed.

Introduction

Timely identification and localization of infectious and non-infectious inflammatory lesions is critical in appropriate treatment of patients. Scintigraphic imaging is a non-invasive method allowing delineation of both localization and number of infectious and inflammatory foci in all parts of the body, based on functional (physiological and/or biochemical) changes of tissues. Focal infectious and inflammatory processes can also be detected by several radiological techniques including computerized tomography (CT), magnetic resonance imaging (MRI) and ultrasonography. However, these techniques show anatomical changes, so infectious and inflammatory foci cannot be detected in an early phase because of the lack of substantial anatomical changes at this time. Also, discrimination of active infectious or inflammatory lesions from residual anatomical changes due to cured processes or surgery is often difficult. In addition, nuclear medicine techniques permit whole-body imaging, whereas CT and MRI routinely provide only information on a part of the body. Over the past years, a variety of radiolabeled compounds detected by gamma cameras have been used for the visualization of infectious and inflammatory disease. The number of these radiolabeled compounds available for diagnosing infection or inflammation is still increasing. Also, recently, positron emission tomography (PET) using ^{18}F-fluorodeoxyglucose (FDG) has entered the field of clinical infectious and inflammatory diseases. This review will focus both on well-established and widely available radiopharmaceuticals as on "new" radiolabeled compounds and the value of

FDG-PET in the diagnosis of infectious and inflammatory processes. Before discussing the various scintigraphic methods, the pathophysiology of inflammation and infection is briefly described.

Inflammation and infection

Inflammation is defined as the response of tissues to any kind of injury in order to bring serum molecules and cells of the immune system to the site of damage. Such injury can be caused by trauma, ischemia, a neoplasm or an infection. Infection simply means "contamination with micro-organisms" [1]. Infection is not always accompanied by inflammation, for example in the case of a severely immunocompromized patient. In general, the inflammatory response is characterized by locally increased blood supply, increased vascular permeability in the affected area, enhanced transudation of plasma proteins and enhanced influx of leukocytes. In response to tissue damage, powerful defense mechanisms are activated, consisting of leukocytes and plasma proteins (opsonins, antibodies, complement). Furthermore, a complex variety of chemical mediators are involved. These are molecules that are generated during the inflammatory response and that modulate the inflammatory process. The migration of leukocytes from the blood stream is facilitated by chemical mediators which upregulate the expression of adhesion molecules on both endothelial cells and leukocytes. First, the leukocytes adhere to the vascular endothelium due to locally enhanced expression of these adhesion molecules. Subsequently, they pass through the endothelium and the basal membrane (diapedesis) and migrate into the inflammatory focus (chemotaxis). This process starts within minutes from the injury and usually resolves in hours or days [1]. It causes the classical symptoms of acute inflammation: rubor (redness), calor (warmth), tumor (edema), dolor (pain) and functio laesa (impaired function). In acute infection or inflammation, infiltrating cells are predominantly polymorphonuclear cells (PMNs). In chronic infection or inflammation, persisting for weeks or months, the cellular infiltrate mainly consists of mononuclear cells, such as lymphocytes, monocytes and macrophages.

Approaches to imaging infectious and inflammatory processes

A wide variety of approaches to scintigraphic imaging of inflammatory and infectious disorders, depicting the different stages of the inflammatory response, have been developed (Table 1). Non-specific radiolabeled compounds show increased extravasation at the site of inflammation by utilizing the locally enhanced vascular permeability. Examples are ^{67}Ga-citrate and radiolabeled non-specific immunoglobulins. The second approach to imaging inflammation is to utilize the influx of leukocytes, either by radiolabeling the patient's leukocytes ex vivo or by directly targeting leukocyte antigens or receptors in vivo via administration of radiolabeled antigranulocyte monoclonal antibodies or receptor-binding ligands (chemotactic peptides, cytokines and complement factors). Most of these radiolabeled compounds preferentially bind to granulocytes and are thus most suitable for visualizing acute inflammatory processes. Radiolabeled interleukin-2 (IL-2) is suitable for imaging chronic inflammatory processes, because the IL-2 receptor is

preferentially expressed on T-lymphocytes. Alternatively, imaging of activated endothelium is possible and this involves targeting activated endothelial adhesion molecules, for example anti-E-selectin. The mechanism of FDG-uptake in inflammatory cells is related to leukocytes using glucose as an energy source only after activation during the metabolic burst [2]. The accumulation of FDG in cells with increased glucose metabolism is specific. Increased glucose metabolism, however, is also present in malignant cells, so FDG-uptake is not specific for inflammatory processes as such. A new class of radiolabeled compounds consists of radiolabeled antibiotics and microbial peptides, which directly bind to micro-organisms. The specific nature of uptake of these radiolabeled compounds in inflammatory processes is still a matter of debate, however.

Characteristics of an ideal radiolabeled compound

General characteristics of an ideal infection-imaging agent should include efficient accumulation and good retention in inflammatory foci, rapid clearance from the background, easy low-hazard preparation and wide availability at low cost. Absence of accumulation in non-target organs, specifically in the blood pool and the bowel is also important. High blood pool activity complicates the imaging of vascular infections and vasculitis. Similarly, accumulation in the bowel would complicate detection of abdominal infection or inflammation. Early diagnostic imaging is generally preferable but not always necessary, as in the case of chronic osteomyelitis for example. A one-day protocol is preferred especially in cases of severe and acute illnesses. Delivering high radiation doses or using radiolabeled compounds with possible side effects is in general unwanted and should be considered only when significant clinical benefit is to be expected. In many cases differentiation between infection and non-infectious inflammation is preferred, but this is not necessary in patients with fever of unknown origin (FUO). In these patients scintigraphic imaging is most often used to evaluate the presence of focal abnormalities, which can subsequently be further evaluated by specific diagnostic procedures. At present, no radiolabeled compound perfectly meets all of these criteria. In clinical practice, the choice of the imaging agent is based on careful evaluation of each individual case.

Table 1 Overview of characteristics of radiopharmaceuticals used for imaging inflammatory processes.

Physiological characteristics	Targeting mechanism	Tracer class	Radiolabeled compound
Enhanced vascular permeability	Non-specific uptake		^{67}Ga-citrate [3-8] Non-specific immunoglobulins [9-11,13-20] Liposomes [21-27] Avidin/^{111}In-biotin [29-32]
Endothelial activation	Antigen binding	Antibodies	F(ab')$_2$-anti-E-selectin [34-37] Anti-ICAM-1 Mab [39,40]
	Binding to E-selectin	Peptide	IMP-178 [38]
Enhanced influx of granulocytes	Granulocyte influx		Radiolabeled granulocytes [41-44,47-49]
	Antigen binding	Antibodies	Anti-NCA-95 IgG: BW 250/183 [53-67] Anti-SSEA-1 IgM: LeuTech® [69-74] Anti-NCA-90 Fab': sulesomab, LeukoScan® [76-89]
	Receptor binding	Chemotactic peptides	f-Met-Leu-Phe [90-96]
		Cytokines	IL-1, IL-1ra [97-99,101,102] IL-8 [103-110] PF-4 derivative: P483H [111,112]
		Complement factors	C5a, C5a-des-Arg [113]
		LTB$_4$-antagonists	RP517 [114,115] DPC11870-11 [116]
	Binding to elastase	Peptides	Human neutrophil elastase inhibitor (EPI-HNE-2) [117]
Enhanced influx of mononuclear cells	Receptor binding	Cytokines	IL-2 [118-125] MCP-1 [126,127]
		Peptides	RP128 [128,129]
		Galactoside	J001X [130-136]
	Antigen binding	Antibodies	Anti-CD4 IgG [137-140]
Increased metabolic requirements	Enhanced glucose uptake		FDG [2,141-174,178,179,182-189]
Presence of micro-organisms	Affinity for micro-organisms	Antimicrobial agents	Ciprofloxacin: Infecton® [190-200,210] Fluconazole [205] Antimicrobial peptides [207-211]

Non-specific radiolabeled compounds

^{67}Ga-citrate

After injection, ^{67}Ga-citrate accumulates as an iron analogue through binding to circulating transferrin. This complex extravasates at the site of inflammation due to locally enhanced vascular permeability. In the inflamed tissue, ^{67}Ga is transferred to lactoferrin that is locally excreted by leukocytes or to siderophores produced by micro-organisms [3]. Physiologically 10 to 25% of the radionuclide is excreted via the kidneys during the first 24 hours. After 24 hours the principal route of excretion is hepatobiliary. After 48 hours about 75% of the injected dose remains in the body and is equally distributed among the liver, bone, bone marrow and soft tissues [4]. ^{67}Ga-citrate has been used extensively in clinical practice in several pathological conditions demonstrating high sensitivity for both acute and chronic infection and non-infectious inflammation [5]. There are

several shortcomings that limit its clinical application, however. Specificity is poor owing to the physiological bowel excretion and accumulation in malignant tissues and areas of bone modeling [6,7]. In addition, the radiopharmaceutical has unfavorable imaging characteristics such as a long physical half-life (78 h) and high-energy gamma radiation (93-889 keV), causing high radiation absorbed doses. Moreover, optimal imaging often requires delayed imaging up to 72 hours after the injection. These unfavorable characteristics and the development of newer radiopharmaceuticals have resulted in the replacement of ^{67}Ga-citrate scintigraphy by scintigraphy with labeled leukocytes in the majority of inflammatory conditions. Leukocyte scanning, however, is of limited value in patients with suspected vertebral osteomyelitis and sequential gallium imaging appears to be a better way to diagnose this condition [5]. Also, in immunocompromized patients, ^{67}Ga-citrate imaging is the procedure of choice for detecting opportunistic respiratory tract infections [5]. Finally, ^{67}Ga-citrate scintigraphy is still the gold standard for radionuclide imaging in patients with FUO, where it is able to detect both acute and chronic inflammatory conditions and neoplasms [5,8]. However, its limited specificity and the generally unfavorable characteristics when compared to FDG-PET will most probably result in replacement of this technique by FDG-PET in patients with FUO in the near future.

Non-specific immunoglobulins

Initially it was thought that human polyclonal immunoglobulin (HIG) was retained in inflammatory processes by interaction with Fc-γ-receptors expressed on infiltrating leukocytes [9]. Later it was shown, however, that radiolabeled HIG accumulates primarily in inflammatory foci by non-specific extravasation due to locally enhanced vascular permeability [10]. HIG has been labeled with ^{111}In and ^{99m}Tc for clinical use. Disadvantages of the use of ^{111}In are a relatively high radiation burden, suboptimal gamma radiation for in vivo imaging, often limited availability and high cost. ^{99m}Tc is a more attractive alternative in most cases because of its short half-life (6 h), availability and lower cost. Both agents have slow blood clearance and physiological uptake in the liver and spleen. A general limitation is the long time span of 24 h between injection and diagnosis. In a comparative study, it was shown that ^{99m}Tc-HIG labeled via the chelator hydrazinonicotinamide (HYNIC) has in vivo characteristics highly similar to those of ^{111}In-HIG and in most cases is suitable to replace the ^{111}In-labeled compound [11]. ^{99m}Tc-HIG imaging, however, has more limited sensitivity in chest disease and in chronic inflammatory processes than ^{111}In-HIG scintigraphy [12]. Direct comparison of ^{111}In-HIG and ^{111}In-leukocytes in 35 patients with various subacute infections showed a slightly, but significantly better overall accuracy of ^{111}In-HIG scintigraphy [13]. The major indication for imaging with radiolabeled HIG is localization of acute infection or inflammation of the musculoskeletal system [14,15]. ^{99m}Tc-HIG scintigraphy appears to be an effective method for monitoring of disease activity in patients with rheumatoid arthritis [16]. In addition, ^{111}In-HIG scintigraphy is clinically useful in pulmonary infection, particularly in immunocompromized patients [17-20]. In conclusion, ^{111}In- or ^{99m}Tc-HIG scintigraphy can be successfully used in various infectious and inflammatory diseases with a diagnostic accuracy comparable to that of radiolabeled leukocytes. When facilities for labeling leukocytes are not available or in severely granulocytopenic patients, HIG scintigraphy can be an alternative for radiolabeled leukocytes. However, commercial kits are not available, impeding its general use in most clinics.

Liposomes

Liposomes are spheres consisting of one or more lipid bilayers surrounding an aqueous space. About 30 years ago they were proposed as vehicles for imaging of infection [21], but the preparations used at that time were cleared from the circulation very rapidly by the mononuclear/phagocyte system. If the surface of the liposomes is coated with a hydrophilic polymer such as polyethylene glycol (PEG), however, they circumvent recognition by the mononuclear/phagocyte system. This results in a prolonged residence time in the circulation and enhanced uptake at pathological sites by extravasation due to locally enhanced vascular permeability [22]. For infection imaging these stabilized PEG-liposomes can be labeled with ^{111}In-oxine or with ^{99m}Tc either using hexamethylpropylene amine oxime (HMPAO) as an internal label or via HYNIC as an external chelator. The labeling procedure is simple and takes only minutes [23]. Because of the unfavorable characteristics of ^{111}In, labeling with ^{99m}Tc is preferred in most cases. In several animal models good accuracy of radiolabeled liposomes when compared to ^{111}In-leukocytes was shown [24,25]. In 35 patients suspected of having infectious or inflammatory disease, sensitivity of imaging with ^{99m}Tc-PEG-liposomes was 94% and specificity was 89% [26]. A subsequent study demonstrated only a moderate relation between ^{99m}Tc-liposomes scintigraphy and conventional verification procedures in nine patients with inflammatory bowel disease [27]. More importantly, this study was prematurely terminated because of unacceptable side effects (tightness in chest, mild hyperventilation and erythema of the face and upper extremities) in three out of nine patients. Although these studies indicate that imaging with ^{99m}Tc-PEG-liposomes is an effective and convenient scintigraphic method to visualize focal infection and inflammation, the side effects impede further use in patients until a new formulation lacking these side effects will be developed. Recent studies have provided increased understanding of these adverse reactions and current research is directed at developing new liposome formulations without these side effects [28].

Avidin/^{111}In-biotin

Avidins are proteins present in eggs of amphibians, reptiles and birds. Streptavidin is a member of the same family and is produced by *Streptomyces avinii*. Biotin is a compound of low molecular weight that can be radiolabeled and that binds to avidin and streptavidin (molecular weight 66 and 60 kD, respectively) with extremely high affinity (K_d=10^{-15} mol/L). Infection imaging with avidin/^{111}In-biotin is based on non-specific accumulation of unlabeled avidin or streptavidin at sites of inflammation due to locally enhanced vascular permeability. Avidin or streptavidin is injected as a pretargeting agent, followed approximately 4 hours later by intravenous injection of ^{111}In-biotin. Free ^{111}In-biotin is cleared rapidly via the kidneys with minimal uptake by normal tissues [29]. Advantages of this method are a good target-to-background radioactivity ratio and early imaging. The alternative use of streptavidin as a pretarget does not improve imaging and it is more immunogenic than avidin [29]. One study demonstrated uptake of avidin/^{111}In-biotin in *Escherichia coli* infections in mice comparable to or slightly higher than uptake of ^{111}In-HIG [29]. Good diagnostic accuracy has also been demonstrated in humans with vascular infection [30] and chronic osteomyelitis [31], especially in the central skeleton and in cases of spondylodiscitis [32].

Limitations of non-specific radiolabeled compounds in infection/inflammation imaging

Although infectious and inflammatory processes can be visualized with radiolabeled compounds without a specific interaction between the agent and a tissue component in the inflammatory focus, this method has several limitations. Extravasation of molecules via diffusion is a slow process requiring prolonged high blood levels to allow for sufficient accumulation in the target tissue. High blood levels, however, entail relatively high background levels, especially in well-perfused tissues. Furthermore, in chronic inflammatory processes the vascular permeability tends to normalize. Finally, because non-specific radiolabeled compounds accumulate as a result of a common feature of infection and inflammation, these agents cannot distinguish between infection and inflammation. It must be emphasized, however, that all radiolabeled compounds accumulate to some extent in this non-specific way in inflammatory foci [33]. This mechanism is of particular importance in evaluating new radiolabeled compounds, because non-specific accumulation can be erroneously interpreted as being specific.

Specific radiolabeled compounds

Imaging of endothelial cell activation

Anti-E-selectin antibodies and antibody fragments

E-selectin is an endothelial adhesion molecule exclusively expressed on the luminal surface of activated endothelial cells and capable of binding to different populations of leukocytes. The endothelial expression of E-selectin is stimulated by interleukin-1 (IL-1), tumor necrosis factor α, and bacterial lipopolysaccharide. A $F(ab')_2$ antibody fragment, derived from an anti-E-selectin monoclonal antibody (Mab) has been synthesized and labeled with ^{111}In. Uptake of ^{111}In-$F(ab')_2$-anti-E-selectin was demonstrated in the inflamed joints of patients with rheumatoid arthritis. Compared with ^{111}In-HIG, ^{111}In-$F(ab')_2$-anti-E-selectin provided superior images in these patients [34]. Imaging with ^{111}In-$F(ab)_2$-anti-E-selectin also identified areas of inflammation in Crohn's disease and ulcerative colitis, concordant with the results of ^{99m}Tc-leucocyte scanning in 14 out of 17 patients [35]. More recently, diagnostic accuracy of ^{99m}Tc-$F(ab')_2$-anti-E-selectin proved to be comparable to ^{111}In-$F(ab')_2$-anti-E-selectin and higher than diagnostic accuracy of conventional bone scanning in patients with rheumatoid arthritis [36]. Another study showed that imaging with ^{111}In-anti-E-selectin-Mab is also a sensitive method for assessment of disease activity in patients with rheumatoid arthritis and that targeting is more intense and specific than using ^{99m}Tc-HIG [37].

IMP-178

Recently, an E-selectin-binding peptide, IMP-178, has been labeled with ^{99m}Tc. In a rat model of induced pyogenic osteomyelitis, ^{99m}Tc-IMP-178 visualized the infection with a moderate target-to-background ratio and showed a fast clearance from blood and from non-inflamed tissues [38].

Anti-intercellular adhesion molecule-1 antibodies

Intercellular adhesion molecule-1 (ICAM-1) is expressed on endothelial cells, but it is strongly upregulated during inflammation. In rat models, imaging with ^{111}In-labeled Mab against rat ICAM-1 correctly detected early acute bleomycin-induced lung injury [39] and acute respiratory distress syndrome [40]. ^{111}In-anti-ICAM-1 Mab was characterized by fast blood clearance and by specific uptake in inflamed tissues.

Imaging of infiltrating granulocytes

Radiolabeled leukocytes

Imaging using ex vivo labeled autologous leukocytes was developed in the 1970s. A blood sample of approximately 50 ml is collected and leukocytes are separated in vitro from red blood cells. These leukocytes are then labeled with radioactive isotopes (^{111}In or ^{99m}Tc) and reinjected. Using standard labeling procedures, only a few granulocytes are damaged by labeling, whereas most lymphocytes are damaged. The damaged cells are rapidly cleared from the circulation after reinjection [41]. After intravenous administration, the radiolabeled leukocytes initially sequestrate in the lungs with subsequent rapid clearance from the lungs. The radiolabel rapidly clears from the blood and in most cases uptake in granulocytic infiltrates is high while a substantial portion of the leukocytes accumulate in the spleen and the liver. Autologous leukocytes can be labeled with ^{111}In using oxine [42]. The use of HMPAO, a lipophilic chelator, allows for efficient labeling of white blood cells with ^{99m}Tc [43]. In contrast to ^{111}In-oxine, some of the ^{99m}Tc-HMPAO is released from the leukocytes after injection and subsequently is excreted via the kidneys (within minutes) and the hepatobiliary system (after several hours) [44]. ^{99m}Tc-labeled leukocytes have replaced ^{111}In-labeled leukocytes for most indications, because of the more optimal radiation characteristics. As a result of the biodistribution of ^{99m}Tc-HMPAO-labeled leukocytes, the use of ^{111}In-labeled leukocytes is preferred for evaluation of the kidneys, bladder and gall bladder. ^{111}In-labeled leukocytes are also preferred if late images are needed as in chronic infection [44]. With regard to diagnostic accuracy, there is no need for a better imaging agent than radiolabeled leukocytes. The preparation of this radiopharmaceutical, however, is laborious: isolating and labeling a patient's white blood cells takes a trained technician approximately 3 hours. In addition, the need to handle potentially contaminated blood can result in transmission of blood-borne pathogens such as hepatitis virus and human immunodeficiency virus to technicians or patients [45,46]. The principal clinical indications for radiolabeled leukocytes include inflammatory bowel disease, osteomyelitis, the follow-up of patients with infections of vascular or orthopedic prostheses and soft tissue infections [44,47,48]. There has always been concern that chronic infections could be missed by labeled leukocyte scans, because these infections generate a smaller granulocyte response than acute infections. However, a study in 155 patients demonstrated that sensitivity of labeled leukocytes for detection of acute infections (90%) was not significantly different from sensitivity for detection of chronic infections (86%) [49].

Anti-granulocyte antibodies and antibody fragments

Ever since it became clear that infectious and inflammatory foci could be visualized by radiolabeled autologous leukocytes, investigators have tried to develop a method aiming to label white blood

cells in vivo. The use of radiolabeled monoclonal antibodies against surface antigens present on granulocytes has the advantage that labeling procedures are easier and do not require handling of potentially contaminated blood. Disadvantages of the use of Mab, however, are the high molecular weight, resulting in slow diffusion into sites of inflammation, a long plasma half-life, and uptake in the liver due to clearance by the reticulo-endothelial system. A long interval is often required between administration of radiolabeled antibodies and acquisition of images in order to improve target-to-background ratios. Use of Mab of murine origin sometimes induces production of human antimouse antibodies (HAMA), which can lead to allergic reactions and altered pharmacokinetics when repeated injections are given [50]. This is, of course, a major limitation for follow-up studies. The use of antibody fragments (Fab' or $F(ab')_2$) or humanization of the antibodies could overcome most of these limitations: theoretically, immunogenicity is lower, blood clearance is faster and accumulation in inflammatory foci is higher. Moreover, since Fab' antibody fragments have an intrinsic lower affinity for the epitope, bone marrow uptake is lower, which is an advantage for imaging of infections of the central skeleton. Although radiolabeled anti-granulocyte antibodies and antibody fragments are included among radiolabeled compounds for specific targeting of infiltrating granulocytes, recent studies have demonstrated that they localize in infectious processes to a large extent by non-specific extravasation due to locally enhanced vascular permeability [51,52]. Binding of the antibodies to infiltrating leukocytes may contribute to the retention of the radiolabel in the inflammatory focus.

Anti-non-specific-cross-reacting antigen-95. One of the most widely used anti-granulocyte antibodies is the commercially available murine anti-NCA-95 IgG (BW 250/183), labeled with ^{99m}Tc, which recognizes the non-specific cross-reacting antigen 95 (NCA-95) expressed on human granulocytes and (pro)myelocytes. This Mab has been used successfully for imaging of various infectious and inflammatory processes [53-55] including subacute infectious endocarditis [56], lung abscesses [57], septic loosening of hip and knee prostheses [58,59] and diabetic foot infections [60]. Peripheral bone infections were also adequately visualized [57,61], but sensitivity decreased in case the focus was located closer to the spine because of physiological bone marrow uptake, so imaging with ^{99m}Tc-anti-NCA-95 is less suitable for diagnosing vertebral osteomyelitis [62]. Pulmonary infections other than abscesses were not visualized [57,63]. ^{99m}Tc-anti-NCA-95 scanning appeared to be a safe and reliable method for detecting infectious foci in neonates and infants with fever of unknown origin [64]. The preparation was also used in the evaluation of patients with inflammatory bowel disease, but it appeared to be less accurate than radiolabeled leukocytes partly due to non-specific bowel uptake [65-67]. Due to the relatively slow blood clearance, imaging 24 hours after injection is generally necessary for correct localization of the inflammatory process. The major drawback of radiolabeled anti-NCA-95, however, is the production of HAMA after the first injection.

Anti-stage specific embryonic antigen-1. Another Mab, anti-stage specific embryonic antigen-1 (anti-SSEA-1) IgM (LeuTech®), recognizes CD15 antigens on granulocytes with high affinity (K_d=10^{-11} mol/L). The in vivo binding exceeds 50%, suggesting involvement of more specific accumulation in inflammatory sites, such as in vivo migration of leukocytes from the circulation to the focus [68]. ^{99m}Tc-anti-SSEA-1 IgM was successfully used in patients with various inflammatory and infectious

diseases, such as osteomyelitis, diabetic foot ulcers and post-surgical infection [69-72] with similar diagnostic accuracy when compared to radiolabeled leukocytes [70]. Imaging with ^{99m}Tc-anti-SSEA-1 IgM also proved to be a highly sensitive test for detection of appendicitis in equivocal cases [72-74]. Presently, ^{99m}Tc-anti-SSEA-1 IgM is being evaluated for early detection of inhalation anthrax [72]. ^{99m}Tc-anti-SSEA-1 IgM is a convenient radiolabeled compound (imaging after 1 hour, easy preparation) and no HAMA production has been found. Disadvantages are high liver uptake and transient mild neutropenia that has been observed after ^{99m}Tc-anti-SSEA-1 injection in several patients. This adverse effect can also be caused by other Mabs as well as some cytokines. In most cases, however, this does not represent a clinical problem and does not impair image quality [75].

Anti-non-specific-cross-reacting antigen-90 Fab'. ^{99m}Tc-labeled anti-NCA-90 Fab' (sulesomab, LeukoScan®), which binds to NCA-90 surface antigen on granulocytes, is a commercially available infection imaging agent. Promising results have been obtained in the scintigraphic detection of endocarditis [76] and nonclassic appendicitis [77]. Scintigraphy using ^{99m}Tc-anti-NCA-90 Fab' also helped reach a final diagnosis in 8 out of 20 patients with FUO [78]. ^{99m}Tc-anti-NCA-90 Fab' proved to be no alternative for radiolabeled leukocytes in patients with inflammatory bowel disease due to limited sensitivity [79,80]. Also, non-specific bowel activity is often present, especially in the delayed images [81]. At first, scintigraphy using ^{99m}Tc-anti-NCA-90 Fab' appeared to provide rapid localization of bone and soft tissue infections with a negligible HAMA response rate and accuracy comparable to that of leukocyte scanning [82-85]. In other studies, however, ^{99m}Tc-anti-NCA-90 Fab' scintigraphy was found to be less specific for the diagnosis of musculoskeletal infections than leukocyte scanning [86-89]. In addition, false-negative results were found in several patients with chronic infections [89]. These studies suggest that ^{99m}Tc-anti-NCA-90 Fab' scintigraphy could be used for imaging of acute orthopedic infections, with its greatest strength being a high negative predictive value. Positive studies may require further correlative imaging.

Chemotactic peptides

A wide variety of peptides that bind to receptors expressed on leukocytes have been tested for the detection of infections. One of the first receptor-binding peptides that was tested for this purpose was formyl-methionyl-leucyl-phenylalanyl (f-Met-Leu-Phe or fMLP), a small chemotactic peptide produced by bacteria, which binds to receptors on granulocytes and monocytes with high affinity (K_d=1-3 x 10^{-9} mol/L). Radiolabeled f-Met-Leu-Phe and synthetic analogues of this peptide showed a high target-to-background ratio and rapid clearance from blood and noninflamed tissue in experimental animal models. The majority of the accumulation of ^{99m}Tc-f-Met-Leu-Phe at sites of infection appears to be receptor mediated [90]. In rabbits with sterile inflammation and *Escherichia coli* and *Staphylococcus aureus* infections, it was demonstrated that localization of infection using ^{99m}Tc-labeled f-Met-Leu-Phe-analogues was possible and appeared to be superior to ^{111}In-labeled leukocytes [91-93]. In a rat model of pancreatitis, uptake of a ^{99m}Tc-labeled f-Met-Leu-Phe-analogue correlated with the presence of granulocyte sequestration assessed by myeloperoxidase activity and histology [94]. Despite radiolabeling at high specific activity, a peptide dose as low as 10 ng/kg still caused transient mild granulocytopenia in Rhesus monkeys [95]. Several antagonists lacking biological activity were developed to circumvent this undesirable biological effect of the

radiolabeled peptide [90]. However, these antagonists had lower uptake in the infectious focus, most likely due to reduced affinity for the receptor [96]. In conclusion, rapid imaging of infection and inflammation with radiolabeled chemotactic peptides is feasible, but the side effects of these peptides seem to impede further clinical development.

Cytokines

Cytokines are (glyco)proteins acting via interaction with specific cell surface receptors expressed mainly on leukocytes, but also on other cell types. Cytokine receptors are usually expressed at low levels on resting cells, but their expression is upregulated during activation. Cytokines potentially can be used to specifically target leukocytes in vivo, because they bind to specific receptors with high affinity in the nanomolar range, they have low molecular weights (<25 kD) and plasma clearance is rapid. Finally, many cytokines are of human origin and are therefore readily available and supposedly non-immunogenic.

Interleukin-1 and interleukin-1-receptor antagonist. IL-1 is an important pro-inflammatory cytokine, which binds with high affinity to a specific receptor, mainly expressed on granulocytes, monocytes and lymphocytes. Studies in mice and rabbits with focal *S. aureus* infection demonstrated specific uptake of radio-iodinated IL-1 at the site of infection [97,98]. Using IL-1 receptor blocking antibodies, it could be shown that accumulation of radio-iodinated IL-1 in the inflammatory focus was mainly due to binding to the IL-1 type II receptor [99]. Unfortunately, side effects (e.g. hypotension, headache) due to the biological activity of IL-1, even at very low doses of 10 ng/kg, precluded clinical application of radiolabeled IL-1. Therefore, attention was focused on the naturally occurring IL-1 receptor antagonist (IL-1ra). This equally sized protein (17 kD) binds IL-1 receptors with similar affinity but lacks biological activity. Doses of up to 10 mg/kg could be safely administered to humans without any side effects [100]. In a comparative study in rabbits with *E. coli* infections, the abscess uptake of radio-iodinated IL-1ra was lower than that of radio-iodinated IL-1 [98,101]. In patients with rheumatoid arthritis, inflamed joints could be visualized within a few hours after injection of ^{123}I-IL-1ra. However, major retention of the radiolabel in the intestinal tract in humans indicated that this agent cannot be used to visualize abdominal lesions [102].

Interleukin-8. Interleukin-8 (IL-8) is a small protein (8.5 kD) belonging to the CXC subfamily of chemokines or chemotactic cytokines, in which the first two cysteines are separated by one amino acid. IL-8 binds with high affinity (0.3-4 x 10^{-9} mol/L) to two different receptors (CXCR1 and CXCR2) expressed on granulocytes and promotes chemotaxis of these cells. In rats with sterile inflammation, uptake of radio-iodinated IL-8 peaked at 1 to 3 hours after injection and subsequently declined with relatively low target-to-background ratios [103]. In a pilot study in eight patients, the same investigators showed that ^{123}I-IL-8 could visualize osteomyelitis and cellulitis correctly [104]. In these studies IL-8 was labeled using the chloramine T method. Despite similar in vitro cell binding characteristics, the labeling method proved to have major effects on the in vivo biodistribution of radio-iodinated IL-8. The scintigraphic imaging characteristics of IL-8 labeled via the Bolton-Hunter method were clearly superior to those of IL-8 labeled via the iodogen method [105]. In rabbits with *E. coli* infection, accumulation of ^{123}I-IL-8 in the abscess was rapid and high. The specific activity

of the ^{123}I-IL-8 preparation was relatively low and as a result an imaging dose of 25 µg/kg of IL-8 was needed, resulting in transient granulocytopenia followed by granulocytosis for several hours [105]. Recently, a ^{99m}Tc-labeled IL-8 preparation was developed using HYNIC as a chelator resulting in a significantly higher specific activity. The labeling of IL-8 with ^{99m}Tc using HYNIC was further optimized by the use of alternative coligands (nicotinic acid and tricine) to stabilize the ^{99m}Tc-protein-complex [106]. Protein doses to be administered were lowered substantially due to much higher specific activity of this new ^{99m}Tc-IL-8 preparation ameliorating concerns about the influence on leukocyte counts when this preparation will be tested in patients in the future. In rabbits with *E. coli* infections, high abscess uptake of ^{99m}Tc-IL-8 and high abscess-to-background ratios were obtained [107]. ^{99m}Tc-IL-8 has also been successfully used in rabbit models of osteomyelitis [108] and colitis [109]. Studies in neutropenic and normal rabbits with turpentine-induced abscesses have shown that accumulation of ^{99m}Tc-IL-8 in the abscess is a highly specific, neutrophil-driven process and that the total fraction of ^{99m}Tc-IL-8 that accumulates in the inflamed tissue is extremely high (up to >15% of injected dose) [110].

Platelet factor 4 derivative. Platelet factor 4 (PF-4), like IL-8, is a member of the CXC subfamily. PF-4 binds to receptors expressed on granulocytes and monocytes. A synthetic peptide, P483H, containing the heparin-binding region of PF-4, complexed with heparin to increase binding to leukocytes and containing a lysine-rich sequence to facilitate rapid renal clearance, has been labeled with ^{99m}Tc. In a rabbit model of *E. coli* infection, ^{99m}Tc-P483H clearly delineated the infectious foci as early as 4 hours after injection. No systemic side effects were observed [111]. In a study of 30 patients with various infections, ^{99m}Tc-P483H safely, rapidly and accurately detected focal infection. Results were comparable to radiolabeled leukocyte imaging [112].

Complement factors

The complement factor C5a and its natural metabolite C5a-des-Arg are involved in several stages of the inflammatory process. C5a-des-Arg only differs from C5a by the absence of the C-terminal Arg-residue of C5a. Both act on a common receptor on different cell types, including neutrophils and monocytes. The receptor binding affinity of C5a is one or two orders of magnitude higher than the affinity of C5a-des-Arg. The biologic activity of C5a-des Arg is considerably lower than that of C5a. In a rabbit model of *E. coli* induced intramuscular infection, ^{99m}Tc-C5a could rapidly visualize the infection with high uptake of the radiolabel in the affected muscle while uptake of ^{99m}Tc-C5a-des-Arg in the abscess was low [113]. The ideal combination of reduced biologic activity and preferable imaging characteristics was, thus, not found in C5a-des-Arg.

Leukotriene B_4-antagonists

RP517. Leukotriene B_4 (LTB_4) is a potent chemoattractant that activates granulocytes and macrophages. It is considered an important mediator in both acute and chronic inflammatory diseases. LTB_4 binds to receptors abundantly expressed on granulocytes after an inflammatory stimulus. In search for an effective infection-imaging agent, the LTB_4 receptor antagonist RP517 was synthesized. In rabbits with *E. coli* infections, ^{99m}Tc-RP517 rapidly visualized the abscesses with high abscess-to-background ratios [114]. ^{99m}Tc-RP517 was also successfully used in dogs with

experimental myocardial inflammation [115]. The disadvantage of ^{99m}Tc-RP517, however, is its hepatobiliary clearance, causing high uptake in the organs of the digestive tract relatively early after the injection, which limits its applicability as an infection-imaging agent [114].

DPC11870-11. Recently, a new hydrophilic LTB_4-antagonist with a comparable receptor binding affinity, DPC11870-11 was developed and labeled with ^{111}In. In rabbits with intramuscular *E. coli* infection, ^{111}In-DPC11870-11 rapidly revealed the infection with high abscess-to-background ratios. No accumulation of radioactivity was observed in the gastrointestinal tract. Blocking experiments with an excess of the nonradiolabeled agent showed a specific receptor-ligand interaction of ^{111}In-DPC11870-11 [116].

Human neutrophil elastase inhibitor

Human neutrophil elastase inhibitor (EPI-HNE-2) is a peptide with a low molecular weight that binds to neutrophil elastase released in inflammatory sites by activated neutrophils. After labeling with ^{99m}Tc, human neutrophil elastase inhibitor accumulated specifically in inflammatory lesions in a monkey model and provided early images with good diagnostic quality. Plasma clearance was rapid and there were no side effects [117].

Imaging of infiltrating mononuclear cells

Cytokines

Interleukin-2. IL-2 is a glycoprotein with a molecular weight of 15.5 kD, which is synthesized and secreted by T-lymphocytes after specific antigen stimulation. During inflammation, activated lymphocytes express high-affinity IL-2 receptors and become a target for radiolabeled IL-2. IL-2 has been labeled with ^{123}I and ^{99m}Tc to enable imaging of chronic infection or inflammation. In several rat models of autoimmune diabetes and in rats with renal allografts, ^{123}I-IL-2 adequately detected areas of lymphocytic infiltration. Specific accumulation of ^{123}I-IL-2 has been confirmed by ex vivo autoradiography [118-120]. ^{123}I-IL-2 has also been used successfully in patients with type 1 diabetes [121]. ^{99m}Tc-IL-2 was able to identify a subgroup of patients with type 1 diabetes with persistent inflammation at the time of diagnosis that might benefit from the use of immunomodulating drugs to preserve β cell function [122]. In patients with active Crohn's disease, ^{123}I-IL-2 allowed imaging of activated T-lymphocytes infiltrating the gut wall. The uptake of ^{123}I-IL-2 decreased after corticosteroid therapy, so this technique could be valuable in monitoring the effect of therapy [123]. Scintigraphic results using ^{123}I-IL-2 in patients with celiac disease was consistent with the histologically determined number of infiltrating IL-2 receptor-positive cells in the jejunal mucosa [124]. ^{99m}Tc-IL-2 also strongly accumulates in the thyroid glands of patients with Hashimoto's thyroiditis and Grave's disease [125]. No side effects were observed. These results suggest that radiolabeled IL-2 could be a suitable radiopharmaceutical for in vivo targeting of mononuclear cell infiltration as present in several autoimmune diseases.

Monocyte chemoattractant protein 1. The chemotactic cytokine monocyte chemoattractant protein 1 (MCP-1), a monomeric polypeptide, is involved in the recruitment of monocytes that express its specific receptor (CCR2B). ^{125}I-MCP-1 showed rapid blood clearance in normal mice and in rabbits

with experimental arterial lesions. The uptake of ^{125}I-MCP-1 in damaged artery walls was higher than in normal vessels and correlated well with the histologically determined number of macrophages [126]. ^{99m}Tc-labeled MCP-1 localized preferentially in subacute inflammation in a rat model of sterile subacute and chronic turpentine-induced inflammation, reflecting the density of macrophages [127]. In the characterization of subacute inflammation, radiolabeled MCP-1 may prove to be useful by in vivo targeting of monocytes and macrophages.

RP128

Tuftsin is a chemotactic tetrapeptide derived from the Fc portion of IgG, which promotes chemotaxis and phagocytosis of neutrophils, monocytes and macrophages by binding to the tuftsinreceptor. RP128 is a bifunctional peptide chelate designed to target this receptor. The ability of ^{99m}Tc-RP128 to detect central nervous system (CNS) inflammation was shown in experimental allergic encephalomyelitis, an animal model of multiple sclerosis. In addition, ^{99m}Tc-RP128 successfully monitored glucocorticoid suppression of inflammation, recording a typical dose-response to increasing steroid concentration [128]. In 10 patients with long-standing rheumatoid arthritis, ^{99m}Tc-RP128 was able to visualize clinically affected joints [129].

J001X

J001X is a non-pyrogenic acylated polygalactoside isolated from the membrane proteoglycans of a non-pathogenic strain of *Klebsiella pneumoniae*. J001X interacts with macrophages, mainly in the activated state, by binding to CD11b, the complement receptor 3 expressed on monocytes, natural killer cells and macrophages, and to CD14, the lipopolysaccharide receptor expressed on monocytes and macrophages. ^{99m}Tc-J001X has been used for the detection of alveolitis and inflamed lymph nodes in experimental chronic berilliosis in baboons [130], radiation-induced inflammatory lesions in pigs [131] and arthritis in a rabbit model [132,133]. In humans, ^{99m}Tc-J001X scintigraphy appeared to be a sensitive and rapid technique for imaging of sarcoidosis [134]. ^{99m}Tc-J001X was also able to visualize active pulmonary involvement in patients with scleroderma [135] and rheumatoid arthritis [136]. In the patients with rheumatoid arthritis, however, sensitivity was low compared with high-resolution CT, pulmonary function tests and bronchoalveolar lavage [136].

Anti CD4 IgG

The abundance of CD4 molecules on inflammatory cells in the synovial membrane renders anti-CD4 monoclonal antibodies or their fragments potentially useful for specific imaging of arthritis. Following intravenous injection, Mabs are present both in the free form and bound to CD4-positive, circulating monocytes and T-cells. In a rat model of experimental arthritis, specific accumulation of ^{99m}Tc-labeled anti-rat CD4 Mab and ^{99m}Tc-anti-CD4-Fab' was shown in the affected joints [137,138]. In patients with rheumatoid arthritis, scintigraphy with ^{99m}Tc-anti-human CD4 Mab demonstrated higher target-to-background ratios in arthritic joints in comparison to HIG [139] . Recently, however, it was shown that the overall contribution of cell-bound Mabs to the imaging of arthritic joints with anti-CD4 Mabs is minimal [140].

Imaging of enhanced glucose uptake: FDG

FDG accumulates in tissues with a high rate of glycolysis, which not exclusively occurs in neoplastic cells. FDG-uptake is 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. ^{18}F is a positron-emitting radionuclide with a physical half-life of 110 minutes. After annihilation of a positron with an electron, two 180°-opposed gamma rays are emitted simultaneously, which can subsequently be detected by a PET camera. Increased uptake and retention of FDG has been shown in lesions with a high concentration of inflammatory cells, such as granulocytes and activated macrophages [2]. In an experimental rat model of turpentine-induced inflammation, FDG-uptake was elevated even more in chronic inflammation than in an acute inflammatory process [141]. In another rat model of *E. coli* infection, FDG-uptake in the infectious process was higher than uptake of ^{67}Ga-citrate, radiolabeled thymidine, methionine and human serum albumin [142]. Since the first report on high FDG-uptake in a human abdominal abscess [143], there have been many reports of FDG-accumulation in different infections and inflammatory lesions [144,145].

Fever of unknown origin

In several studies, the percentage of FDG-PET scans helpful in the diagnostic process in patients with FUO varied from 37% to 69% [146-149], which is very high compared to radiological techniques and ^{67}Ga-citrate scintigraphy. Although comparing these studies is difficult, because FDG-PET was performed at different stages of the diagnostic process, no structured diagnostic protocol was used and the patient characteristics differed, FDG-PET appears to be a valuable new imaging technique in these patients. The impossibility to differentiate between malignancy and infection or inflammation appears to be an advantage rather than a drawback in the investigation of patients with FUO. Another major advantage of FDG-PET in the work-up of patients with FUO is the vascular FDG-uptake in patients with vasculitis [150-152]. In a direct comparison between FDG-PET and ^{67}Ga-citrate scintigraphy in patients with FUO, FDG-PET proved to be superior [146,147]. Based on the results of these studies and resulting from the favorable characteristics of FDG-PET, conventional scintigraphic techniques may be replaced by FDG-PET in the investigation of patients with FUO in institutions where this technique is available. However, for a final validation of FDG-PET in patients with FUO and for determination of its exact position in the order of diagnostic tests, a larger prospective study of FDG-PET being part of a structured diagnostic protocol is warranted.

Osteomyelitis and spondylodiscitis

FDG-PET has been used successfully in diagnosing acute osteomyelitis [153,154], 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 and interobserver agreement was found for FDG-PET comparable to scintigraphy with antigranulocyte antibodies and ^{111}In-labeled leukocytes

[153,155-159]. In the central skeleton, accuracy of FDG-PET was even higher than for antigranulocyte antibody scintigraphy [155]. 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 spondylodiscitis [160-162]. FDG-PET proved to be superior to MRI, ^{67}Ga-citrate scintigraphy and three phase bone scan in these patients [160,162]. FDG-PET was also able to differentiate between mild infection and degenerative changes [162]. 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. In conclusion, FDG-PET is very useful in cases of suspected osteomyelitis of the central skeleton, spondylodiscitis or chronic low-grade infections of the peripheral skeleton.

Prosthetic joint infection

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 47 to 73% [163-167]. This limited specificity probably results from persisting FDG-uptake around the prosthesis for many years after arthroplasty, even in uncomplicated cases [163,167]. Location of FDG-uptake is probably important since FDG-uptake along the interface between bone and prosthesis appears to be more specific for infection [159,168]. However, FDG-PET should not be routinely used for this indication in a clinical setting until the criteria for differentiation between septic and aseptic loosening are more clearly defined.

Miscellaneous infectious diseases

FDG-PET seemed to have higher sensitivity in detecting blood vessel graft infection than conventional imaging techniques in a small number of patients [159,169]. In children with chronic granulomatous disease, a primary immunodeficiency leading to granuloma formation and numerous infections, FDG-PET was able to differentiate active infected lesions from chronic granuloma [170]. In patients with Echinococcosis, a serious parasitic infection, FDG-PET correctly identified the active lesions and appeared to be helpful in assessing response to treatment [171]. Recently, successful use of FDG-PET in detection of infected liver and renal cysts in patients with autosomal dominant polycystic kidney disease was reported [172]. FDG-PET also appears to be a promising imaging technique in the early detection of complications and for the differential diagnosis of central nervous system lesions in patients with HIV or AIDS [173,174]. A possible pitfall of FDG-PET in these patients, however, is the difficulty in differentiating between persisting generalized lymphadenopathy and lymphoma.

Vasculitis

Increased FDG-uptake has been found in patients with giant cell arteritis [175,176], Takayasu arteritis [147,177,178], periaortitis due to Wegener's granulomatosis, and unspecified large vessel vasculitis [152,179-182]. In a prospective study, vascular FDG-uptake was seen in 76% of 25 patients with biopsy-proven temporal arteritis or polymyalgia rheumatica [150]. In 15 patients with aortitis due to giant cell arteritis (n=14) or Takayasu arteritis (n=1) at the time of diagnosis and during

follow-up (n=7), FDG-PET identified more vascular regions involved in the inflammatory process when compared to MRI [178]. In conclusion, FDG-PET appears to be useful for diagnosing and determining the extent of various types of vasculitis. Furthermore, FDG-PET could become a useful tool for evaluating the effect of treatment.

Inflammatory bowel disease

High FDG-uptake has been reported in areas with inflammation in patients with inflammatory bowel disease [183-185]. Specificity of FDG-PET was comparable to MRI and antigranulocyte antibody scintigraphy in 59 patients with Crohn's disease, but sensitivity of FDG-PET was significantly higher [185]. FDG-PET also correctly detected histologically confirmed eosinophilic colitis, collagenous colitis and bacterial colitis in a small number of patients [186]. FDG-PET could become a useful tool to detect disease activity in the terminal ileum and colon in patients with inflammatory bowel disease, but physiological, non-specific bowel uptake could be an important problem in clinical practice. More data are needed to justify routine application of PET in the management of inflammatory bowel disease.

Sarcoidosis and rheumatoid arthritis

In several patients with sarcoidosis, FDG-uptake in hilar and mediastinal lymph nodes and erythema nodosum has been described [187,188]. FDG-uptake levels appeared to reflect disease activity [188]. FDG-PET does not have a major role in the initial diagnosis of sarcoidosis, because conventional diagnostic techniques are very well able to establish this diagnosis in most cases. FDG-PET may prove to be useful in evaluating response to treatment, but larger prospective studies are needed to define the role of FDG-PET in these patients. In patients with rheumatoid arthritis, FDG-PET allowed quantification of metabolic changes in joint inflammation comparable to volumetric changes visualized with MRI, but FDG-uptake was not associated with treatment outcome [189].

Imaging the presence of micro-organisms

Ciprofloxacin

Ciprofloxacin is a fluoroquinolone that binds to bacterial DNA gyrase, which is present in all dividing bacteria. Since it binds only to living bacteria, even to most bacteria that are resistant to this antibiotic, the use of ^{99m}Tc-labeled ciprofloxacin (Infecton®) theoretically allows distinction between sterile inflammation and infection. ^{99m}Tc-ciprofloxacin is mainly excreted via the kidneys, it has low liver metabolism and bowel uptake is usually very low [190]. The lack of bone marrow uptake is particularly useful for the detection of bone infections. In patients with known or suspected sites of various bacterial infections, sensitivity of scintigraphy with ^{99m}Tc-ciprofloxacin varied from 70 to 85% and specificity was 82 to 96% [191-194]. Comparison between ^{99m}Tc-ciprofloxacin and leukocyte imaging gave comparable sensitivities and specificity was 96% and 77%, respectively [191]. ^{99m}Tc-ciprofloxacin was shown to be a very sensitive and quite specific marker of bone and joint infections [195-197]: sensitivity of ^{99m}Tc-ciprofloxacin imaging was higher when compared to scintigraphy with ^{99m}Tc-HMPAO-leukocytes [195] and three-phase bone scanning in combination with ^{67}Ga-citrate scintigraphy [196]. ^{99m}Tc-ciprofloxacin has also been used successfully in patients with suspected infections of hip or knee prostheses [198,199]. In addition, ^{99m}Tc-ciprofloxacin imaging appeared

to be useful in the diagnosis and follow-up of pelvic inflammatory disease [200]. Lately, the specificity of ^{99m}Tc-ciprofloxacin has been discussed extensively [201]. In one study, results of ^{99m}Tc-ciprofloxacin imaging in rabbits suggested good sensitivity but lack of specificity for the detection of *S. aureus* infection of knee prostheses [202]. In patients with suspected osteoarticular infections and patients with osteoarticular diseases without signs of infection, ^{99m}Tc-ciprofloxacin scintigraphy did not discriminate between infected and aseptic osteoarticular diseases [203]. In a retrospective study in patients suspected of osteoarticular infections and controls with joint complaints without signs of infection, low specificity of ^{99m}Tc-ciprofloxacin scintigraphy was found. Evaluation of tracer uptake at late imaging did not improve discrimination between sterile and non-sterile inflammation. Additionally, articular uptake was seen in many control patients [204].

Fluconazole

More recently, the antifungal drug fluconazole, which binds to fungal cytochrome P450, has been labeled with ^{99m}Tc. In mouse models, ^{99m}Tc-fluconazole rapidly detected *Candida albicans* and *Aspergillus fumigatus* infections without visualizing bacterial infections or sterile inflammatory processes [205]. Biodistribution studies with ^{18}F-fluconazole in a rabbit model of infection, however, suggested non-specific uptake in the infection due to increased vascular permeability [206].

Antimicrobial peptides

Various natural and synthetic antimicrobial peptides have been investigated for specific imaging of bacterial infections. Neutrophil defensins or human neutrophil peptides (HNPs) are stored in the granules of neutrophils. In addition to their direct antimicrobial activity, these peptides have chemo-attractive activity for monocytes and lymphocytes. Use of ^{99m}Tc-HNP-1 in experimental thigh infections in mice resulted in low abscess-to-background ratios that decreased even further with time [207,208]. In these models, ^{99m}Tc-HNP-1 was shown to bind to bacteria rather than to leukocytes, but this agent still needs extensive optimization to enable reliable distinction between bacterial infection and sterile inflammation. Human antimicrobial peptide ubiquicidin (UBI) and human lactoferrin also bind to micro-organisms and have chemoattractive activity for monocytes and lymphocytes. ^{99m}Tc-labeled UBI 29-41 (residues 29–41 of ubiquicidin) and UBI 18-35 (residues 18–35 of ubiquicidin) do not accumulate in sterile inflammation and lack immunological adverse effects [209]. In animal models of bacterial and fungal infection, ^{99m}Tc-labeled fragments of UBI 29-41 and UBI 18-35 have better in vitro and in vivo behavior than human lactoferrin and defensin, showing higher binding activity to bacteria than to activated leukocytes [209-211].

Conclusions

Scintigraphy using autologous leukocytes, labeled with ^{111}In or ^{99m}Tc, is still considered the ”gold standard” nuclear medicine technique for the imaging of infection and inflammation, but the range of radiolabeled compounds available for this indication is expanding rapidly. A gradual shift from basic, non-specific, cumbersome and even hazardous techniques to more intelligent approaches, based on small agents binding to their targets with high affinity, is ongoing. In general, the lower

molecular weight should also lead to enhanced blood clearance reducing blood pool activity. New agents should also obviate the need to handle blood as this presents potential hazards of transmission of hepatitis virus or human immunodeficiency virus to both patients and medical personnel. Radiolabeled compounds are being designed enabling specific distinction between infection and non-infectious inflammatory disease and between acute and chronic processes. The ideal agent will thus be determined by the clinical situation. The advantages of ^{99m}Tc as a radionuclide will be fully explored. Labeling with high specific activity will reduce the doses used resulting in less undesirable agonistic activities. Undesirable agonistic activities will also be alleviated by chemical modification of the agonist. Furthermore, FDG-PET may prove to be as useful in the rapid detection and management of infectious and inflammatory diseases as it is in the management of malignant diseases.

References

1 Roitt IM. Essential immunology. 9th ed. Oxford: Blackwell Scientific, 1997.
2 Kubota R, Yamada S, Kubota K et al. Intratumoral distribution of fluorine-18-fluorodeoxyglucose in vivo: high accumulation in macrophages and granulation tissues studied by microautoradiography. J Nucl Med 1992;33:1972-1980.
3 Weiner R. The role of transferrin and other receptors in the mechanism of ^{67}Ga localization. Int J Rad Appl Instrum B 1990;17:141-149.
4 Hoffer P. Gallium: mechanisms. J Nucl Med 1980;21:282-285.
5 Palestro CJ. The current role of gallium imaging in infection. Semin Nucl Med 1994;24:128-141.
6 Perkins PJ. Early gallium-67 abdominal imaging: pitfalls due to bowel activity. AJR Am J Roentgenol 1981;136:1016-1017.
7 Bekerman C, Hoffer PB, Bitran JD. The role of gallium-67 in the clinical evaluation of cancer. Semin Nucl Med 1984;14: 296-323.
8 Knockaert DC, Mortelmans LA, De Roo MC, Bobbaers HJ. Clinical value of gallium-67 scintigraphy in evaluation of fever of unknown origin. Clin Infect Dis 1994;18:601-605.
9 Fischman AJ, Rubin RH, White JA et al. Localization of Fc and Fab fragments of nonspecific polyclonal IgG at focal sites of inflammation. J Nucl Med 1990;31:1199-1205.
10 Fischman AJ, Fucello AJ, Pellegrino-Gensey JL et al. Effect of carbohydrate modification on the localization of human polyclonal IgG at focal sites of bacterial infection. J Nucl Med 1992;33:1378-1382.
11 Dams ET, Oyen WJ, Boerman OC et al. Technetium-99m labeled to human immunoglobulin G through the nicotinyl hydrazine derivative: a clinical study. J Nucl Med 1998;39:119-124.
12 Chianelli M, Mather SJ, Martin-Comin J, Signore A. Radiopharmaceuticals for the study of inflammatory processes: a review. Nucl Med Commun 1997;18:437-455.
13 Oyen WJ, Claessens RA, van der Meer JW, Corstens FH. Detection of subacute infectious foci with indium-111-labeled autologous leukocytes and indium-111-labeled human nonspecific immunoglobulin G: a prospective comparative study. J Nucl Med 1991;32:1854-1860.
14 Oyen WJ, Claessens RA, van Horn JR, van der Meer JW, Corstens FH. Scintigraphic detection of bone and joint infections with indium-111- labeled nonspecific polyclonal human immunoglobulin G. J Nucl Med 1990;31:403-412.
15 Nijhof MW, Oyen WJ, van Kampen A et al. Evaluation of infections of the locomotor system with indium-111- labeled human IgG scintigraphy. J Nucl Med 1997;38:1300-1305.
16 Liberatore M, Clemente M, Iurilli AP et al. Scintigraphic evaluation of disease activity in rheumatoid arthritis: a comparison of technetium-99m human non-specific immunoglobulins, leucocytes and albumin nanocolloids. Eur J Nucl Med 1992;19:853-857.
17 Oyen WJ, Claessens RA, Raemaekers JM et al. Diagnosing infection in febrile granulocytopenic patients with indium-111-labeled human immunoglobulin G. J Clin Oncol 1992;10:61-68.
18 Buscombe JR, Oyen WJ, Grant A et al. Indium-111-labeled polyclonal human immunoglobulin: identifying focal infection in patients positive for human immunodeficiency virus. J Nucl Med 1993;34:1621-1625.

19 Buscombe JR, Oyen WJ, Corstens FH, Ell PJ, Miller RF. A comparison of ^{111}In-HIG scintigraphy and chest radiology in the identification of pulmonary infection in patients with HIV infection. Nucl Med Commun 1995;16:327-335.
20 Buscombe JR, Oyen WJ, Corstens FH. Use of polyclonal IgG in HIV infection and AIDS. Q J Nucl Med 1995;39:212-220.
21 Morgan JR, Williams LA, Howard CB. Technetium-labelled liposome imaging for deep-seated infection. Br J Radiol 1985;58:35-39.
22 Boerman OC, Storm G, Oyen WJ et al. Sterically stabilized liposomes labeled with indium-111 to image focal infection. J Nucl Med 1995;36:1639-1644.
23 Laverman P, Dams ET, Oyen WJ et al. A novel method to label liposomes with ^{99m}Tc by the hydrazino nicotinyl derivative. J Nucl Med 1999;40:192-197.
24 Oyen WJ, Boerman OC, Storm G et al. Labelled Stealth liposomes in experimental infection: an alternative to leukocyte scintigraphy? Nucl Med Commun 1996;17:742-748.
25 Oyen WJ, Boerman OC, Storm G et al. Detecting infection and inflammation with technetium-99m-labeled Stealth liposomes. J Nucl Med 1996;37:1392-1397.
26 Dams ET, Oyen WJ, Boerman OC et al. 99mTc-PEG liposomes for the scintigraphic detection of infection and inflammation: clinical evaluation. J Nucl Med 2000;41:622-630.
27 Brouwers AH, De Jong DJ, Dams ET et al. Tc-99m-PEG-Liposomes for the evaluation of colitis in Crohn's disease. J Drug Target 2000;8:225-233.
28 Szebeni J. Complement activation-related pseudoallergy caused by liposomes, micellar carriers of intravenous drugs, and radiocontrast agents. Crit Rev Ther Drug Carrier Syst 2001;18:567-606.
29 Rusckowski M, Fritz B, Hnatowich DJ. Localization of infection using streptavidin and biotin: an alternative to nonspecific polyclonal immunoglobulin. J Nucl Med 1992;33:1810-1815.
30 Samuel A, Paganelli G, Chiesa R et al. Detection of prosthetic vascular graft infection using avidin/indium- 111-biotin scintigraphy. J Nucl Med 1996;37:55-61.
31 Rusckowski M, Paganelli G, Hnatowich DJ et al. Imaging osteomyelitis with streptavidin and indium-111-labeled biotin. J Nucl Med 1996;37:1655-1662.
32 Lazzeri E, Manca M, Molea N et al. Clinical validation of the avidin/indium-111 biotin approach for imaging infection/inflammation in orthopaedic patients. Eur J Nucl Med 1999;26:606-614.
33 Rennen HJ, Makarewicz J, Oyen WJ et al. The effect of molecular weight on nonspecific accumulation of (99m)T-labeled proteins in inflammatory foci. Nucl Med Biol 2001;28:401-408.
34 Chapman PT, Jamar F, Keelan ET, Peters AM, Haskard DO. Use of a radiolabeled monoclonal antibody against E-selectin for imaging of endothelial activation in rheumatoid arthritis. Arthritis Rheum 1996;39:1371-1375.
35 Bhatti M, Chapman P, Peters M, Haskard D, Hodgson HJ. Visualising E-selectin in the detection and evaluation of inflammatory bowel disease. Gut 1998;43:40-47.
36 Jamar F, Houssiau FA, Devogelaer JP et al. Scintigraphy using a technetium 99m-labelled anti-E-selectin Fab fragment in rheumatoid arthritis. Rheumatology (Oxford) 2002;41:53-61.
37 Jamar F, Chapman PT, Manicourt DH et al. A comparison between ^{111}In-anti-E-selectin mAb and ^{99m}Tc-labelled human non-specific immunoglobulin in radionuclide imaging of rheumatoid arthritis. Br J Radiol 1997;70:473-481.
38 Gratz S, Behe M, Boerman OC et al. (99m)Tc-E-selectin binding peptide for imaging acute osteomyelitis in a novel rat model. Nucl Med Commun 2001;22:1003-1013.
39 Weiner RE, Sasso DE, Gionfriddo MA et al. Early detection of bleomycin-induced lung injury in rat using indium- 111-labeled antibody directed against intercellular adhesion molecule-1. J Nucl Med 1998;39:723-728.
40 Weiner RE, Sasso DE, Gionfriddo MA et al. Early detection of oleic acid-induced lung injury in rats using (111)In-labeled anti-rat intercellular adhesion molecule-1. J Nucl Med 2001;42:1109-1115.
41 Thakur ML and McAfee JG. The significance of chromosomal aberrations in indium-111-labeled lymphocytes. J Nucl Med 1984;25:922-927.
42 McAfee JG and Thakur ML. Survey of radioactive agents for in vitro labeling of phagocytic leukocytes. I. Soluble agents. J Nucl Med 1976;17:480-487.
43 Peters AM, Danpure HJ, Osman S et al. Clinical experience with 99mTc-hexamethylpropylene-amineoxime for labelling leucocytes and imaging inflammation. Lancet 1986;2:946-949.
44 Peters AM. The utility of [99mTc]HMPAO-leukocytes for imaging infection. Semin Nucl Med 1994;24:110-127.
45 Lange JM, Boucher CA, Hollak CE et al. Failure of zidovudine prophylaxis after accidental exposure to HIV-1. N Engl J Med 1990;322:1375-1377.
46 Fleury HJ, Pinson P, Faure M, Masquelier B, Dupon M. HIV-1 transmission during scintigraphy. Lancet 2003;362:210.

47 Liberatore M, Iurilli AP, Ponzo F et al. Clinical usefulness of technetium-99m-HMPAO-labeled leukocyte scan in prosthetic vascular graft infection. J Nucl Med 1998;39:875-879.

48 Larikka MJ, Ahonen AK, Junila JA et al. Extended combined ^{99m}Tc-white blood cell and bone imaging improves the diagnostic accuracy in the detection of hip replacement infections. Eur J Nucl Med 2001;28:288-293.

49 Datz FL and Thorne DA. Effect of chronicity of infection on the sensitivity of the In-111-labeled leukocyte scan. AJR Am J Roentgenol 1986;147:809-812.

50 Becker W, Goldenberg DM, Wolf F. The use of monoclonal antibodies and antibody fragments in the imaging of infectious lesions. Semin Nucl Med 1994;24:142-153.

51 Skehan SJ, White JF, Evans JW et al. Mechanism of accumulation of ^{99m}Tc-sulesomab in inflammation. J Nucl Med 2003;44:11-18.

52 Lipp RW, Wirnsberger GH, Ratschek M et al. The influence of vascular diathesis on the localization of inflammatory foci in renal allografts with a specific antigranulocyte antibody. Eur J Nucl Med 1996;23:395-400.

53 Joseph K, Hoffken H, Bosslet K, Schorlemmer HU. In vivo labelling of granulocytes with ^{99m}Tc anti-NCA monoclonal antibodies for imaging inflammation. Eur J Nucl Med 1988;14-8:367-373.

54 Lind P, Langsteger W, Koltringer P et al. Immunoscintigraphy of inflammatory processes with a technetium-99m-labeled monoclonal antigranulocyte antibody (MAb BW 250/183). J Nucl Med 1990;31:417-423.

55 Steinstrasser A and Oberhausen E. Granulocyte labelling kit BW 250/183--results of the European multicenter trial. Nuklearmedizin 1996;35:1-11.

56 Morguet AJ, Munz DL, Ivancevic V et al. Immunoscintigraphy using technetium-99m-labeled anti-NCA-95 antigranulocyte antibodies as an adjunct to echocardiography in subacute infective endocarditis. J Am Coll Cardiol 1994;23:1171-1178.

57 Peltier P, Potel G, Lovat E, Baron D, Chatal JF. Detection of lung and bone infection with anti-granulocyte monoclonal antibody BW 250/183 radiolabelled with ^{99m}Tc. Nucl Med Commun 1993;14:766-774.

58 Boubaker A, Delaloye AB, Blanc CH et al. Immunoscintigraphy with antigranulocyte monoclonal antibodies for the diagnosis of septic loosening of hip prostheses. Eur J Nucl Med 1995;22:139-147.

59 Klett R, Kordelle J, Stahl U et al. Immunoscintigraphy of septic loosening of knee endoprosthesis: a retrospective evaluation of the antigranulocyte antibody BW 250/183. Eur J Nucl Med Mol Imaging 2003;30:1463-1466.

60 Dominguez-Gadea L, Martin-Curto LM, de la CH, Crespo A. Diabetic foot infections: scintigraphic evaluation with ^{99m}Tc-labelled anti-granulocyte antibodies. Nucl Med Commun 1993;14:212-218.

61 Scheidler J, Leinsinger G, Pfahler M, Kirsch CM. Diagnosis of osteomyelitis. Accuracy and limitations of antigranulocyte antibody imaging compared to three-phase bone scan. Clin Nucl Med 1994;19:731-737.

62 Gratz S, Braun HG, Behr TM et al. Photopenia in chronic vertebral osteomyelitis with technetium-99m-antigranulocyte antibody (BW 250/183). J Nucl Med 1997;38:211-216.

63 Prvulovich EM, Miller RF, Costa DC et al. Immunoscintigraphy with a ^{99m}Tc-labelled anti-granulocyte monoclonal antibody in patients with human immunodeficiency virus infection and AIDS. Nucl Med Commun 1995;16:838-845.

64 Gratz S, Behr TM, Herrmann A et al. Immunoscintigraphy (BW 250/183) in neonates and infants with fever of unknown origin. Nucl Med Commun 1998;19:1037-1045.

65 Segarra I, Roca M, Baliellas C et al. Granulocyte-specific monoclonal antibody technetium-99m-BW 250/183 and indium-111 oxine-labelled leucocyte scintigraphy in inflammatory bowel disease. Eur J Nucl Med 1991;18:715-719.

66 Papos M, Nagy F, Narai G et al. Anti-granulocyte immunoscintigraphy and [99mTc]hexamethylpropyleneamine-oxime-labeled leukocyte scintigraphy in inflammatory bowel disease. Dig Dis Sci 1996;41:412-420.

67 Gyorke T, Duffek L, Bartfai K et al. The role of nuclear medicine in inflammatory bowel disease. A review with experiences of aspecific bowel activity using immunoscintigraphy with ^{99m}Tc anti-granulocyte antibodies. Eur J Radiol 2000;35:183-192.

68 Rennen HJ, Boerman OC, Oyen WJ, Corstens FH. Imaging infection/inflammation in the new millennium. Eur J Nucl Med 2001;28:241-252.

69 Thakur ML, Marcus CS, Henneman P et al. Imaging inflammatory diseases with neutrophil-specific technetium-99m-labeled monoclonal antibody anti-SSEA-1. J Nucl Med 1996;37:1789-1795.

70 Gratz S, Behr T, Herrmann A et al. Intraindividual comparison of 99mTc-labelled anti-SSEA-1 antigranulocyte antibody and ^{99m}Tc-HMPAO labelled white blood cells for the imaging of infection. Eur J Nucl Med 1998;25:386-393.

71 Thakur ML, Marcus CS, Kipper SL et al. Imaging infection with LeuTech. Nucl Med Commun 2001;22:513-519.

72 LeuTech. BioDrugs 2002;16:319-320.

73 Kipper SL, Rypins EB, Evans DG et al. Neutrophil-specific ^{99m}Tc-labeled anti-CD15 monoclonal antibody imaging for diagnosis of equivocal appendicitis. J Nucl Med 2000;41:449-455.

74 Rypins EB and Kipper SL. Scintigraphic determination of equivocal appendicitis. Am Surg 2000;66:891-895.
75 Signore A, Annovazzi A, Corsetti F et al. Biological imaging for the diagnosis of inflammatory conditions. BioDrugs 2002;16:241-259.
76 Gratz S, Raddatz D, Hagenah G et al. 99mTC-labelled antigranulocyte monoclonal antibody FAB' fragments versus echocardiography in the diagnosis of subacute infective endocarditis. Int J Cardiol 2000;75:75-84.
77 Barron B, Hanna C, Passalaqua AM et al. Rapid diagnostic imaging of acute, nonclassic appendicitis by leukoscintigraphy with sulesomab, a technetium 99m-labeled antigranulocyte antibody Fab' fragment. LeukoScan Appendicitis Clinical Trial Group. Surgery 1999;125:288-296.
78 Maugeri D, Santangelo A, Abbate S et al. A new method for diagnosing fever of unknown origin (FUO) due to infection of muscular-skeletal system in elderly people: leukoscan Tc- 99m labelled scintigraphy. Eur Rev Med Pharmacol Sci 2001;5:123-126.
79 Stokkel MP, Reigman HE, Pauwels EK. Scintigraphic head-to-head comparison between ^{99m}Tc-WBCs and ^{99m}Tc-LeukoScan in the evaluation of inflammatory bowel disease: a pilot study. Eur J Nucl Med Mol Imaging 2002;29: 251-254.
80 Charron M, Di Lorenzo C, Kocoshis SA et al. (99m)Tc antigranulocyte monoclonal antibody imaging for the detection and assessment of inflammatory bowel disease newly diagnosed by colonoscopy in children. Pediatr Radiol 2001;31: 796-800.
81 Ivancevic V, Wolter A, Munz DL. Nonspecific bowel activity in imaging inflammation with Tc-99m labelled monoclonal anti-NCA-90 Fab' fragment MN3. Nuklearmedizin 2001;40:71-74.
82 Becker W, Bair J, Behr T et al. Detection of soft-tissue infections and osteomyelitis using a technetium-99m-labeled anti-granulocyte monoclonal antibody fragment. J Nucl Med 1994;35:1436-1443.
83 Becker W, Palestro CJ, Winship J et al. Rapid imaging of infections with a monoclonal antibody fragment (LeukoScan). Clin Orthop 1996;(329):263-272.
84 Harwood SJ, Valdivia S, Hung GL, Quenzer RW. Use of Sulesomab, a radiolabeled antibody fragment, to detect osteomyelitis in diabetic patients with foot ulcers by leukoscintigraphy. Clin Infect Dis 1999;28:1200-1205.
85 Hakki S, Harwood SJ, Morrissey MA et al. Comparative study of monoclonal antibody scan in diagnosing orthopaedic infection. Clin Orthop 1997;(335):275-285.
86 Devillers A, Garin E, Polard JL et al. Comparison of Tc-99m-labelled antileukocyte fragment Fab' and Tc-99m- HMPAO leukocyte scintigraphy in the diagnosis of bone and joint infections: a prospective study. Nucl Med Commun 2000;21:747-753.
87 Ivancevic V, Perka C, Hasart O et al. Imaging of low-grade bone infection with a technetium-99m labelled monoclonal anti-NCA-90 Fab' fragment in patients with previous joint surgery. Eur J Nucl Med Mol Imaging 2002;29:547-551.
88 Ryan PJ. Leukoscan for orthopaedic imaging in clinical practice. Nucl Med Commun 2002;23:707-714.
89 Gratz S, Schipper ML, Dorner J et al. LeukoScan for Imaging Infection in Different Clinical Settings: A Retrospective Evaluation and Extended Review of the Literature. Clin Nucl Med 2003;28:267-276.
90 Babich JW, Tompkins RG, Graham W, Barrow SA, Fischman AJ. Localization of radiolabeled chemotactic peptide at focal sites of Escherichia coli infection in rabbits: evidence for a receptor-specific mechanism. J Nucl Med 1997;38: 1316-1322.
91 Babich JW, Graham W, Barrow SA et al. Technetium-99m-labeled chemotactic peptides: comparison with indium-111-labeled white blood cells for localizing acute bacterial infection in the rabbit. J Nucl Med 1993;34:2176-2181.
92 Fischman AJ, Babich JW, Barrow SA et al. Detection of acute bacterial infection within soft tissue injuries using a ^{99m}Tc-labeled chemotactic peptide. J Trauma 1995;38:223-227.
93 van der Laken CJ, Boerman OC, Oyen WJ et al. Technetium-99m-labeled chemotactic peptides in acute infection and sterile inflammation. J Nucl Med 1997;38:1310-1315.
94 Hartwig W, Carter EA, Jimenez RE et al. Chemotactic peptide uptake in acute pancreatitis: correlation with tissue accumulation of leukocytes. J Appl Physiol 1999;87:743-749.
95 Fischman AJ, Rauh D, Solomon H et al. In vivo bioactivity and biodistribution of chemotactic peptide analogs in nonhuman primates. J Nucl Med 1993;34:2130-2134.
96 Pollak A, Goodbody AE, Ballinger JR et al. Imaging inflammation with ^{99m}Tc-labeled chemotactic peptides: analogues with reduced neutropenia. Nucl Med Commun 1996;17:132-139.
97 van der Laken CJ, Boerman OC, Oyen WJ et al. Specific targeting of infectious foci with radioiodinated human recombinant interleukin-1 in an experimental model. Eur J Nucl Med 1995;22:1249-1255.
98 van der Laken CJ, Boerman OC, Oyen WJ et al. Imaging of infection in rabbits with radioiodinated interleukin-1 (alpha and beta), its receptor antagonist and a chemotactic peptide: a comparative study. Eur J Nucl Med 1998;25:347-352.

99 van der Laken CJ, Boerman OC, Oyen WJ et al. Preferential localization of systemically administered radiolabeled interleukin 1alpha in experimental inflammation in mice by binding to the type II receptor. J Clin Invest 1997;100: 2970-2976.

100 Granowitz EV, Porat R, Mier JW et al. Pharmacokinetics, safety and immunomodulatory effects of human recombinant interleukin-1 receptor antagonist in healthy humans. Cytokine 1992;4:353-360.

101 van der Laken CJ, Boerman OC, Oyen WJ et al. Different behaviour of radioiodinated human recombinant interleukin-1 and its receptor antagonist in an animal model of infection. Eur J Nucl Med 1996;23:1531-1535.

102 Barrera P, van der Laken CJ, Boerman OC et al. Radiolabelled interleukin-1 receptor antagonist for detection of synovitis in patients with rheumatoid arthritis. Rheumatology (Oxford) 2000;39:870-874.

103 Hay RV, Skinner RS, Newman OC et al. Scintigraphy of acute inflammatory lesions in rats with radiolabelled recombinant human interleukin-8. Nucl Med Commun 1997;18:367-378.

104 Gross MD, Shapiro B, Fig LM et al. Imaging of human infection with (131)I-labeled recombinant human interleukin-8. J Nucl Med 2001;42:1656-1659.

105 van der Laken CJ, Boerman OC, Oyen WJ et al. Radiolabeled interleukin-8: specific scintigraphic detection of infection within a few hours. J Nucl Med 2000;41:463-469.

106 Rennen HJ, van Eerd JE, Oyen WJ et al. Effects of coligand variation on the in vivo characteristics of Tc-99m-labeled interleukin-8 in detection of infection. Bioconjug Chem 2002;13:370-377.

107 Rennen HJ, Boerman OC, Oyen WJ, van der Meer JW, Corstens FH. Specific and rapid scintigraphic detection of infection with ^{99m}Tc- labeled interleukin-8. J Nucl Med 2001;42:117-123.

108 Gratz S, Rennen HJ, Boerman OC et al. (99m)Tc-interleukin-8 for imaging acute osteomyelitis. J Nucl Med 2001;42: 1257-1264.

109 Gratz S, Rennen HJ, Boerman OC, Oyen WJ, Corstens FH. Rapid imaging of experimental colitis with (99m)Tc-interleukin-8 in rabbits. J Nucl Med 2001;42:917-923.

110 Rennen HJ, Boerman OC, Oyen WJ, Corstens FH. Kinetics of (99m)tc-labeled interleukin-8 in experimental inflammation and infection. J Nucl Med 2003;44:1502-1509.

111 Moyer BR, Vallabhajosula S, Lister-James J et al. Technetium-99m-white blood cell-specific imaging agent developed from platelet factor 4 to detect infection. J Nucl Med 1996;37:673-679.

112 Palestro CJ, Weiland FL, Seabold JE et al. Localizing infection with a technetium-99m-labeled peptide: initial results. Nucl Med Commun 2001;22:695-701.

113 Rennen HJ, Oyen WJ, Cain SA et al. Tc-99m-labeled C5a and C5a des Arg(74) for infection imaging. Nucl Med Biol 2003;30:267-272.

114 Brouwers AH, Laverman P, Boerman OC et al. A ^{99m}Tc-labelled leukotriene B4 receptor antagonist for scintigraphic detection of infection in rabbits. Nucl Med Commun 2000;21:1043-1050.

115 Riou LM, Ruiz M, Sullivan GW et al. Assessment of myocardial inflammation produced by experimental coronary occlusion and reperfusion with ^{99m}Tc-RP517, a new leukotriene B4 receptor antagonist that preferentially labels neutrophils in vivo. Circulation 2002;106:592-598.

116 van Eerd JE, Oyen WJ, Harris TD et al. A bivalent leukotriene B(4) antagonist for scintigraphic imaging of infectious foci. J Nucl Med 2003;44:1087-1091.

117 Rusckowski M, Qu T, Pullman J et al. Inflammation and infection imaging with a 99mTc-neutrophil elastase inhibitor in monkeys. J Nucl Med 2000;41:363-374.

118 Signore A, Parman A, Pozzilli P, Andreani D, Beverley PC. Detection of activated lymphocytes in endocrine pancreas of BB/W rats by injection of ^{123}I-interleukin-2: an early sign of type 1 diabetes. Lancet 1987;2:537-540.

119 Signore A, Chianelli M, Toscano A et al. A radiopharmaceutical for imaging areas of lymphocytic infiltration: ^{123}I-interleukin-2. Labelling procedure and animal studies. Nucl Med Commun 1992;13:713-722.

120 Abbs IC, Pratt JR, Dallman MJ, Sacks SH. Analysis of activated T cell infiltrates in rat renal allografts by gamma camera imaging after injection of ^{123}iodine-interleukin 2. Transpl Immunol 1993;1:45-51.

121 Signore A, Picarelli A, Chianelli M et al. I-interleukin-2 scintigraphy: a new approach to assess disease activity in autoimmunity. J Pediatr Endocrinol Metab 1996;9:139-144.

122 Signore A, Chianelli M, Parisella MG et al. In vivo imaging of insulitis in autoimmune diabetes. J Endocrinol Invest 1999;22:151-158.

123 Signore A, Chianelli M, Annovazzi A et al. ^{123}I-interleukin-2 scintigraphy for in vivo assessment of intestinal mononuclear cell infiltration in Crohn's disease. J Nucl Med 2000;41:242-249.

124 Signore A, Chianelli M, Annovazzi A et al. Imaging active lymphocytic infiltration in coeliac disease with iodine- 123-interleukin-2 and the response to diet. Eur J Nucl Med 2000;27:18-24.

125 Procaccini E, Chianelli M, Pantano P, Signore A. Imaging of autoimmune diseases. Q J Nucl Med 1999;43:100-112.
126 Ohtsuki K, Hayase M, Akashi K, Kopiwoda S, Strauss HW. Detection of monocyte chemoattractant protein-1 receptor expression in experimental atherosclerotic lesions: an autoradiographic study. Circulation 2001;104:203-208.
127 Blankenberg FG, Tait JF, Blankenberg TA, Post AM, Strauss HW. Imaging macrophages and the apoptosis of granulocytes in a rodent model of subacute and chronic abscesses with radiolabeled monocyte chemotactic peptide-1 and annexin V. Eur J Nucl Med 2001;28:1384-1393.
128 Paul C, Peers SH, Woodhouse LE et al. The detection and quantitation of inflammation in the central nervous system during experimental allergic encephalomyelitis using the radiopharmaceutical ^{99m}Tc-RP128. J Neurosci Methods 2000;98:83-90.
129 Caveliers V, Goodbody AE, Tran LL et al. Evaluation of ^{99m}Tc-RP128 as a potential inflammation imaging agent: human dosimetry and first clinical results. J Nucl Med 2001;42:154-161.
130 Diot P, Le Pape A, Nolibe D et al. Scintigraphy with J001X, a Klebsiella membrane glycolipid, for the early diagnosis of chronic berylliosis: results from an experimental model. Br J Ind Med 1992;49:359-364.
131 Perin F, Pittet JC, Hoffschir D et al. Scintigraphic potentials of J001X acylated poly-galactoside for imaging inflammatory lesions in pigs. Nucl Med Biol 1993;20:963-971.
132 Goupille P, Valat JP, Le Pape A. Imaging of synovitis in rheumatoid arthritis with radionuclide tracers. J Rheumatol 1994;21:1975-1976.
133 Miot-Noirault E, Perin F, Routledge L, Normier G, Le Pape A. Macrophage targeting with technetium-99m labelled J001 acylated poly- galactoside for scintigraphy of inflammation: optimization and assessment of imaging specificity in experimental arthritis. Eur J Nucl Med 1996;23:61-68.
134 Diot P, Lemarie E, Baulieu JL et al. Scintigraphy with J001 macrophage targeting glycolipopeptide. A new approach for sarcoidosis imaging. Chest 1992;102:670-676.
135 Diot P, Diot E, Lemarie E et al. Imaging of pulmonary disease in scleroderma with J001X scintigraphy. Thorax 1994;49: 504-508.
136 Goupille P, Diot P, Valat JP et al. Imaging of pulmonary disease in rheumatoid arthritis using J001X scintigraphy: preliminary results. Eur J Nucl Med 1995;22:1411-1415.
137 Kinne RW, Becker W, Simon G et al. Joint uptake and body distribution of a technetium-99m-labeled anti-rat- CD4 monoclonal antibody in rat adjuvant arthritis. J Nucl Med 1993;34:92-98.
138 Kinne RW, Becker W, Koscheck T et al. Rat adjuvant arthritis: imaging with technetium-99m-anti-CD4 Fab' fragments. J Nucl Med 1995;36:2268-2275.
139 Kinne RW, Becker W, Schwab J et al. Comparison of ^{99m}Tc-labelled specific murine anti-CD4 monoclonal antibodies and nonspecific human immunoglobulin for imaging inflamed joints in rheumatoid arthritis. Nucl Med Commun 1993;14:667-675.
140 Kinne RW, Wolski A, Palombo-Kinne E et al. Minimal contribution of cell-bound antibodies to the immunoscintigraphy of inflamed joints with ^{99m}Tc-anti-CD4 monoclonal antibodies. Nuklearmedizin 2002;41:129-134.
141 Yamada S, Kubota K, Kubota R, Ido T, Tamahashi N. High accumulation of fluorine-18-fluorodeoxyglucose in turpentine- induced inflammatory tissue. J Nucl Med 1995;36:1301-1306.
142 Sugawara Y, Gutowski TD, Fisher SJ, Brown RS, Wahl RL. Uptake of positron emission tomography tracers in experimental bacterial infections: a comparative biodistribution study of radiolabeled FDG, thymidine, L-methionine, 67Ga-citrate, and 125I-HSA. Eur J Nucl Med 1999;26:333-341.
143 Tahara T, Ichiya Y, Kuwabara Y et al. High [18F]-fluorodeoxyglucose uptake in abdominal abscesses: a PET study. J Comput Assist Tomogr 1989;13:829-831.
144 De Winter F, Vogelaers D, Gemmel F, Dierckx RA. Promising role of 18-F-fluoro-D-deoxyglucose positron emission tomography in clinical infectious diseases. Eur J Clin Microbiol Infect Dis 2002;21:247-257.
145 Zhuang H and Alavi A. 18-fluorodeoxyglucose positron emission tomographic imaging in the detection and monitoring of infection and inflammation. Semin Nucl Med 2002;32:47-59.
146 Blockmans D, Knockaert D, Maes A et al. Clinical value of [(18)F]fluoro-deoxyglucose positron emission tomography for patients with fever of unknown origin. Clin Infect Dis 2001;32:191-196.
147 Meller J, Altenvoerde G, Munzel U et al. Fever of unknown origin: prospective comparison of [18F]FDG imaging with a double-head coincidence camera and gallium-67 citrate SPET. Eur J Nucl Med 2000;27:1617-1625.
148 Lorenzen J, Buchert R, Bohuslavizki KH. Value of FDG PET in patients with fever of unknown origin. Nucl Med Commun 2001;22:779-783.
149 Bleeker-Rovers CP, de Kleijn EM, Corstens FH, van der Meer JW, Oyen WJ. Clinical value of FDG PET in patients with fever of unknown origin and patients suspected of focal infection or inflammation. Eur J Nucl Med Mol Imaging 2004;31:29-37.

150 Blockmans D, Stroobants S, Maes A, Mortelmans L. Positron emission tomography in giant cell arteritis and polymyalgia rheumatica: evidence for inflammation of the aortic arch. Am J Med 2000;108:246-249.

151 Peters AM. Nuclear medicine in vasculitis. Rheumatology (Oxford) 2000;39:463-470.

152 Bleeker-Rovers CP, Bredie SJ, van der Meer JW, Corstens FH, Oyen WJ. Fluorine 18 fluorodeoxyglucose positron emission tomography in the diagnosis and follow-up of three patients with vasculitis. Am J Med 2004;116:50-53.

153 Kalicke T, Schmitz A, Risse JH et al. Fluorine-18 fluorodeoxyglucose PET in infectious bone diseases: results of histologically confirmed cases. Eur J Nucl Med 2000;27:524-528.

154 Sugawara Y, Braun DK, Kison PV et al. Rapid detection of human infections with fluorine-18 fluorodeoxyglucose and positron emission tomography: preliminary results. Eur J Nucl Med 1998;25:1238-1243.

155 Guhlmann A, Brecht-Krauss D, Suger G et al. Fluorine-18-FDG PET and technetium-99m antigranulocyte antibody scintigraphy in chronic osteomyelitis. J Nucl Med 1998;39:2145-2152.

156 De Winter F, van de WC, Vogelaers D et al. Fluorine-18 fluorodeoxyglucose-position emission tomography: a highly accurate imaging modality for the diagnosis of chronic musculoskeletal infections. J Bone Joint Surg Am 2001;28: 651-660.

157 Zhuang H, Duarte PS, Pourdehand M, Shnier D, Alavi A. Exclusion of chronic osteomyelitis with F-18 fluorodeoxyglucose positron emission tomographic imaging. Clin Nucl Med 2000;25:281-284.

158 Meller J, Koster G, Liersch T et al. Chronic bacterial osteomyelitis: prospective comparison of (18)F-FDG imaging with a dual-head coincidence camera and (111)In-labelled autologous leucocyte scintigraphy. Eur J Nucl Med Mol Imaging 2002;29:53-60.

159 Chacko TK, Zhuang H, Nakhoda KZ, Moussavian B, Alavi A. Applications of fluorodeoxyglucose positron emission tomography in the diagnosis of infection. Nucl Med Commun 2003;24:615-624.

160 Gratz S, Dorner J, Fischer U et al. 18F-FDG hybrid PET in patients with suspected spondylitis. Eur J Nucl Med Mol Imaging 2002;29:516-524.

161 Schmitz A, Risse JH, Grunwald F et al. Fluorine-18 fluorodeoxyglucose positron emission tomography findings in spondylodiscitis: preliminary results. Eur Spine J 2001;10:534-539.

162 Stumpe KD, Zanetti M, Weishaupt D et al. FDG positron emission tomography for differentiation of degenerative and infectious endplate abnormalities in the lumbar spine detected on MR imaging. AJR Am J Roentgenol 2002;179: 1151-1157.

163 Zhuang H, Chacko TK, Hickeson M et al. Persistent non-specific FDG uptake on PET imaging following hip arthroplasty. Eur J Nucl Med Mol Imaging 2002;29:1328-1333.

164 Love C, Pugliese PV, Afriyie MO et al. 5. Utility of F-18 FDG Imaging for Diagnosing the Infected Joint Replacement. Clin Positron Imaging 2000;3:159.

165 Van Acker F, Nuyts J, Maes A et al. FDG-PET, ^{99m}tc-HMPAO white blood cell SPET and bone scintigraphy in the evaluation of painful total knee arthroplasties. Eur J Nucl Med 2001;28:1496-1504.

166 Manthey N, Reinhard P, Moog F et al. The use of [18 F]fluorodeoxyglucose positron emission tomography to differentiate between synovitis, loosening and infection of hip and knee prostheses. Nucl Med Commun 2002;23: 645-653.

167 Kisielinski K, Cremerius U, Reinartz P, Niethard FU. Fluordeoxyglucose positron emission tomography detection of inflammatory reactions due to polyethylene wear in total hip arthroplasty. J Arthroplasty 2003;18:528-532.

168 Chacko TK, Zhuang H, Stevenson K, Moussavian B, Alavi A. The importance of the location of fluorodeoxyglucose uptake in periprosthetic infection in painful hip prostheses. Nucl Med Commun 2002;23:851-855.

169 Stumpe KD, Dazzi H, Schaffner A, von Schulthess GK. Infection imaging using whole-body FDG-PET. Eur J Nucl Med 2000;27:822-832.

170 Gungor T, Engel-Bicik I, Eich G et al. Diagnostic and therapeutic impact of whole body positron emission tomography using fluorine-18-fluoro-2-deoxy-D-glucose in children with chronic granulomatous disease. Arch Dis Child 2001;85: 341-345.

171 Reuter S, Schirrmeister H, Kratzer W et al. Pericystic metabolic activity in alveolar echinococcosis: assessment and follow-up by positron emission tomography. Clin Infect Dis 1999;29:1157-1163.

172 Bleeker-Rovers CP, Sevaux RG, Van Hamersvelt HW, Corstens FH, Oyen WJ. Diagnosis of renal and hepatic cyst infections by 18-F- fluorodeoxyglucose positron emission tomography in autosomal dominant polycystic kidney disease. Am J Kidney Dis 2003;41:E18-E21.

173 O'Doherty MJ, Barrington SF, Campbell M, Lowe J, Bradbeer CS. PET scanning and the human immunodeficiency virus-positive patient. J Nucl Med 1997;38:1575-1583.

174 Santiago JF, Jana S, Gilbert HM et al. Role of Fluorine-18-fluorodeoxyglucose in the work-up of febrile AIDS patients: experience with dual head coincedence imaging. Clinical Positron Imaging 1999;2:301-309.

175 De Winter F, Petrovic M, van de WC et al. Imaging of giant cell arteritis: evidence of splenic involvement using FDG positron emission tomography. Clin Nucl Med 2000;25:633-634.

176 Turlakow A, Yeung HW, Pui J et al. Fludeoxyglucose positron emission tomography in the diagnosis of giant cell arteritis. Arch Intern Med 2001;161:1003-1007.

177 Malik IS, Harare O, AL Nahhas A, Beatt K, Mason J. Takayasu's arteritis: management of left main stem stenosis. Heart 2003;89:e9.

178 Meller J, Grabbe E, Becker W, Vosshenrich R. Value of F-18 FDG hybrid camera PET and MRI in early takayasu aortitis. Eur Radiol 2003;13:400-405.

179 Belhocine T, Blockmans D, Hustinx R, Vandevivere J, Mortelmans L. Imaging of large vessel vasculitis with (18)FDG PET: illusion or reality? A critical review of the literature data. Eur J Nucl Med Mol Imaging 2003;30:1305-1313.

180 Wenger M, Gasser R, Donnemiller E et al. Images in cardiovascular medicine. Generalized large vessel arteritis visualized by 18fluorodeoxyglucose-positron emission tomography. Circulation 2003;107:923

181 Meller J, Strutz F, Siefker U et al. Early diagnosis and follow-up of aortitis with [(18)F]FDG PET and MRI. Eur J Nucl Med Mol Imaging 2003;5:730-736.

182 Bleeker-Rovers CP, Bredie SJ, van der Meer JW, Corstens FH, Oyen WJ. F-18-fluorodeoxyglucose positron emission tomography in diagnosis and follow-up of patients with different types of vasculitis. Neth J Med 2003;61:323-329.

183 Bicik I, Bauerfeind P, Breitbach T, von Schulthess GK, Fried M. Inflammatory bowel disease activity measured by positron-emission tomography. Lancet 1997;350:262.

184 Skehan SJ, Issenman R, Mernagh J, Nahmias C, Jacobson K. ^{18}F-fluorodeoxyglucose positron tomography in diagnosis of paediatric inflammatory bowel disease. Lancet 1999;354:836-837.

185 Neurath MF, Vehling D, Schunk K et al. Noninvasive assessment of Crohn's disease activity: a comparison of ^{18}F-fluorodeoxyglucose positron emission tomography, hydromagnetic resonance imaging, and granulocyte scintigraphy with labeled antibodies. Am J Gastroenterol 2002;97:1978-1985.

186 Kresnik E, Gallowitsch HJ, Mikosch P et al. (18)F-FDG positron emission tomography in the early diagnosis of enterocolitis: preliminary results. Eur J Nucl Med Mol Imaging 2002;29:1389-1392.

187 Lewis PJ and Salama A. Uptake of fluorine-18-fluorodeoxyglucose in sarcoidosis. J Nucl Med 1994;35:1647-1649.

188 Brudin LH, Valind SO, Rhodes CG et al. Fluorine-18 deoxyglucose uptake in sarcoidosis measured with positron emission tomography. Eur J Nucl Med 1994;21:297-305.

189 Palmer WE, Rosenthal DI, Schoenberg OI et al. Quantification of inflammation in the wrist with gadolinium-enhanced MR imaging and PET with 2-[F-18]-fluoro-2-deoxy-D-glucose. Radiology 1995;196:647-655.

190 De Winter F, van de WC, Dumont F et al. Biodistribution and dosimetry of 99mTc-ciprofloxacin, a promising agent for the diagnosis of bacterial infection. Eur J Nucl Med 2001;28:570-574.

191 Vinjamuri S, Hall AV, Solanki KK et al. Comparison of ^{99m}Tc infecton imaging with radiolabelled white-cell imaging in the evaluation of bacterial infection. Lancet 1996;347:233-235.

192 Hall AV, Solanki KK, Vinjamuri S, Britton KE, Das SS. Evaluation of the efficacy of 99mTc-Infecton, a novel agent for detecting sites of infection. J Clin Pathol 1998;51:215-219.

193 Sundram FX, Wong WY, Ang ES et al. Evaluation of technetium-99m ciprofloxacin (Infecton) in the imaging of infection. Ann Acad Med Singapore 2000;29:699-703.

194 Britton KE, Wareham DW, Das SS et al. Imaging bacterial infection with (99m)Tc-ciprofloxacin (Infecton). J Clin Pathol 2002;55:817-823.

195 Sonmezoglu K, Sonmezoglu M, Halac M et al. Usefulness of ^{99m}Tc-ciprofloxacin (infecton) scan in diagnosis of chronic orthopedic infections: comparative study with 99mTc-HMPAO leukocyte scintigraphy. J Nucl Med 2001;42:567-574.

196 Yapar Z, Kibar M, Yapar AF et al. The efficacy of technetium-99m ciprofloxacin (Infecton) imaging in suspected orthopaedic infection: a comparison with sequential bone/gallium imaging. Eur J Nucl Med 2001;28:822-830.

197 Malamitsi J, Giamarellou H, Kanellakopoulou K et al. Infecton: a ^{99m}Tc-ciprofloxacin radiopharmaceutical for the detection of bone infection. Clin Microbiol Infect 2003;9:101-109.

198 Larikka MJ, Ahonen AK, Niemela O et al. Comparison of ^{99m}Tc ciprofloxacin, ^{99m}Tc white blood cell and three- phase bone imaging in the diagnosis of hip prosthesis infections: improved diagnostic accuracy with extended imaging time. Nucl Med Commun 2002;23:655-661.

199 Larikka MJ, Ahonen AK, Niemela O et al. ^{99m}Tc-ciprofloxacin (Infecton) imaging in the diagnosis of knee prosthesis infections. Nucl Med Commun 2002;23:167-170.

200 Sharma R, Mondal A, Sharma M et al. Tc-99m Infecton scan in possible pelvic inflammatory disease. Clin Nucl Med 2001;26:208-211.

201 Solanki KK, Das SS, Britton KE. Infection is not specific for bacterial osteo-articular infective pathology. Eur J Nucl Med Mol Imaging 2003;30:181-182.

202 Sarda L, Saleh-Mghir A, Peker C et al. Evaluation of (99m)Tc-ciprofloxacin scintigraphy in a rabbit model of Staphylococcus aureus prosthetic joint infection. J Nucl Med 2002;43:239-245.
203 Sarda L, Cremieux AC, Lebellec Y et al. Inability of ^{99m}Tc-ciprofloxacin scintigraphy to discriminate between septic and sterile osteoarticular diseases. J Nucl Med 2003;44:920-926.
204 Dumarey N, Blocklet D, Appelboom T, Tant L, Schoutens A. Infecton is not specific for bacterial osteo-articular infective pathology. Eur J Nucl Med Mol Imaging 2002;29:530-535.
205 Lupetti A, Welling MM, Mazzi U, Nibbering PH, Pauwels EK. Technetium-99m labelled fluconazole and antimicrobial peptides for imaging of Candida albicans and Aspergillus fumigatus infections. Eur J Nucl Med Mol Imaging 2002;29: 674-679.
206 Fischman AJ, Alpert NM, Livni E et al. Pharmacokinetics of ^{18}F-labeled fluconazole in rabbits with candidal infections studied with positron emission tomography. J Pharmacol Exp Ther 1991;259:1351-1359.
207 Welling MM, Hiemstra PS, van den Barselaar MT et al. Antibacterial activity of human neutrophil defensins in experimental infections in mice is accompanied by increased leukocyte accumulation. J Clin Invest 1998;102:1583-1590.
208 Welling MM, Nibbering PH, Paulusma-Annema A et al. Imaging of bacterial infections with ^{99m}Tc-labeled human neutrophil peptide-1. J Nucl Med 1999;40:2073-2080.
209 Lupetti A, Welling MM, Pauwels EK, Nibbering PH. Radiolabelled antimicrobial peptides for infection detection. Lancet Infect Dis 2003;3:223-229.
210 Welling MM, Lupetti A, Balter HS et al. ^{99m}Tc-labeled antimicrobial peptides for detection of bacterial and Candida albicans infections. J Nucl Med 2001;42:788-794.
211 Welling MM, Paulusma-Annema A, Balter HS, Pauwels EK, Nibbering PH. Technetium-99m labelled antimicrobial peptides discriminate between bacterial infections and sterile inflammations. Eur J Nucl Med 2000;27:292-301.

Chapter 2.1

^{18}F-fluorodeoxyglucose positron emission tomography in the diagnosis and follow-up of three patients with vasculitis

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Introduction

Vasculitis is a serious condition characterized by inflammation and necrosis of the blood vessel walls. Early and accurate assessment is important for successful management; however, diagnosis can be complicated by the absence of specific symptoms and signs, the limited specificity of biochemical tests, and the limitations of conventional imaging techniques in detecting frequently subtle vessel abnormalities. Although the American College of Rheumatology 1990 criteria for the classification of vasculitis (ACR criteria) are considered the gold standard for diagnosing vasculitis [1-11], diagnosis and assessment of the extent and location of the disease is often difficult or sometimes impossible. In a study of 198 patients suspected of vasculitis, these criteria were not effective in diagnosing specific types of vasculitis [12].

Imaging techniques are used in types of vasculitis in which it is difficult to obtain histological proof and may also be used to guide selection of a site for biopsy. In addition, a noninvasive tool to evaluate the effect of treatment during follow-up is warranted. In this respect, it would be more helpful to evaluate metabolic activity in the vessel wall. For this purpose, ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) is a promising new imaging technique. FDG accumulates in cells with a high rate of glycolysis [13], a metabolic process that is present in neoplastic cells and activated leukocytes. Lesions with a high concentration of inflammatory cells, such as granulocytes and activated macrophages, show increased uptake and retention of FDG [14,15]. Furthermore, FDG is cleared very rapidly from almost all other sites of the body, including the blood compartment. In this report, we describe the use of FDG-PET in the diagnosis and management of vasculitis in three patients who had different types of the disease, as well as review the literature to date.

Case Reports

Patient A was a 66-year-old man with a history of recurrent erythema nodosum since 1991. The results of a deep skin biopsy showed vasculitis of the small and medium arteries. Fatigue, weight loss, and recurrent arthralgias and myalgias were noted, in addition to an elevated erythrocyte sedimentation rate of 110 mm/h (normal, 1 to 5 mm/h), microcytic anemia, and an episode of iridocyclitis. The diagnosis of polyarteritis nodosa was made according to the ACR criteria. Treatment with prednisone (60 mg/d) resulted in the disappearance of symptoms, and after the dose was tapered to 5 mg/d he had no complaints for almost 10 years. Two months after prednisone treatment was stopped, severe pain developed in the lower legs with localized erythema nodosum and the erythrocyte sedimentation rate increased to 107 mm/h. Duplex ultrasonography demonstrated a nodular thickening of the wall of the femoral artery in both legs. PET imaging showed increased patchy uptake of FDG in the femoral and popliteal arteries in both legs (Figure 1A). Recurrent polyarteritis nodosa was diagnosed. After treatment with high-dose prednisone (60 mg/d), his symptoms again disappeared. Three months later, results of duplex ultrasonography and FDG-PET imaging (Figure 1B) were normal.

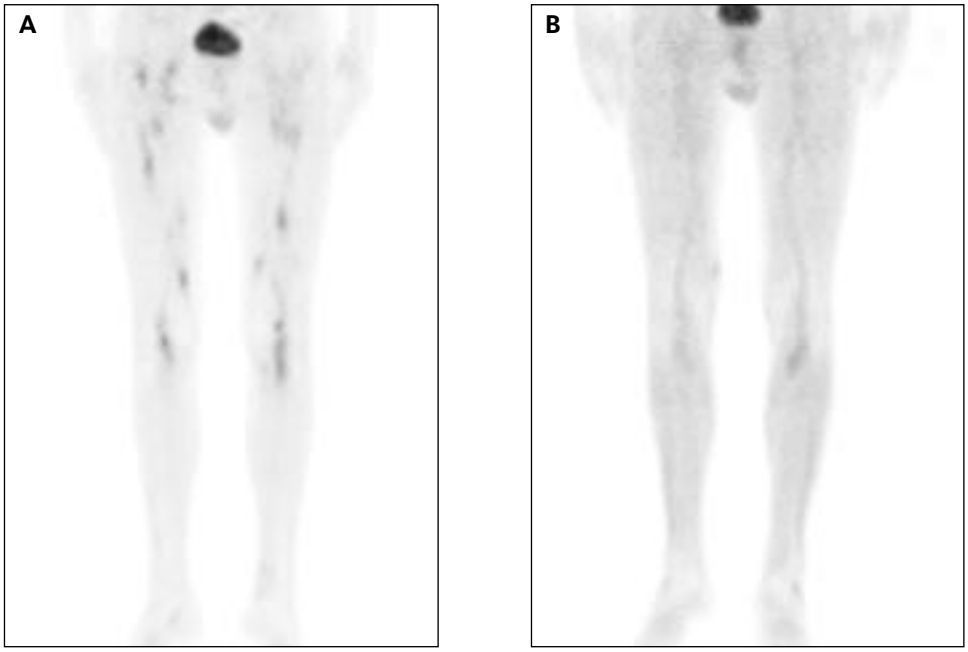

Figure 1 Increased patchy uptake of FDG in the femoral and popliteal arteries in both legs in patient A, who had recurrent polyarteritis nodosa after discontinuation of corticosteroid therapy (Figure 1A). Normal FDG-PET scan 3 months after restarting high-dose corticosteroid treatment (Figure 1B).

Patient B, a 77-year-old woman, was found to have Wegener's granulomatosis in 1988 based on complaints of purulent nasal discharge, a saddle nose, an elevated erythrocyte sedimentation rate, a positive antineutrophil cytoplasmic antibody (ANCA) screen, and granulomatous inflammation in a nasal biopsy specimen, according to the ACR criteria. Her symptoms disappeared after treatment with high-dose prednisone (60 mg/d). The prednisone dose was reduced to 5 mg/d and she remained well until July 2002, when she complained of fatigue and progressive shortness of breath without coughing, sputum production, or edema. Physical examination revealed no abnormalities except for a low-grade systolic murmur that was heard in the right second intercostal space and over both carotid arteries. The erythrocyte sedimentation rate was slightly elevated at 28 mm/h, C-reactive protein level was 9.3 mg/dL (normal <1.0 mg/dL), and ANCA titer was normal. A chest radiograph was normal, but a ventilation-perfusion scan showed a notably decreased perfusion of the entire right lung with normal ventilation. Computed tomography (CT) angiography demonstrated a dilated ascending aorta with a diameter of 5.7 cm, with a pathologically thickened wall that compressed the proximal right pulmonary artery. PET showed increased uptake of FDG in the ascending aorta (Figure 2A). A differential diagnosis of active vasculitis of the aorta, mycotic aneurysm, or malignancy of the vessel wall, such as sarcoma, was considered. Because of her medical history and negative blood cultures, vasculitis seemed most likely and she was treated with prednisone (60 mg/d) and metoprolol (100 mg/d). Her symptoms improved shortly thereafter. A ventilation-perfusion scan performed 6 weeks later showed an improvement of the perfusion of

the right lung. Results of FDG-PET imaging repeated after 6 weeks were normal (Figure 2B). The prednisone dose was tapered, and the patient's condition improved further.

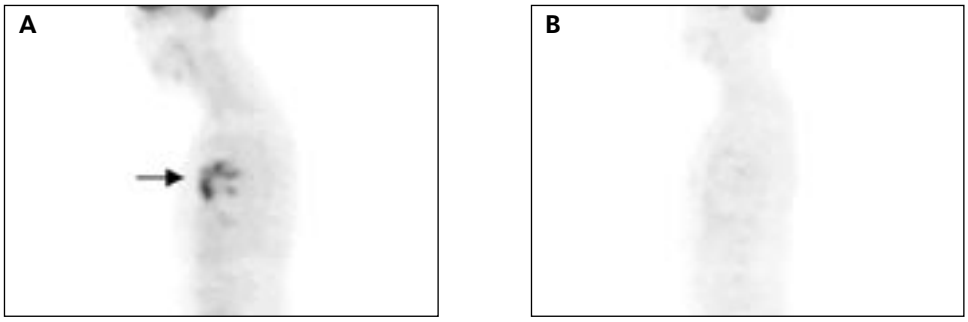

Figure 2 Increased uptake of FDG in the thoracic aorta (arrow) in patient B, who had Wegener's granulomatosis and was diagnosed with active vasculitis of the thoracic aorta (Figure 2A). Normal FDG-PET scan after 6 weeks of corticosteroid treatment (Figure 2B).

Patient C, a 76-year-old woman, had a medical history of hypertension since 1981, and diabetes mellitus and hyperparathyroidism since 2001. She presented with complaints of headache, fatigue, weight loss, and jaw claudication. The findings from the physical examination were normal except for absent pulsation of both temporal arteries. The erythrocyte sedimentation rate was 68 mm/h. Color duplex ultrasonography demonstrated thickening of both temporal arteries and a temporal artery biopsy specimen revealed signs of active arteritis with multinucleated giant cells. PET imaging showed increased uptake of FDG in the subclavian and carotid arteries on both sides (Figure 3). Temporal arteritis was diagnosed according to the ACR criteria. After treatment with prednisone 60 mg/d, her symptoms disappeared within a few days and the erythrocyte sedimentation rate normalized. The prednisone dose was slowly reduced to 5 mg/d. FDG-PET imaging has not been repeated.

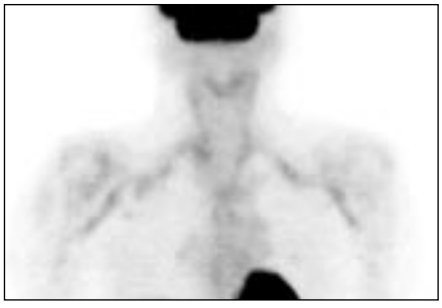

Figure 3 Increased FDG-uptake in both subclavian and carotid arteries in patient C, who had temporal arteritis.

Discussion

These three cases illustrate the promising role of FDG-PET in imaging vascular inflammation. Compared with CT and magnetic resonance imaging (MRI), this technique allows whole body screening, without disturbance by metallic implants and side effects. Unlike conventional nuclear medicine techniques, it also allows early imaging (one hour) [16], higher spatial resolution, and high interobserver agreement [17]. Its disadvantages are the relatively high cost, limited availability, and more limited anatomic information as compared with CT and MRI. In the three patients with vasculitis presented here, PET showed increased vascular uptake of FDG that was consistent with vascular inflammation. In patient A and especially patient B, in whom biopsy was not possible, diagnosis with conventional diagnostic modalities was difficult and FDG-PET greatly attributed to an early diagnosis of vasculitis. In these two patients, FDG-PET was also used successfully for follow-up of the inflammatory process. A marked decrease in uptake of FDG corresponded with improvement of symptoms and laboratory results.

Besides several case reports and a case series involving patients with giant cell arteritis [18-20], Takayasu arteritis [21-24], periaortitis due to Wegener's granulomatosis [25], aortitis [26], or unspecified large vessel vasculitis [27,28], two prospective studies exploring the diagnostic value of FDG-PET imaging in giant cell vasculitis have been published [29,30] (Table 1). In the study by Blockmans et al. [29], vascular uptake of FDG was seen in 76% of the 25 patients with biopsy-proven temporal arteritis or polymyalgia rheumatica. Uptake in the large thoracic arteries had a positive predictive value of 93% and a negative predictive value of 80% [29]. Meller et al. [30] compared FDG-PET with MRI in 15 patients with aortitis due to giant cell arteritis (n=14) or Takayasu arteritis (n=1) at the time of diagnosis and during follow-up (n=7). They concluded that FDG-PET was effective in the diagnosis and follow-up of patients with aortitis because it identified more vascular regions involved in the inflammatory process than did MRI.

Although inflammation of the arterial wall is most prominent in vasculitis, inflammation also contributes to atherogenesis. Increased accumulation of FDG has also been shown in atherosclerosis [31,32]. In our experience, however, uptake in vasculitis is much higher than in atherosclerosis, so a distinction between these two diagnoses should be possible.

In conclusion, our observations and review of the literature suggest that FDG-PET is effective for diagnosing and determining the extent of various forms of vasculitis. Furthermore, it could be useful for evaluating the effect of treatment. These results warrant a prospective study to further determine the role of FDG-PET in the diagnosis and follow-up of patients with different types of vasculitis.

Table 1 Studies of FDG-PET in vasculitis

First Author [Reference]	Study Design	Type of Vasculitis (No. of Patients)	Conclusions
De Winter [19]	Case report	Giant cell arteritis (n=1)	Uptake in thoracic vessels and spleen
Turlakow [20]	Case report	Giant cell arteritis (n=1)	Uptake in aorta and subclavian, carotid, vertebral, iliac arteries
Blockmans [18]	Case series	Polymyalgia rheumatica (n=5), giant cell arteritis (n=6)	Useful in investigation of polymyalgia rheumatica and giant cell arteritis
Blockmans [29]	Prospective consecutive series of 69 patients suspected of giant cell arteritis	Polymyalgia rheumatica (n=6), giant cell arteritis (n=19)	Uptake in thoracic arteries; sensitivity of 56% and specificity of 98%
Meller [30]	Prospective consecutive series of 15 patients with aortitis	Giant cell arteritis (n=14), Takayasu arteritis (n=1)	Uptake in aorta in all patients, normalization of uptake correlated with normalization of clinical and laboratory results
Hara [21]	Case report	Takayasu arteritis (n=1)	Uptake in aorta and brachiocephalic, subclavian, carotid, pulmonary arteries
Meller [22]	Prospective ^{67}Ga vs. FDG in fever of unknown origin	Takayasu arteritis (n=1)	Uptake in thoracic aorta; ^{67}Ga negative
Malik [23]	Case report	Takayasu arteritis (n=1)	Uptake in aorta
Meller [24]	Ongoing prospective consecutive series	Takayasu arteritis (n=5)	Uptake in aorta in all patients
Blockmans [25]	Case report	Wegener's granulomatosis (n=1)	Uptake in both lungs, nose, and shoulders; no uptake in vessels
Derdelinckx [26]	Case report	Aortitis thoracic aorta (n=1)	Uptake in aortic arch
Wiest [27]	Case report	Large vessel vasculitis (n=1)	Uptake in all large arteries
Wenger [28]	Case report	Unspecified large vessel vasculitis (n=1)	Uptake in aorta and subclavian, carotid, and iliac arteries

References

1 Hunder GG, Arend WP, Bloch DA et al. The American College of Rheumatology 1990 criteria for the classification of vasculitis. Introduction. Arthritis Rheum 1990;33:1065-1067.

2 Bloch DA, Michel BA, Hunder GG et al. The American College of Rheumatology 1990 criteria for the classification of vasculitis. Patients and methods. Arthritis Rheum 1990;33:1068-1073.

3 Lie JT. Illustrated histopathologic classification criteria for selected vasculitis syndromes. American College of Rheumatology Subcommittee on Classification of Vasculitis. Arthritis Rheum 1990;33:1074-1087.

4 Lightfoot RW, Jr., Michel BA, Bloch DA et al. The American College of Rheumatology 1990 criteria for the classification of polyarteritis nodosa. Arthritis Rheum 1990;33:1088-1093.

5 Masi AT, Hunder GG, Lie JT et al. The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). Arthritis Rheum 1990;33:1094-1100.

6 Leavitt RY, Fauci AS, Bloch DA et al. The American College of Rheumatology 1990 criteria for the classification of Wegener's granulomatosis. Arthritis Rheum 1990;33:1101-1107.

7 Calabrese LH, Michel BA, Bloch DA et al. The American College of Rheumatology 1990 criteria for the classification of hypersensitivity vasculitis. Arthritis Rheum 1990;33:1108-1113.

8 Mills JA, Michel BA, Bloch DA et al. The American College of Rheumatology 1990 criteria for the classification of Henoch-Schonlein purpura. Arthritis Rheum 1990;33:1114-1121.

9 Hunder GG, Bloch DA, Michel BA et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum 1990;33:1122-1128.

10 Arend WP, Michel BA, Bloch DA et al. The American College of Rheumatology 1990 criteria for the classification of Takayasu arteritis. Arthritis Rheum 1990;33:1129-1134.
11 Fries JF, Hunder GG, Bloch DA et al. The American College of Rheumatology 1990 criteria for the classification of vasculitis. Summary. Arthritis Rheum 1990;33:1135-1136.
12 Rao JK, Allen NB, Pincus T. Limitations of the 1990 American College of Rheumatology classification criteria in the diagnosis of vasculitis. Ann Intern Med 1998;129:345-352.
13 Bar-Shalom R, Valdivia AY, Blaufox MD. PET imaging in oncology. Semin Nucl Med 2000;30:150-185.
14 Kubota R, Yamada S, Kubota K et al. Intratumoral distribution of fluorine-18-fluorodeoxyglucose in vivo: high accumulation in macrophages and granulation tissues studied by microautoradiography. J Nucl Med 1992;33:1972-1980.
15 Brown RS, Leung JY, Fisher SJ et al. Intratumoral distribution of tritiated fluorodeoxyglucose in breast carcinoma: I. Are inflammatory cells important? J Nucl Med 1995;36:1854-1861.
16 Sugawara Y, Braun DK, Kison PV et al. Rapid detection of human infections with fluorine-18 fluorodeoxyglucose and positron emission tomography: preliminary results. Eur J Nucl Med 1998;25:1238-1243.
17 Kalicke T, Schmitz A, Risse JH et al. Fluorine-18 fluorodeoxyglucose PET in infectious bone diseases: results of histologically confirmed cases. Eur J Nucl Med 2000;27:524-528.
18 Blockmans D, Maes A, Stroobants S et al. New arguments for a vasculitic nature of polymyalgia rheumatica using positron emission tomography. Rheumatology (Oxford) 1999;38:444-447.
19 De Winter F, Petrovic M, van de WC et al. Imaging of giant cell arteritis: evidence of splenic involvement using FDG positron emission tomography. Clin Nucl Med 2000;25:633-634.
20 Turlakow A, Yeung HW, Pui J et al. Fludeoxyglucose positron emission tomography in the diagnosis of giant cell arteritis. Arch Intern Med 2001;161:1003-1007.
21 Hara M, Goodman PC, Leder RA. FDG-PET finding in early-phase Takayasu arteritis. J Comput Assist Tomogr 1999;23: 16-18.
22 Meller J, Altenvoerde G, Munzel U et al. Fever of unknown origin: prospective comparison of [18F]FDG imaging with a double-head coincidence camera and gallium-67 citrate SPET. Eur J Nucl Med 2000;27:1617-1625.
23 Malik IS, Harare O, AL Nahhas A, Beatt K, Mason J. Takayasu's arteritis: management of left main stem stenosis. Heart 2003;89:e9.
24 Meller J, Grabbe E, Becker W, Vosshenrich R. Value of F-18 FDG hybrid camera PET and MRI in early takayasu aortitis. Eur Radiol 2003;13:400-405.
25 Blockmans D, Baeyens H, Van Loon R, Lauwers G, Bobbaers H. Periaortitis and aortic dissection due to Wegener's granulomatosis. Clin Rheumatol 2000;19:161-164.
26 Derdelinckx I, Maes A, Bogaert J, Mortelmans L, Blockmans D. Positron emission tomography scan in the diagnosis and follow-up of aortitis of the thoracic aorta. Acta Cardiol 2000;55:193-195.
27 Wiest R, Gluck T, Schonberger J et al. Clinical image: occult large vessel vasculitis diagnosed by PET imaging. Rheumatol Int 2001;20:250.
28 Wenger M, Gasser R, Donnemiller E et al. Images in cardiovascular medicine. Generalized large vessel arteritis visualized by ^{18}fluorodeoxyglucose-positron emission tomography. Circulation 2003;107:923.
29 Blockmans D, Stroobants S, Maes A, Mortelmans L. Positron emission tomography in giant cell arteritis and polymyalgia rheumatica: evidence for inflammation of the aortic arch. Am J Med 2000;108:246-249.
30 Meller J, Strutz F, Siefker U et al. Early diagnosis and follow-up of aortitis with [(18)F]FDG PET and MRI. Eur J Nucl Med Mol Imaging 2003;5:730-736.
31 Lederman RJ, Raylman RR, Fisher SJ et al. Detection of atherosclerosis using a novel positron-sensitive probe and 18-fluorodeoxyglucose (FDG). Nucl Med Commun 2001;22:747-753.
32 Yun M, Jang S, Cucchiara A, Newberg AB, Alavi A. ^{18}F FDG uptake in the large arteries: a correlation study with the atherogenic risk factors. Semin Nucl Med 2002;32:70-76.

Chapter 2.2

Diagnosis of renal and hepatic cyst infections by ^{18}F-fluorodeoxyglucose positron emission tomography in autosomal dominant polycystic kidney disease

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Abstract

Background: Infection of a renal or hepatic cyst is a serious complication of autosomal dominant polycystic kidney disease (ADPKD). Although crucial for successful management, early diagnosis is difficult, largely due to nonspecific symptoms and limitations of conventional imaging techniques. Because of an increased metabolic rate, inflammatory cells take up large amounts of glucose. ^{18}F-fluorodeoxyglucose (FDG) therefore represents a promising agent for detection of cyst infections using positron emission tomography (PET).

Methods: We studied the results of seven FDG-PET scans in three ADPKD patients suspected of renal or hepatic cyst infection. Two PET scans were performed in patient A (PET 1 and 2), one PET scan was performed in patient B (PET 3), and four PET scans were performed in patient C (PET 4, 5, 6 and 7).

Results: FDG-PET identified the infected cysts in two episodes of renal cyst infection (PET 2 and 3), two episodes of hepatic cyst infection (PET 6 and 7) and one episode of both renal and hepatic cyst infection (PET 1). In patient C, FDG-PET was normal after six weeks of antibiotic treatment for hepatic cyst infection (PET 4) and again at a time when hepatic cyst infection was suspected, but eventually colchicine intoxication was diagnosed (PET 5).

Conclusions: In these patients FDG-PET proved very helpful in diagnosing and in excluding renal and hepatic cyst infections. It is concluded that FDG-PET is a promising new imaging technique enabling early identification of renal and hepatic cyst infections in ADPKD patients.

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common hereditary disorders affecting approximately one in 500 to 1000 individuals. It accounts for 8-10% of the cases of end-stage renal disease [1]. Infection of a single cyst within a polycystic kidney is a well-recognized and potentially serious complication of ADPKD, but the exact incidence of this complication is not known [1,2]. Hepatic cysts are common in patients with ADPKD, but usually remain asymptomatic. Infection of hepatic cysts occurs in up to 3% of patients with end-stage renal failure, but in less than 1% without end-stage renal failure [3]. Complications of cyst infections include abscess formation, sepsis and death. Although crucial for successful management, early diagnosis of cyst infection often is difficult. Symptoms and signs are nonspecific and diagnostic accuracy of conventional imaging techniques is reduced because of the changed anatomy of cystic kidneys and liver. Ultrasound, computer tomography (CT), and magnetic resonance imaging (MRI) cannot reliably differentiate infected from non-infected cysts in ADPKD patients [2,4]. Scintigraphic techniques have been used only sporadically [5-7].

^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) has become an established imaging tool in oncology and is now entering the field of clinical infectious diseases [8]. FDG is an analogue of glucose. Following cellular uptake, it is metabolically trapped and consequently provides an image, which portrays glucose utilization. Inflammatory cells take up large amounts of glucose as a result of an increased metabolic rate [9]. FDG therefore represents a promising

agent for detection of infected cysts. In this report the potential value of FDG-PET in cyst infection is demonstrated by presenting the results of seven FDG-PET scans in three ADPKD patients suspected of renal or hepatic cyst infection.

Cases

Patient A, a 73-year-old man, had a medical history of ADPKD, left-sided nephrectomy because of recurrent hemorrhage in 1999 and renal transplantation in May 2001. In August 2001 he was admitted because of fever and abdominal pain. Physical examination revealed a slightly enlarged liver and an enlarged, painless right kidney. C-reactive protein (CRP) was 99 mg/L (normal <10 mg/L), kreatinine, leukocytes and liver enzymes were normal. Blood cultures repeatedly grew *Enterococcus faecium*, but urine cultures were negative. He was treated with teicoplanin, but the fever persisted. Abdominal ultrasound and abdominal CT demonstrated multiple hepatic and renal cysts without signs of infection and a normal renal transplant. Because hepatic or renal cyst infection was suspected, a PET scan was performed (PET 1). PET demonstrated increased FDG-uptake in the peripheral border of several liver cysts and one focus in the right kidney, suggesting infection. Antibiotic treatment was changed to chloramphenicol. Two weeks later his temperature normalized. In October 2001 he was readmitted because of fever. Physical examination had not changed. CRP was 72 mg/L and blood cultures were again positive for *Enterococcus faecium* and urine culture showed *Pseudomonas aeruginosa* and *Escherichia coli.* Chloramphenicol was discontinued and amoxicillin and teicoplanin were started. A PET scan (PET 2) demonstrated large and irregular uptake dorsally in the right kidney extending to the right liver lobe (Figure 1). Abdominal CT showed an infiltrate in the right kidney in contact with the liver. The patient's condition deteriorated and surgery was considered impossible. Because of the dorsal localization percutaneous drainage was not feasible. Antibiotic therapy was changed to ciprofloxacin, but his condition continued to deteriorate and he died of sepsis. Autopsy was not performed.

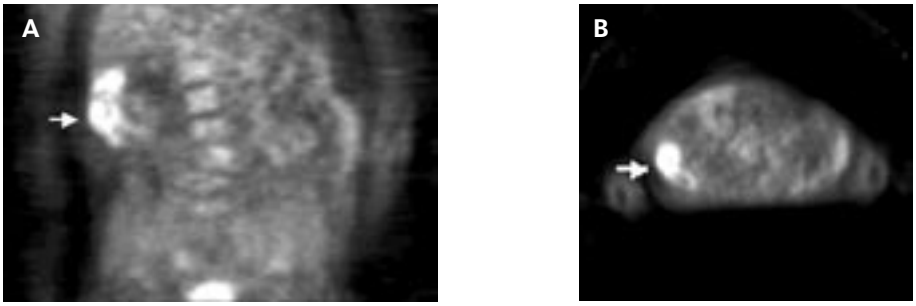

Figure 1 Patient A with a history of ADPKD and renal transplantation presented with fever. Coronal (Figure 1A) and transverse (Figure 1B) projection of PET 2: the arrow indicates the large and irregular FDG-uptake dorsally in the right kidney extending to the right liver lobe, suggesting infection.

Patient B, a 52-year-old man, had a medical history of ADPKD and a right-sided nephrectomy in preparation of subsequent renal transplantation in April 2002. Two weeks before admission, he was treated with ciprofloxacin orally because of a lower urinary tract infection with *Pseudomonas aeruginosa*. On admission, he complained of fever and chills without abdominal pain. Physical examination revealed an enlarged left kidney, which was not painful. CRP was 284 mg/L, leukocytes were 16.0 x 10^9/L (normal 3.5-11.0 x 10^9/L), and kreatinine and liver enzymes were normal. *Pseudomonas aeruginosa* was cultured from urine and blood. Renal cyst infection was suspected and ceftazidime was started. After 2 days his temperature normalized. One week later a PET scan (PET 3) showed increased uptake in multiple foci in the left kidney compatible with cyst infection. After two weeks ceftazidime was changed to ciprofloxacin orally for a total duration of 8 weeks. Because of renal cyst infection during immunosuppressive treatment, left-sided nephrectomy was performed 6 weeks after diagnosis to prevent recurrence of infection. The resected kidney showed old hemorrhages and calcification, but no signs of active infection. The patient has made a complete recovery.

Patient C, a 54-year-old woman, had a medical history of ADPKD, hemodialysis since 1997, right-sided nephrectomy in 1996 and left-sided nephrectomy in 1999 because of infection, and infected liver cysts in 1997. In October 2000 she was admitted with fever. Physical examination revealed an enlarged liver. CRP was 264 mg/L, alkaline phosphatase was 171 U/L (normal <120 U/L), and other liver enzymes and leukocytes were normal. Blood cultures grew *Enterococcus faecium*. Abdominal CT scan demonstrated multiple liver cysts without signs of infection. She was treated with ciprofloxacin. After three days her temperature normalized and she was discharged. After six weeks, treatment was stopped and she remained well. However, CRP was still elevated (40 mg/L) and a PET scan (PET 4) was performed to exclude cyst infection. FDG-PET proved to be normal and CRP slowly decreased. In May 2001 she was admitted with nausea, vomiting, abdominal pain and diarrhea, but no fever. Physical examination had not changed. CRP was 157 mg/L and creatine kinase was elevated to 974 U/L (normal <170 U/L). Blood and feces cultures were negative. Hepatic cyst infection was suspected, but a PET scan (PET 5) was again normal. Eventually a diagnosis of accidental colchicine-intoxication was made and hepatic cyst infection was considered highly unlikely. After discontinuation of colchicine, her symptoms resolved and laboratory results normalized. In February 2002 she was admitted with fever and abdominal discomfort. Physical examination revealed a painful, enlarged liver. CRP was 257 mg/L and blood cultures grew *Escherichia coli*. Hepatic cyst infection was suspected and she was treated with ciprofloxacin. FDG-PET (PET 6) showed increased uptake in two foci in the liver indicating cyst infection (Figure 2). After two days her fever disappeared and one week later she was discharged. CRP decreased slowly to 35 mg/L without complete normalization. Because of her extensive medical history and deteriorated condition, surgery was thought impossible and ciprofloxacin was continued. In August 2002 she complained of nausea and vomiting without fever. Physical examination had not changed, but CRP had increased to 198 mg/L. FDG-PET (PET 7) showed two foci of increased uptake dorsolaterally in the liver, different from the foci on the previous PET scan that had disappeared. New hepatic cyst infection was diagnosed, but before antibiotic treatment was adjusted or cultures were obtained, she suddenly died the next day. Autopsy was not performed.

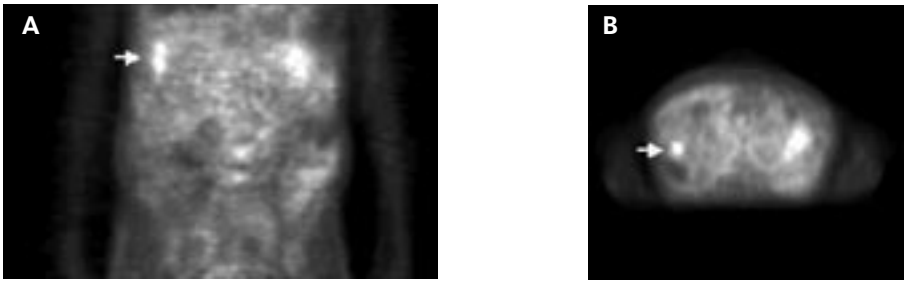

Figure 2 Patient C with a history of ADPKD, hemodialysis and bilateral nephrectomy presented with fever and abdominal discomfort. Coronal (Figure 2A) and transverse (Figure 2B) projection of PET 6: the arrow indicates the increased FDG-uptake in the liver, suggesting hepatic cyst infection. Physiological FDG-uptake by the stomach is visible on the left side.

Discussion

These cases illustrate some of the difficulties in diagnosis and treatment of renal and hepatic cyst infections in ADPKD patients. A major problem in diagnosing cyst infection is the absence of a "gold standard". Cyst infection is a clinical diagnosis usually based on the presence of fever, tenderness of one kidney or the liver in combination with positive blood cultures [2,4,5]. Treatment of cyst infections requires lipid-soluble antibiotics, which penetrate the cyst wall [10,11] and some authors even suggest that failure of conventional antibiotic therapy, despite favorable in vitro sensitivities, may be the best single diagnostic indicator of the likelihood of cyst infection [4,5].

Despite advances in available imaging modalities, confirmation of infection of a cyst remains difficult. CT and ultrasonography are unable to specifically indicate the presence of infection in renal or hepatic cysts [2,4]. CT findings, such as thickening and irregularity of the cyst wall and increased attenuation of the cyst contents are not specific for cyst infection since these signs may also be caused by hemorrhage into a cyst [12]. In patients A and C, an abdominal CT scan did not show any of these signs when a probable diagnosis of cyst infection was made. CT is probably only helpful in detecting underlying abnormalities or complications, such as stones, obstruction, or abscess formation. Successful isolation of infected renal and hepatic cysts in ADPKD patients with MRI has been reported [13,14], but experience is limited. Scintigraphic techniques, using ^{67}Ga-citrate (^{67}Ga) and ^{111}In-leukocytes, have been advocated, but uptake by overlying bowel can be confusing [4]. In addition, ^{67}Ga scintigraphy, obtained in 12 ADPKD patients with renal cyst infection, showed positive results in only six cases [5], suggesting ^{67}Ga imaging is not very helpful in diagnosing cyst infections in these patients. The successful use of ^{111}In-leukocyte imaging in ADPKD has been described only in two case reports [6,7]. Moreover, the preparation of this radiopharmaceutical is laborious and can be hazardous due to handling of potentially contaminated blood [15]. Compared to conventional nuclear medicine techniques, advantages of FDG-PET in diagnosing inflammation are early imaging (one hour), higher spatial resolution, resulting in more anatomic information, high target-to-background ratio [16], low radiation burden [17], and high inter observer agreement [18]. Disadvantages are higher cost and limited availability.

Previously, FDG-PET has proved valuable in diagnosing soft tissue infections, osteomyelitis, intravascular infections and fever of unknown origin [8]. Kaim et al. described an ADPKD patient with an infected renal cyst that could not be identified by ultrasound, CT, and MRI. A combined PET and CT system in an experimental set-up was able to exactly localize the infected cyst in this case and CT-guided percutaneous puncture followed in the same procedure [19]. Diagnosing infections in kidneys with normal or slightly reduced function could be difficult because of physiological renal excretion of FDG. Most cyst infections, however, seem to occur in a later stage of ADPKD [2,3] when renal function is already impaired. Clearance of FDG occurs predominantly through the kidneys and it is not reabsorbed by the kidneys in contrast to glucose. FDG appears in the renal collecting system, the ureters, and the bladder, but the renal parenchyma no longer contains noticeable amounts of activity by the time PET scans are acquired. However, the renal calyces contain prominent activity in most patients, especially in patients with ectatic renal calyces [20]. In spite of this, FDG-PET has been successfully used in the detection of renal cell carcinoma in patients with normal renal function [21].

Sensitivity and specificity of FDG-PET in diagnosing cyst infections can not be defined because of the small number of PET scans performed in ADPKD patients suspected of cyst infection, but in our three patients, FDG-PET was very helpful in diagnosing and in excluding renal and hepatic cyst infection. FDG-PET identified the infected cysts in five episodes of renal (PET 1, 2, 3) and hepatic (PET 1, 6, 7) cyst infection. In patient C, FDG-PET was normal six weeks after antibiotic treatment for probable hepatic cyst infection (PET 4). In this patient, FDG-PET was also normal at a time when hepatic cyst infection was suspected, but colchicine intoxication was diagnosed eventually (PET 5), suggesting FDG-uptake in liver cysts is specific for infection in ADPKD patients. In conclusion, the results of these seven PET scans in three ADPKD patients have illustrated that FDG-PET is a promising new imaging technique enabling early identification of renal and hepatic cyst infections in ADPKD patients with end-stage renal disease.

References

1 Gabow PA. Autosomal dominant polycystic kidney disease. N Engl J Med 1993;329:332-342.
2 Sklar AH, Caruana RJ, Lammers JE, Strauser GD. Renal infections in autosomal dominant polycystic kidney disease. Am J Kidney Dis 1987;10:81-88.
3 Grunfeld JP, Albouze G, Jungers P et al. Liver changes and complications in adult polycystic kidney disease. Adv Nephrol Necker Hosp 1985;14:1-20.
4 Gibson P and Watson ML. Cyst infection in polycystic kidney disease: a clinical challenge. Nephrol Dial Transplant 1998;13:2455-2457.
5 Schwab SJ, Bander SJ, Klahr S. Renal infection in autosomal dominant polycystic kidney disease. Am J Med 1987;82: 714-718.
6 Gilbert BR, Cerqueira MD, Eary JF et al. Indium-111 white blood cell scan for infectious complications of polycystic renal disease. J Nucl Med 1985;26:1283-1286.
7 Fortner A, Taylor A, Jr., Alazraki N, Datz FL. Advantage of indium-111 leukocytes over ultrasound in imaging an infected renal cyst. J Nucl Med 1986;27:1147-1149.
8 De Winter F, Vogelaers D, Gemmel F, Dierckx RA. Promising role of 18-F-fluoro-D-deoxyglucose positron emission tomography in clinical infectious diseases. Eur J Clin Microbiol Infect Dis 2002;21:247-257.
9 Peters AM. Nuclear medicine in vasculitis. Rheumatology (Oxford) 2000;39:463-470.

10 Bennett WM, Elzinga L, Pulliam JP, Rashad AL, Barry JM. Cyst fluid antibiotic concentrations in autosomal-dominant polycystic kidney disease. Am J Kidney Dis 1985;6:400-404.
11 Fick GM and Gabow PA. Natural history of autosomal dominant polycystic kidney disease. Annu Rev Med 1994;45: 23-29.
12 Levine E and Grantham JJ. The role of computed tomography in the evaluation of adult polycystic kidney disease. Am J Kidney Dis 1981;1:99-105.
13 Chicoskie C, Chaoui A, Kuligowska E, Dember LM, Tello R. MRI isolation of infected renal cyst in autosomal dominant polycystic kidney disease. Clin Imaging 2001;25:114-117.
14 Telenti A, Torres VE, Gross JB, Jr. et al. Hepatic cyst infection in autosomal dominant polycystic kidney disease. Mayo Clin Proc 1990;65:933-942.
15 Rennen HJ, Boerman OC, Oyen WJ, Corstens FH. Imaging infection/inflammation in the new millennium. Eur J Nucl Med 2001;28:241-252.
16 Sugawara Y, Gutowski TD, Fisher SJ, Brown RS, Wahl RL. Uptake of positron emission tomography tracers in experimental bacterial infections: a comparative biodistribution study of radiolabeled FDG, thymidine, L-methionine, 67Ga-citrate, and 125I-HSA. Eur J Nucl Med 1999;26:333-341.
17 Schelbert HR, Hoh CK, Royal HD et al. Procedure guideline for tumor imaging using fluorine-18-FDG. Society of Nuclear Medicine. J Nucl Med 1998;39:1302-1305.
18 Guhlmann A, Brecht-Krauss D, Suger G et al. Fluorine-18-FDG PET and technetium-99m antigranulocyte antibody scintigraphy in chronic osteomyelitis. J Nucl Med 1998;39:2145-2152.
19 Kaim AH, Burger C, Ganter CC et al. PET-CT-guided percutaneous puncture of an infected cyst in autosomal dominant polycystic kidney disease: case report. Radiology 2001;221:818-821.
20 von Schulthess GK, Kacl G, Stumpe KDM. Clinical Positron Emission Tomography: correlation with morphological cross-sectional imaging.2000;56-57.
21 Ramdave S, Thomas GW, Berlangieri SU et al. Clinical role of F-18 fluorodeoxyglucose positron emission tomography for detection and management of renal cell carcinoma. J Urol 2001;166:825-830.

Chapter 2.3

^{18}F-fluorodeoxyglucose positron emission tomography leading to a diagnosis of septic thrombophlebitis of the portal vein: description of a case history and review of the literature

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Abstract

Pylephlebitis or septic thrombophlebitis of the portal vein is a serious infectious disorder. Early diagnosis is difficult, due to non-specific symptoms and signs, limitations of diagnostic modalities and the lack of familiarity of physicians with this entity. We report the history of a 73-year-old man with fever of unknown origin in whom laboratory tests, blood and urine cultures, chest X-ray, abdominal ultrasound, and ^{111}Indium-leukocyte scintigraphy did not reveal the cause of the fever. ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) subsequently pointed to the diagnosis of pylephlebitis, which was confirmed by computed tomography and percutaneous puncture. We conclude that FDG-PET allows detecting inflammatory foci in patients with fever of unknown origin and offers to make the diagnosis of pylephlebitis at an early stage.

Introduction

Septic or suppurative thrombophlebitis of the portal vein, also named pylephlebitis, is a rare but life-threatening complication of intra-abdominal infections, most commonly caused by diverticulitis [1]. A wide variety of other causes have been described, including appendicitis, necrotizing pancreatitis, hemorrhoidal disease, foreign body perforation, perforated ileal diverticulum, acute cholecystitis, amoebic colitis, and inflammatory bowel disease [2]. The incidence of pylephlebitis has greatly declined since the introduction of antibiotics and modern surgical techniques [3]. In the past, most cases were diagnosed at laparotomy or autopsy. Mortality rates were very high: 50% overall [4] and 80% if pylephlebitis was not caused by appendicitis [1]. Recognition and prompt institution of adequate antibiotics has resulted in improved prognosis [5,6]. The high morbidity and mortality observed with suppurative pylephlebitis is at least in part attributable to the nonspecificity of the symptoms and signs, the limitations of available diagnostic modalities, and the increasing lack of familiarity of physicians with this entity. In the past, radiographic diagnosis of pylephlebitis usually relied on the presence of gas in the portal area and thrombus in the portal vein on angiography [4]. Contrast computed tomography (CT) [7,8], ultrasonography [8,9], magnetic resonance imaging (MRI) [10], and MR angiography [11] have proved valuable in the diagnosis of portal vein thrombosis, but have limitations in some cases [12,13]. Here, we present a case of fever of unknown origin in which ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) pointed to the diagnosis of pylephlebitis. A concise review of the literature on pylephlebitis is also presented.

Case report

A previously healthy 73-year-old man was admitted to our hospital because of a three-week history of fatigue, fever, chills, nausea, and vague left upper abdominal discomfort. In addition, he complained of a foul taste in his mouth that rendered him anorectic with subsequent weight loss. He was not taking any medication. On physical examination, he had a temperature of 37.9°C, a blood pressure of 110/52 mmHg, and a heart rate of 100 bpm. There was no jaundice. Bowel sounds were normal, the abdomen was nontender, and no hepatomegaly or palpable masses were found. Rectal examination

was also normal. Initial laboratory studies revealed normal total and direct bilirubin, AST and ALT, alkaline phosphatase 189 U/l (normal <120 U/l), GGT 124 U/l (normal <50 U/l), albumin 22 g/l (normal 37-53 g/l), and normal amylase. The white cell count was elevated to 18.6 x 10^9/l (normal 3.5-11.0 x 10^9/l) with 90% granulocytes and 6% band forms. CRP was 86 mg/l (normal <10 mg/l) and increased to 204 mg/l before treatment was started. All blood cultures and a urine culture remained sterile during his prolonged hospital stay. A chest X-ray and radiographic studies of the upper gastro-intestinal system were normal. An abdominal ultrasound demonstrated slightly enlarged lymph nodes in the liver hilus, which were not considered abnormal at that time. In the second week of his hospital stay a radiographic study of the colon showed extensive diverticulosis. A transthoracic echocardiography and ^{111}Indium-leukocyte scintigraphy were normal. Endoscopy revealed ulcerative esophagitis, but esophageal biopsy was normal. The patient had recurrent and ever progressing fever for more than three weeks and a PET scan was performed, which demonstrated increased FDG-uptake from the liver hilus to the right liver lobe (Figure 1). Contrast enhanced abdominal CT scanning, performed on the same day, showed thrombosis of the portal vein, slightly enlarged lymph nodes in the liver hilus, and extensive collaterals without evidence of abscesses, diverticulitis, or other abdominal infection (Figure 2). Based on these findings, septic thrombophlebitis of the portal vein was suspected. With an ultrasound-guided percutaneous needle aspiration of the portal vein, purulent material was obtained and treatment with intravenous ceftriaxon and metronidazole was started. The puncture material revealed Gram-negative rods, but a culture remained negative. The patient did not receive anticoagulant treatment. After two days his abdominal discomfort disappeared, his temperature normalized and his abnormal taste sensations resolved. Within two weeks CRP and liver enzymes had returned to normal. Treatment was changed to oral ciprofloxacin and metronidazole and he was discharged. Ultrasound one month after diagnosis showed no change in the thrombosis of the portal vein and revealed multiple collateral veins. Antibiotics were continued for a total of six weeks. Since then, the patient has been well without signs of portal hypertension. Endoscopy one year later showed no signs of esophageal varices and the esophageal inflammation had disappeared.

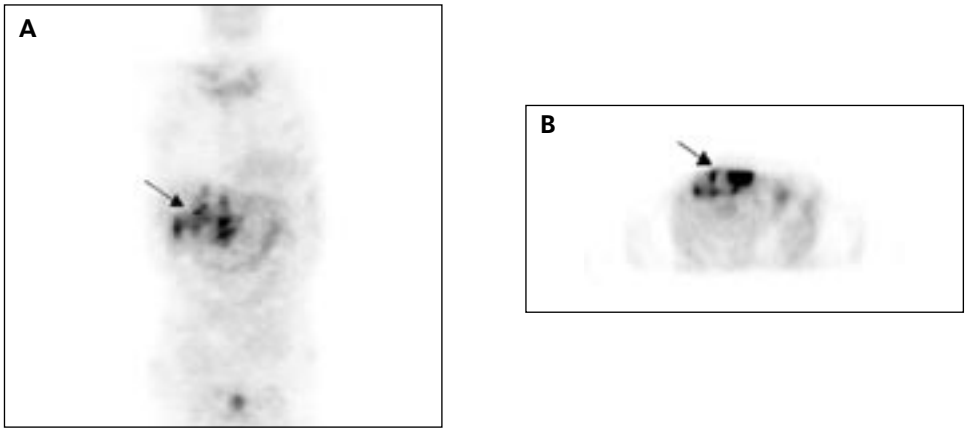

Figure 1 PET-scan: arrows indicate the increased FDG-uptake from the liver hilus to the right liver lobe indicating septic thrombophlebitis of the portal vein. (A: coronal projection, B: transverse projection).

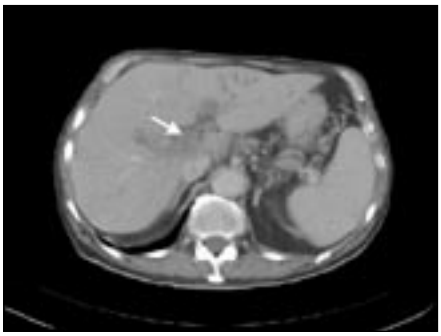

Figure 2 Abdominal CT scan (after intravenously administered contrast medium): thrombosis of the portal vein (arrow), slightly enlarged lymph nodes in the liver hilus, and extensive collaterals.

Discussion

Although imaging techniques have greatly improved over the recent years, diagnosing pylephlebitis remains difficult and in many cases the diagnosis has been made serendipitously [3,9], as in the case we describe here. In this patient, FDG-PET clearly revealed the site of the inflammatory process. FDG-PET has become an established imaging tool in oncology during recent years and is now entering the field of clinical infectious diseases. Following cellular uptake of FDG, an analogue of glucose, it is metabolically trapped and consequently provides an image, which portrays glucose utilization. Inflammatory cells take up large amounts of glucose as a result of an increased metabolic rate [14,15]. This uptake mechanism, however, is non-specific. FDG-PET is not able to differentiate between infection, non-infectious inflammatory disease and malignancy, so additional diagnostic measures are often necessary. In this case, for example, the needle aspiration was needed to establish a final diagnosis. In a prospective study of 58 patients with fever of unknown origin, FDG-PET imaging yielded diagnostic information in 41% of the patients in whom the probability of a diagnosis was only 64% [16]. Imaging techniques are necessary in most cases of pylephlebitis since the clinical features are non-specific. Symptoms include fever, chills, abdominal pain, diarrhea, and occasionally mild jaundice. Distortion of taste perception, also called dysgeusia, can be caused by various disorders [17], but in this patient the cause of his abnormal taste remains unresolved. Tender hepatomegaly is often observed, but may be absent [2]. Plemmons et al. reviewed all published cases of pylephlebitis from 1979 to 1993. In all 19 cases, fever was a presenting symptom, but abdominal pain or discomfort was present in only 74%. In six of these cases the cause of pylephlebitis was unknown and hepatic abscesses were present in 10 (53%) [6]. Laboratory studies may also be of limited value. Most patients showed leucocytosis, but liver tests were significantly abnormal in only 25% [4]. Blood cultures were positive in approximately 50-80% of pylephlebitis patients [6,18]. The more common isolated bacteria are *Escherichia coli*, *Proteus mirabilis*, *Bacteroides fragilis*, and aerobic Gram-negative bacilli [6,19]. The overall mortality rate in the cases, reviewed by Plemmons [6], was 32% and especially a diverticular cause of pylephlebitis was associated with fatal outcome. Patients who died, showed severe sepsis before appropriate

antibiotic treatment was started, suggesting that uncontrolled infection is most life threatening in these patients rather than complications directly related to thrombosis [6].

Angiography demonstrates occlusion of the portal system when pylethrombosis is present [20]. Less invasive imaging techniques, such as CT, MRI, and (color duplex) ultrasonography have largely replaced angiography in diagnosing portal vein thrombosis. The presence of an intraluminal echogenic thrombus provides the best ultrasonographic evidence of portal vein thrombosis. Additional signs include dilation of vessels proximal to the occlusion, the presence of collateral vessels, and the absence of an identifiable portal vein [21]. Conversely, patent vessels may show increased intraluminal echogenicity because of artefact or erythrocyte rouleau formation and is, therefore, not sufficient evidence for a diagnosis of portal vein thrombosis [13]. Ultrasonographic examination using duplex Doppler technique is helpful in confirming the diagnosis of portal vein thrombosis and cavernous transformation of the portal vein, a possible complication of chronic obstruction of the portal venous system leading to portal hypertension [21]. CT scanning can show a thrombus as a filling defect in the contrast-enhanced lumen [7,8] and may identify the underlying cause of the disease. On MRI images, portal vein thrombosis causes an area of abnormal signal within the lumen [13]. MR angiography has also been shown to be of value in the evaluation of flow and patency within the portal system and diagnosing cavernous transformation of the portal vein [11]. These imaging techniques are usually able to demonstrate portal vein thrombosis, but differentiation between thrombosis and thrombophlebitis is not possible. Here FDG-PET has a major advantage. In this case, the suspected site of infection was further visualized by CT; percutaneous puncture revealed pus, thereby confirming the diagnosis pylephlebitis. This demonstrates the potential value of FDG-PET as a new imaging technique in patients with fever of unknown origin and patients suspected of pylephlebitis. Although increased FDG-uptake in thrombosis has been described [22], we postulate that FDG-PET should be able to differentiate between non-infectious portal vein thrombosis and thrombophlebitis, because of much higher FDG-uptake in the intense inflammatory process in pylephlebitis.

As soon as pylephlebitis is suspected, antibiotics with adequate coverage of Gram-negative aerobic bacilli, anaerobes, and *Streptococcus* species should be initiated. The ideal duration of antibiotic therapy is unclear. Given the frequency of hepatic abscesses as a complication of pylephlebitis, however, a minimum of four weeks seems prudent. Patients with demonstrated liver abscesses complicating pylephlebitis should probably receive at least six weeks of antibiotic therapy, in some cases with percutaneous or surgical drainage [6]. The role of anticoagulation in the treatment of pylephlebitis remains controversial. All available publications appear to have been based on limited data and personal experience, since no formal study has ever been done [3,6,18,23]. These considerations and the potential risk of anticoagulant treatment did us decide to omit anticoagulant treatment in this patient. Treatment should include localization and extirpation or decompression of any septic foci found, such as an inflamed appendix or diverticular abscess. The most serious complication with highest mortality rates is severe sepsis unresponsive to treatment [6]. The development of catastrophic vascular complications of portal thrombosis, such as acute portal hypertension with variceal hemorrhage or bowel infarction, is very uncommon in

pylephlebitis [6,18]. Follow-up CT examinations of five patients with pylephlebitis showed complete resolution of thrombosis in two patients and cavernous transformation in three patients [5]. In our patient extensive collaterals had already formed before portal vein thrombosis was diagnosed and, as is expected in such a late stage, no improvement was found after one month. This patient has not shown any signs of portal hypertension thus far.

In conclusion, septic thrombophlebitis of the portal vein is a serious infectious disorder, which is difficult to diagnose. In this patient, FDG-PET proved to be a powerful technique to diagnose this infectious condition.

References

1 Case Records of the Massachusetts General Hospital: case 18 1977. New England Journal of Medicine 1977;296:1051-1057.
2 Drabick JJ and Landry FJ. Suppurative pylephlebitis. South Med J 1991;84:1396-1398.
3 Harch JM, Radin RD, Yellin AE, Donovan AJ. Pylethrombosis. Serendipitous radiologic diagnosis. Arch Surg 1987;122:1116-1119.
4 Bolt RJ. Diseases and the hepatic blood vessels. In: Gastroenterology 4th ed. Philadelphia: Saunders, WB 1985;3259-3277.
5 Lim GM, Jeffrey RB, Jr., Ralls PW, Marn CS. Septic thrombosis of the portal vein: CT and clinical observations. J Comput Assist Tomogr 1989;13:656-658.
6 Plemmons RM, Dooley DP, Longfield RN. Septic thrombophlebitis of the portal vein (pylephlebitis): diagnosis and management in the modern era. Clin Infect Dis 1995;21:1114-1120.
7 Mathieu D, Vasile N, Grenier P. Portal thrombosis: dynamic CT features and course. Radiology 1985;154:737-741.
8 Miller VE and Berland LL. Pulsed Doppler duplex sonography and CT of portal vein thrombosis. AJR Am J Roentgenol 1985;145:73-76.
9 Van Gansbeke D, Avni EF, Delcour C, Engelholm L, Struyven J. Sonographic features of portal vein thrombosis. AJR Am J Roentgenol 1985;144:749-752.
10 Zirinsky K, Markisz JA, Rubenstein WA et al. MR imaging of portal venous thrombosis: correlation with CT and sonography. AJR Am J Roentgenol 1988;150:283-288.
11 Edelman RR, Zhao B, Liu C et al. MR angiography and dynamic flow evaluation of the portal venous system. AJR Am J Roentgenol 1989;153:755-760.
12 Martin K, Balfe DM, Lee JK. Computed tomography of portal vein thrombosis: unusual appearances and pitfalls in diagnosis. J Comput Assist Tomogr 1989;13:811-816.
13 Parvey HR, Raval B, Sandler CM. Portal vein thrombosis: imaging findings. AJR Am J Roentgenol 1994;162:77-81.
14 Bar-Shalom R, Valdivia AY, Blaufox MD. PET imaging in oncology. Semin Nucl Med 2000;30:150-185.
15 Kubota R, Yamada S, Kubota K et al. Intratumoral distribution of fluorine-18-fluorodeoxyglucose in vivo: high accumulation in macrophages and granulation tissues studied by microautoradiography. J Nucl Med 1992;33:1972-1980.
16 Blockmans D, Knockaert D, Maes A et al. Clinical value of [(18)F]fluoro-deoxyglucose positron emission tomography for patients with fever of unknown origin. Clin Infect Dis 2001;32:191-196.
17 Mott AE, Grushka M, Sessle BJ. Diagnosis and management of taste disorders and burning mouth syndrome. Dent Clin North Am 1993;37:33-71.
18 Singh P, Yadav N, Visvalingam V, Indaram A, Bank S. Pylephlebitis--diagnosis and management. Am J Gastroenterol 2001;96:1312-1313.
19 Perez-Cruet MJ, Grable E, Drapkin MS, Jablons DM, Cano G. Pylephlebitis associated with diverticulitis. South Med J 1993;86:578-580.
20 Witte CL, Brewer ML, Witte MH, Pond GB. Protean manifestations of pylethrombosis. A review of thirty-four patients. Ann Surg 1985;202:191-202.

21 Cohen J, Edelman RR, Chopra S. Portal vein thrombosis: a review. Am J Med 1992;92:173-182.
22 Raman S, Nunez R, Oliver WC, Dworkin HJ. F-18 FDG positron emission tomographic image of an aortic aneurysmal thrombus. Clin Nucl Med 2002;27:213-214.
23 Baril N, Wren S, Radin R, Ralls P, Stain S. The role of anticoagulation in pylephlebitis. Am J Surg 1996;172:449-452.

Chapter 2.4

Diagnosis of *Candida* lung abscesses by ^{18}F-fluorodeoxyglucose positron emission tomography

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Abstract

In three patients with catheter-associated candidemia, ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) led to the diagnosis of *Candida* lung abscesses, which was confirmed by computed tomography and favorable response to antifungal therapy. It is concluded that FDG-PET is a promising new imaging technique enabling early identification of sites of disseminated candidiasis and that it can be used in the evaluation of therapy.

Introduction

Candida spp. are an important cause of nosocomial bloodstream infection, associated with a mortality of 30-40% [1]. Patients at high risk for candidiasis are those receiving total parenteral nutrition (TPN) and critically ill patients [2-4]. Catheter-associated candidemia may lead to seeding of *Candida* spp. to multiple organs. Timely identification and localization of the infectious lesions is critical, but this is often difficult, especially in patients without signs pointing to a specific localization. We report three cases of *Candida* lung abscesses associated with central venous catheter (CVC)-related candidemia diagnosed by ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET).

Cases

Patient A, a 45-year-old woman, had received TPN since September 2003 because of short bowel syndrome resulting from acute bowel ischemia. In January 2004, she was admitted because of fever. Blood cultures repeatedly grew *C. albicans*, which was also cultured from the catheter tip after removal. Ophthalmologic examination revealed lesions compatible with *Candida* chorioretinitis. The MIC for fluconazole was 0.125 µg/ml. She was treated with fluconazole 400 mg qd intravenously, but the fever persisted. Blood cultures remained positive for *C. albicans* for seven days after start of fluconazole, and the dose was increased to 800 mg qd. Chest X-ray and abdominal ultrasound were both normal. Nine days after admission, FDG-PET was performed, which demonstrated increased FDG-uptake in the upper and lower lobes of the right lung. High-resolution chest computed tomography (CT) subsequently showed several densities with hypodense centers in the upper and lower lobes of the right lung, compatible with fungal abscesses. High-resolution chest CT after six weeks showed regression of the pulmonary densities. After nine weeks, FDG-PET was normal and treatment with fluconazole was discontinued.

Patient B, a 39-year-old woman, had received TPN because of chronic intestinal pseudo-obstruction since October 2003. In November 2003, she was admitted because of fever and rigors. Blood cultures repeatedly grew *C. albicans*, which was also cultured from the catheter tip after removal. The MIC for fluconazole was 0.125 µg/ml. She was treated with fluconazole 400 mg qd intravenously. Fever persisted and her clinical condition deteriorated. Blood cultures remained positive for *C. albicans*

for two days after start of fluconazole. Abdominal ultrasound and doppler ultrasonography of the subclavian and internal jugular veins were both normal. Chest X-ray was judged to be normal, but showed a small infiltrate in the left lower lobe upon re-examination. PET, performed one week after admission, demonstrated increased FDG-uptake in multiple foci in both lungs and subpleural, suggesting abscesses (Figure 1A). Two days later she developed pleuritic chest pain and a pleural rub on the right side. Chest CT showed multiple densities in both lungs compatible with fungal abscesses. Fluconazole was replaced by caspofungin. After three weeks, caspofungin was replaced by oral fluconazole. After seven weeks, chest CT showed regression of the lung abscesses. After nine weeks, FDG-PET was normal (Figure 1B) and antifungal treatment was stopped.

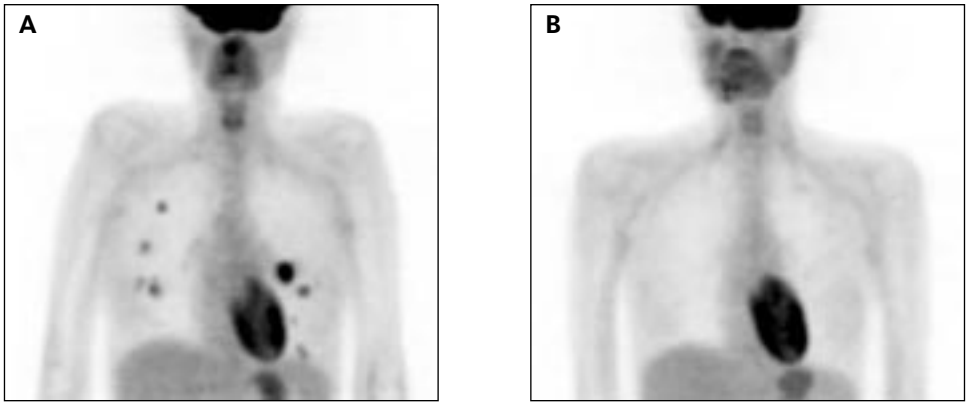

Figure 1 In patient B, positron emission tomography (PET) demonstrated increased uptake of ^{18}F-fluorodeoxyglucose (FDG) in multiple foci in both lungs, suggesting abscesses (Figure 1A). After three months, FDG-PET was normal (Figure 1B).

Patient C, a 65-year-old woman, was treated with prednisone and azathioprine since 1995 because of mixed connective tissue disease. In May 2004, she was admitted to the intensive care unit with *Streptococcus pneumoniae* pneumonia for which mechanical ventilation was initiated. Blood cultures remained sterile. On the tenth hospital day, blood cultures grew *C. glabrata*. However, *C. albicans* and *C. glabrata* were both isolated from the CVC after removal. The MIC for fluconazole were 4 and 8 µg/ml, respectively. She was treated with fluconazole 400 mg qd intravenously, but the fever persisted and the dose was increased to 800 mg daily. Chest X-ray showed infiltrative changes in the left lower lobe, which had not changed. Abdominal CT revealed no signs of focal infection. Doppler ultrasonography of the subclavian and internal jugular vein was normal. The fever still persisted and blood cultures were positive for *C. glabrata* for thirteen days after start of fluconazole. PET, performed after 12 days of therapy, showed increased FDG-uptake in multiple foci in both lungs suggesting abscesses. Fluconazole was replaced by caspofungin. One week later, chest CT showed infiltrative changes in both upper lobes, compatible with metastatic infectious foci. After 6 weeks of antifungal treatment, chest CT showed regression of the infiltrative changes and caspofungin was discontinued. FDG-PET has not been repeated.

Discussion

These cases illustrate the difficulties in diagnosis and treatment of complicated catheter-related candidiasis. FDG-PET clearly revealed the sites of the disseminated *Candida* infection, which was confirmed by clinical signs (patient B), findings on chest CT, and response to antifungal therapy (patients A, B and C). In patients A and B, FDG-uptake normalized after prolonged treatment in agreement with favorable clinical and laboratory response, enabling evaluation of the effect of antifungal treatment.

Candida species adhere avidly to vascular catheters. CVCs, even when not the primary source of candidemia, may continue to serve as the source of sustained fungemia as organisms adhere to the catheter surface and subsequently seed to target organs [5]. In a retrospective study in our hospital, 43 out of 147 patients who were treated for candidemia developed disseminated disease [6]. Documented *Candida* lung abscesses, however, are rare. In a study of 11 patients diagnosed with pulmonary candidiasis at necropsy, six cases were attributed to CVCs [7].

In patients A, B and C, chest X-ray did not reveal the lung abscesses, and is therefore not an appropriate diagnostic method to exclude disseminated pulmonary candidiasis. CT and ultrasonography are useful for diagnosing disseminated candidiasis, but are less suitable as a screening method in patients with candidemia suspected of disseminated infection without clues for specific sites of infection. Furthermore, these imaging techniques are not able to detect infectious foci in an early phase because of the lack of substantial anatomical changes at that time. Also, discrimination between active infection and residual changes remains difficult, which is a drawback during follow-up of the effect of treatment.

Scintigraphic imaging allows delineation of the localization of foci in all parts of the body, based on functional changes of tissues. FDG-PET, an established imaging tool in oncology, has entered the field of clinical infectious diseases. After cellular uptake, FDG, an analogue of glucose, is metabolically trapped and consequently provides an image, which portrays glucose utilization. Inflammatory cells take up large amounts of glucose as a result of an increased metabolic rate [8]. Previously, FDG-PET has proved valuable in diagnosing soft tissue infections, osteomyelitis, intravascular infections and fever of unknown origin [9,10]. Compared to conventional nuclear medicine techniques (^{67}gallium citrate and labeled leukocytes), advantages of FDG-PET are early imaging, and higher spatial resolution, resulting in more anatomic information [11].

In conclusion, FDG-PET appears to be a promising new imaging technique enabling early identification of sites of disseminated *Candida* infection as well as for evaluating the effect of antifungal treatment.

References

1 Edmond MB, Wallace SE, McClish DK et al. Nosocomial bloodstream infections in United States hospitals: a three-year analysis. Clin Infect Dis 1999;29:239-244.

2 Charles PE, Doise JM, Quenot JP et al. Candidemia in critically ill patients: difference of outcome between medical and surgical patients. Intensive Care Med 2003;29:2162-2169.

3 Lin C, Lin MT, Hsieh DY et al. Microbiology difference between colonized catheters and catheter-related bloodstream infections. Hepatogastroenterology 2003;50:1821-1824.

4 Stratov I, Gottlieb T, Bradbury R, O'Kane GM. Candidaemia in an Australian teaching hospital: relationship to central line and TPN use. J Infect 1998;36:203-207.

5 Walsh TJ and Rex JH. All catheter-related candidemia is not the same: assessment of the balance between the risks and benefits of removal of vascular catheters. Clin Infect Dis 2002;34:600-602.

6 Oude Lashof AM, Donnelly JP, Meis JF, van der Meer JW, Kullberg BJ. Duration of antifungal treatment and development of delayed complications in patients with candidaemia. Eur J Clin Microbiol Infect Dis 2003;22:43-48.

7 Rose HD and Sheth NK. Pulmonary candidiasis. A clinical and pathological correlation. Arch Intern Med 1978;138: 964-965.

8 Kubota R, Yamada S, Kubota K et al. Intratumoral distribution of fluorine-18-fluorodeoxyglucose in vivo: high accumulation in macrophages and granulation tissues studied by microautoradiography. J Nucl Med 1992;33:1972-1980.

9 De Winter F, Vogelaers D, Gemmel F, Dierckx RA. Promising role of 18-F-fluoro-D-deoxyglucose positron emission tomography in clinical infectious diseases. Eur J Clin Microbiol Infect Dis 2002;21:247-257.

10 Bleeker-Rovers CP, de Kleijn EM, Corstens FH, van der Meer JW, Oyen WJ. Clinical value of FDG PET in patients with fever of unknown origin and patients suspected of focal infection or inflammation. Eur J Nucl Med Mol Imaging 2004;31:29-37.

11 Rennen HJ, Boerman OC, Oyen WJ, Corstens FH. Imaging infection/inflammation in the new millennium. Eur J Nucl Med 2001;28:241-252.

Chapter 3

^{18}F-fluorodeoxyglucose positron emission tomography in diagnosis and follow-up of patients with different types of vasculitis

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Abstract

Background: ^{18}F-fluorodeoxyglucose (FDG) accumulates in inflammatory cells due to an increased metabolic rate. Therefore, FDG positron emission tomography (PET) represents a promising imaging technique in patients with vasculitis. The aim of this study was to assess the value of FDG-PET in the diagnosis of different types of vasculitis.

Methods: The results of FDG-PET performed because of suspected vasculitis or because of fever of unknown origin with results indicating vasculitis were reviewed. These results were compared to the final diagnosis, based on the "American College of Rheumatology 1990 criteria".

Results: FDG-PET was ordered because of suspected vasculitis in 20 patients, because of fever of unknown origin in two patients, and for follow-up of vasculitis in five patients. Fourteen patients were diagnosed with vasculitis (giant cell arteritis n=5, polymyalgia rheumatica n=2, polyarteritis nodosa n=3, Takayasu n=1, Churge-Strauss n=1, Wegener's granulomatosis n=1, vasculitis of the skin n=1), two patients were diagnosed with fibromuscular dysplasia and one patient had media necrosis of the aorta. In five patients no diagnosis could be reached. FDG-PET results were considered to be true positive in 10 patients, true negative in 14 patients and false negative in three patients resulting in a positive predictive value of 100% and a negative predictive value of 82%.

Conclusions: FDG-PET appears to be a promising new imaging technique in diagnosing and determining the extent of various forms of vasculitis. Furthermore, FDG-PET may become a useful tool for evaluating the effect of treatment of vasculitis.

Introduction

Early and accurate diagnosis and assessment of the extent of vasculitis is important for adequate therapeutic measures and improvement of prognosis. Diagnosing vasculitis is often difficult due to the absence of specific symptoms and signs, the limited specificity of available biochemical tests and the limited sensitivity of detecting the frequently subtle vessel abnormalities with conventional imaging techniques. The various kinds of vasculitis are classified based on the type of inflammation, the predominant size of the involved arteries, and the extent and location of the inflammation. The "American College of Rheumatology 1990 criteria for the classification of vasculitis" (ACR criteria) [1-11] are considered to be the gold standard. Although these criteria were established for research, they are often used for clinical diagnosis of vasculitis. In a study of 198 patients suspected of vasculitis, however, the ACR criteria functioned poorly in the clinical diagnosis of specific types of vasculitis [12]. In clinical practice, diagnosing vasculitis and evaluating the extent and the location of the disease is difficult or even impossible in many cases. In those types of vasculitis in which it is difficult to obtain histological proof, imaging techniques are used for diagnosis. Vasculitis of the medium-sized and large blood vessels can be detected by several radiological techniques including classic angiography, computerized tomography (CT), magnetic resonance imaging (MRI) and ultrasonography. Since these techniques only show anatomical changes of the vessel lumen, inflammation of the vessel wall cannot be detected in an early phase due to the lack of substantial anatomical changes at this time. Also, to distinguish active

inflammatory lesions from residual anatomical changes due to previous inflammation is difficult or even impossible.

Scintigraphic imaging is a non-invasive method allowing delineation of both localization and number of foci in all parts of the body, based on functional changes of tissues. ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) has become an established imaging tool in oncology and is now entering the field of infectious and inflammatory diseases [13]. FDG accumulates in organ tissues with a high rate of glycolysis [14], which not exclusively occurs in neoplastic cells. Lesions with a high concentration of activated inflammatory cells also show increased uptake of FDG [15,16]. Furthermore, from almost all other sites of the body, including the blood compartment, it is cleared very rapidly. FDG-PET could thus be a promising new imaging technique for evaluation of metabolic activity in the vessel wall in both diagnosis and follow-up of patients with vasculitis. FDG accumulation on PET scanning has been reported in patients with giant cell arteritis and polymyalgia rheumatica [17-20], Takayasu arteritis [20-24], periaortitis due to Wegener's granulomatosis [25], aortitis [20,26], unspecified large vessel vasculitis [27,28] and infectious vasculitis [29]. To further assess the role of FDG-PET imaging in diagnosis and follow-up of patients with different types of vasculitis, we evaluated the results of FDG-PET scans, performed either because of suspected vasculitis or because of fever of unknown origin with results suggesting the presence of vasculitis.

Materials and methods

Patients

The results of all FDG-PET scans ordered from January 1999 to April 2003 in the Radboud University Nijmegen Medical Centre because of suspected vasculitis or because of fever of unknown origin with results suggesting the presence of vasculitis were reviewed. Fever of unknown origin was defined according to the revised Petersdorf criteria: a febrile illness of >3 weeks duration, a temperature of >38.3°C on several occasions, and no diagnosis after one week of evaluation in the hospital or three visits to the outpatient department [30]. The patients were evaluated with other imaging modalities and laboratory tests as was considered clinically appropriate. Patients were included if the diagnostic process had been completed at the time of data-analysis in April 2003. The patients with fever of unknown origin are also included in a retrospective study investigating the diagnostic contribution of FDG-PET in patients with fever of unknown origin that has been published elsewhere [31].

FDG-PET

A dedicated, full-ring PET scanner (ECAT-EXACT, Siemens/CTI, Knoxville, TN., USA) was used for data acquisition. Prior to FDG-injection patients had fasted for at least 6 hours. Intake of sugar-free liquids was permitted. Immediately prior to the procedure, the patients were hydrated with 500 ml of water. One hour after intravenous injection of 200-220 MBq FDG (Tyco Healthcare/ Mallinckrodt Medical, Petten, The Netherlands) and 10 to 15 mg furosemide, emission images or emission and transmission images of the area between the proximal femora and the base of the skull were acquired (10 minute per bed position). When only an emission study was recorded, the

images were not corrected for attenuation and were reconstructed using filtered back-protection (Butterworth filter with a cut-off frequency of 0.4 Nyquist). When emission and transmission studies were recorded, 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.

Interpretation

FDG-PET scans were interpreted by two staff members of the department of nuclear medicine blinded for other diagnostic test results and the final diagnosis. FDG-PET scans were rated as normal or abnormal. Results were judged to be abnormal if focal accumulation of the tracer was detected outside of the areas of physiological uptake. Normally no visible FDG-uptake is present in blood vessel walls. Disagreements were resolved by consensus.

Clinical assessment of test results and diagnosis

Results were considered to be true positive when abnormal vascular FDG-uptake was present in patients with a clinical diagnosis of vasculitis. Abnormal results were categorized as false positive when the abnormality was not related to the illness or when no final diagnosis could be reached. A normal FDG-PET scan was considered to be true negative when no cause of the symptoms was identified despite an extensive diagnostic work-up. In cases of suspected vasculitis, the diagnostic work-up had to be complete according to the ACR criteria. A normal FDG-PET scan was considered false negative when vasculitis was diagnosed except for vasculitis limited to the brain because of known low sensitivity of FDG-PET due to high physiological FDG-uptake in the brain or vasculitis limited to the legs, because the legs are not routinely imaged if not specially mentioned on the FDG-PET request. A final diagnosis of vasculitis was based on the ACR criteria. When this was not possible, a probable diagnosis was made based on clinical follow-up and conventional radiological studies. No criteria defining an exacerbation or recurrence of a known vasculitis syndrome are available. To define a probable exacerbation or recurrence, the clinical diagnosis based on a combination of recurrence of symptoms resembling the symptoms at the time of the first episode with vasculitis, an elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) and other biochemical tests were used. The final or probable clinical diagnosis served as a standard of reference and was used for the comparisons with the FDG-PET results.

Results

From January 1999 to April 2003, 25 patients were referred for a total of 30 FDG-PET scans because of suspected vasculitis or because of fever of unknown origin with FDG-PET results indicating vasculitis. Three patients had to be excluded because of insufficient data in follow-up, so the results of 27 FDG-PET scans in 22 patients were evaluated. Of these patients, two were male and 20 were female with a median age of 60 years (range 17 to 81 years). Nine patients had at least one period of hospitalization with a median duration of 14 days (range 8 to 62 days). Thirteen patients only visited the outpatient department.

The clinical diagnoses of the patients are shown in Table 1. Fourteen patients (64%) were diagnosed with vasculitis based on the ACR criteria. Fibromuscular dysplasia was diagnosed in two patients: one patient was diagnosed with fibromuscular dysplasia of the right renal artery and the hepatic artery based on typical changes on angiography, which is the gold standard for diagnosing this disease. In the other patient, a probable diagnosis of fibromuscular dysplasia of the carotid arteries was reached based on typical changes on magnetic resonance angiography (MRA). One patient suspected of vasculitis of the thoracic aorta because of a progressively dilating ascending aorta and a variable elevation of CRP was eventually diagnosed with media necrosis of the ascending aorta after replacement of the affected part with an aortic graft. No signs of vasculitis or infection were found and the definite cause of the media necrosis remained unresolved. Possibly the media necrosis was caused by previous aortitis in this patient with a combined immunodeficiency. In five patients suspected of vasculitis, no cause of their symptoms could be established after a median follow-up of 7 months (range 1 to 17 months): one patient had persisting symptoms without treatment and died of cerebral hemorrhage 17 months after FDG-PET (no autopsy was performed), two patients had persisting symptoms while treated with non-steroidal anti-inflammatory drugs for one and six months, respectively, in one patient symptoms completely disappeared after prednisone treatment and in one patient severity of symptoms decreased and ESR normalized spontaneously.

Table 1 Clinical diagnosis in 22 patients suspected of vasculitis or with fever of unknown origin and FDG-PET results indicating vasculitis

Category	No. of cases
Vasculitis	14
Giant cell arteritis	5
Polymyalgia rheumatica	2
Polyarteritis nodosa	3
Takayasu	1
Churge-Strauss	1
Wegener's granulomatosis	1
Vasculitis skin (unspecified)	1
Fibromuscular dysplasia	2
Media necrosis aorta (of unknown origin)	1
No diagnosis	5

The median duration of symptoms before FDG-PET was performed was five weeks (range 2 weeks to 41 months). In three patients (14%) the symptoms persisted for more than six months before FDG-PET was ordered. The first FDG-PET scan was requested because of suspected vasculitis in 20 patients and because of fever of unknown origin in the remaining two patients. Table 2 shows the classification of the FDG-PET results. Ten of the total number of 22 "first" FDG-PET scans were abnormal (45%) and all these abnormal FDG-PET results were found in patients with active vasculitis and were thus considered to be true positive. Examples are shown in figures 1 and 2. In two patients with active temporal arteritis and in one patient with vasculitis limited to the skin who had not been treated with corticosteroids, the results of FDG-PET were classified as false negative. Normal FDG-PET results were categorized as true negative in five patients in whom no diagnosis could be reached, in two patients with fibromuscular dysplasia, and in the patient with

media necrosis. One patient with a history of Takayasu arteritis, which had been inactive for almost four years, was suspected of recurrence of active vasculitis because of painful shoulders and a slightly elevated ESR. Symptoms spontaneously disappeared, ESR normalized and no diagnosis of recurrence of active vasculitis was made, so the normal FDG-PET results were also considered to be true negative in this case.

Table 2 Classification of the results of 27 FDG-PET scans in patients suspected of vasculitis or with fever of unknown origin with FDG-PET results indicating vasculitis

Category	True positive	True negative	False negative	False positive
Vasculitis (diagnosis)	10	1	3	0
Vasculitis (control)	0	5	0	0
Fibromuscular dysplasia	0	2	0	0
Media necrosis aorta	0	1	0	0
No diagnosis	0	5	0	0
Total	10	14	3	0

In three patients with polyarteritis nodosa, one patient with temporal arteritis and one patient with Wegener's granulomatosis, a second FDG-PET scan was performed to evaluate the effect of treatment with a median time between the first and second FDG-PET scans of 11 weeks (range 4 to 25 weeks). FDG-PET results were normal in these five patients who all had a good clinical and biochemical response to therapy (Table 2). After the second FDG-PET scan proved to be normal, corticosteroid dose was tapered in all five patients without relapse of symptoms thus far. The results of these FDG-PET scans were considered to be true negative. The sensitivity of all 27 FDG-PET scans in these 22 patients was 77%, specificity was 100%, positive predictive value was 100% and negative predictive value was 82%.

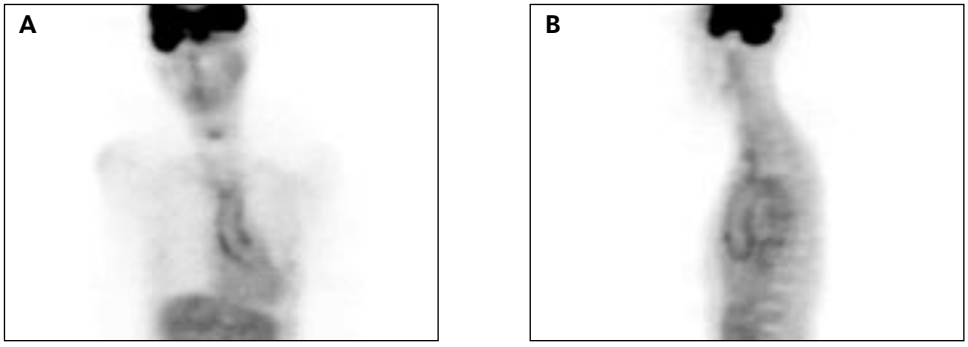

Figure 1 This 80-year-old woman was diagnosed with temporal arteritis in 1999 based on the ACR criteria including typical changes on temporal artery biopsy. She responded well to high dose prednisone, which was slowly tapered to 5 mg. She remained well until January 2002 when she presented with headaches, painful shoulders and weight loss (8 kg). Physical examination had not changed and revealed absence of pulsation of the temporal arteries, but was otherwise normal. ESR was slightly elevated to 22 mm/h (normal <12 mm/h). She did not respond to prednisone 20 mg daily. Since recurrence of giant cell arteritis was suspected, FDG-PET was performed to evaluate whether her symptoms were caused by active vasculitis. PET demonstrated increased FDG-uptake especially in the ascending aorta indicating active aortitis (Figure 1A: coronal projection, Figure 1B: sagittal projection). She was diagnosed with reactivation of giant cell arteritis and her symptoms disappeared again after high dose prednisone treatment.

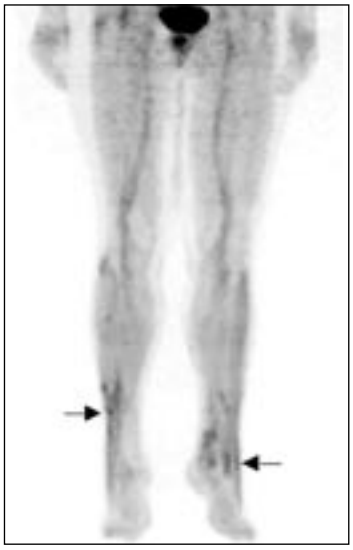

Figure 2 This previously healthy 60-year-old woman presented with myalgia of the lower legs, skin ulcerations on both legs, livedo reticularis and mild polyneuropathy. A skin biopsy showed fibrosing panniculitis and necrotizing vasculitis of medium-sized arteries. Polyarteritis nodosa was diagnosed according to the ACR criteria. FDG-PET was performed to determine the extent of the vasculitis. Increased FDG-uptake was found in both femoral arteries and several superficial lesions on the lower legs (arrows); the latter were probably caused by the skin ulcerations. No vascular FDG-uptake was noticed elsewhere (not shown). She was treated with high dose prednisone and her symptoms disappeared.

Discussion

In this study we retrospectively evaluated the utility of FDG-PET in diagnosis and follow-up of vasculitis. The results demonstrate that vascular FDG-uptake is increased in different types of active vasculitis. To our knowledge, increased FDG-uptake on PET scanning has not been reported before in patients with polyarteritis nodosa or Churge-Strauss syndrome. In addition, a remarkable decrease in FDG-uptake corresponded well with improvement of symptoms and laboratory results in five patients, suggesting that vascular FDG-uptake is only seen in active vasculitis and not in non-inflammatory vascular disease such as fibromuscular dysplasia or in inactive disease. Although inflammation of the arterial wall is most prominent in vasculitis, inflammation also contributes to atherogenesis. In an atherosclerotic rabbit model, increased FDG accumulation was shown in the affected arteries [32]. FDG-uptake in the femoral and iliac arteries was increased in 133 patients with at least one risk factor for atherosclerosis when compared to 23 controls [33]. In our experience, FDG-uptake in vasculitis is much higher than in atherosclerosis, so a distinction between these two diagnoses may very well be possible.

Besides several case reports and a case series in patients with giant cell arteritis or polymyalgia rheumatica [17,19,20], Takayasu arteritis [20-24], periaortitis due to Wegener's granulomatosis [25], aortitis of the thoracic aorta [20,26] and large vessel vasculitis [27,28], only two prospective studies exploring the diagnostic value of FDG-PET imaging in vasculitis have been published. Blockmans et al. [18] found a sensitivity of FDG-uptake in the large thoracic arteries for the diagnosis of temporal arteritis or polymyalgia rheumatica of 56%, a specificity of 98%, a positive predictive value of 93% and a negative predictive value of 80% in 25 patients with biopsy-proven temporal arteritis or polymyalgia rheumatica. The extent of the vasculitis to a much larger part of the arterial

system than is usually suspected in giant cell arteritis, was remarkable. It was also suggested that the results of this study support the hypothesis that polymyalgia rheumatica is caused by the same kind of vasculitis [18], therefore these patients were included in the present study. Meller et al. [20] compared FDG-PET with MRI in 15 patients with aortitis due to giant cell aortitis (n=14) or Takayasu arteritis (n=1) at the time of diagnosis and during follow-up (n=7). It was concluded that FDG-PET is a valuable technique as well in diagnosis as in follow-up of patients with aortitis, because it identified more vascular regions involved in the inflammatory process than did MRI [20]. Sensitivity of FDG-uptake in vasculitis in the study by Blockmans et al. seems to be lower when compared to the results of the present study (56 versus 77%). However, we found false negative results in two out of seven patients diagnosed with temporal arteritis or polymyalgia rheumatica suggesting that sensitivity of FDG-PET may be lower in these patients than in patients with other types of vasculitis. Due to high uptake in the brain, the small diameter of the vessel, and the relatively high background of the skin, direct evaluation of the temporal arteries is not possible on whole body PET imaging. This could explain the difficulty of detecting giant cell arteritis by FDG-PET, especially in cases where vasculitis is really limited to the temporal arteries.

Conventional scintigraphic techniques have also been used occasionally in patients with vasculitis. In a prospective study of 19 patients with biopsy-proven temporal arteritis, ^{67}Ga-citrate scintigraphy (^{67}Ga) had a 94% specificity and a 90% positive predictive value with normalization of ^{67}Ga-uptake after 6 months of steroid therapy [34]. In one study radiolabeled leukocyte scintigraphy seemed to be superior to conventional angiography and CT for detecting and monitoring vasculitic involvement of the respiratory tract [35]. In Takayasu arteritis, however, ^{111}In-leukocyte scintigraphy had a low sensitivity for active disease [36]. Compared to conventional nuclear medicine techniques, advantages of FDG-PET in diagnosing inflammation are early imaging (one hour), resulting in early reporting [37], tomographic information with higher spatial resolution, resulting in more anatomic information, and high inter observer agreement [38].

Recently, imaging techniques for demonstrating anatomic blood vessel changes in vasculitis, such as CT angiography, MRI, and color duplex ultrasonography, have greatly improved. This improvement and the invasive nature of classic angiography causes an inclination to perform these imaging techniques instead of angiography in diagnosis and follow-up of patients with vasculitis. CT angiography is able to detect luminal and vessel wall changes in patients with Takayasu arteritis with high accuracy [39,40]. Vascular wall thickening is also an important finding on MRI in the acute phase of Takayasu arteritis, subsiding after appropriate therapy [41,42]. Mural edema is a characteristic pattern of active and progressive Takayasu arteritis, which is absent in the chronically active state [43]. In patients with giant cell arteritis, MRA is potentially useful for follow-up of the effect of treatment [44,45]. Duplex ultrasonography is able to demonstrate luminal changes, aneurysms, and a hypoechoic halo, most probably caused by vessel wall edema, in patients with temporal arteritis and Takayasu arteritis [46-48]. In a study of 86 patients with biopsy-proven temporal arteritis, it was concluded that color duplex ultrasonography made only a modest contribution to diagnosing temporal arteritis [49]. In another study, duplex ultrasonography was found to be a non-invasive, relatively inexpensive, and efficient method, suitable for repeated

follow-up in patients with Takayasu arteritis [40]. However, ultrasonography is limited in the extent to which it can detect all diseased vessels, especially the pulmonary arteries, the aorta, and the visceral vessels. Positive aspects of FDG-PET imaging compared to CT, MRI and ultrasonography are whole body screening, high contrast resolution, absence of disturbance by metallic implants (CT, MRI) and absence of contrast-related side effects (CT). Also, FDG-PET shows functional changes caused by activation of inflammatory cells and does not depend on anatomical changes in contrast to CT, MRI and ultrasonography. Disadvantages of FDG-PET are higher cost, still limited availability and more limited anatomic information due to lower spatial resolution as compared to CT and MRI.

In conclusion, FDG-PET appears to be a valuable new imaging technique in diagnosing and determining the extent of various forms of vasculitis. Furthermore, FDG-PET may become a useful tool for evaluating the effect of treatment of vasculitis that cannot reliably be visualized by conventional techniques. However, for a validation of FDG-PET in patients with suspected vasculitis and for determination of its exact position in the follow-up of response to treatment, prospective studies in a larger number of patients are warranted.

References

1 Hunder GG, Arend WP, Bloch DA et al. The American College of Rheumatology 1990 criteria for the classification of vasculitis. Introduction. Arthritis Rheum 1990;33:1065-1067.
2 Bloch DA, Michel BA, Hunder GG et al. The American College of Rheumatology 1990 criteria for the classification of vasculitis. Patients and methods. Arthritis Rheum 1990;33:1068-1073.
3 Lie JT. Illustrated histopathologic classification criteria for selected vasculitis syndromes. American College of Rheumatology Subcommittee on Classification of Vasculitis. Arthritis Rheum 1990;33:1074-1087.
4 Lightfoot RW, Jr., Michel BA, Bloch DA et al. The American College of Rheumatology 1990 criteria for the classification of polyarteritis nodosa. Arthritis Rheum 1990;33:1088-1093.
5 Masi AT, Hunder GG, Lie JT et al. The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). Arthritis Rheum 1990;33:1094-1100.
6 Leavitt RY, Fauci AS, Bloch DA et al. The American College of Rheumatology 1990 criteria for the classification of Wegener's granulomatosis. Arthritis Rheum 1990;33:1101-1107.
7 Calabrese LH, Michel BA, Bloch DA et al. The American College of Rheumatology 1990 criteria for the classification of hypersensitivity vasculitis. Arthritis Rheum 1990;33:1108-1113.
8 Mills JA, Michel BA, Bloch DA et al. The American College of Rheumatology 1990 criteria for the classification of Henoch-Schonlein purpura. Arthritis Rheum 1990;33:1114-1121.
9 Hunder GG, Bloch DA, Michel BA et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum 1990;33:1122-1128.
10 Arend WP, Michel BA, Bloch DA et al. The American College of Rheumatology 1990 criteria for the classification of Takayasu arteritis. Arthritis Rheum 1990;33:1129-1134.
11 Fries JF, Hunder GG, Bloch DA et al. The American College of Rheumatology 1990 criteria for the classification of vasculitis. Summary. Arthritis Rheum 1990;33:1135-1136.
12 Rao JK, Allen NB, Pincus T. Limitations of the 1990 American College of Rheumatology classification criteria in the diagnosis of vasculitis. Ann Intern Med 1998;129:345-352.
13 Bleeker-Rovers CP, Bredie SJ, van der Meer JW, Corstens FH, Oyen WJ. Fluorine 18 fluorodeoxyglucose positron emission tomography in the diagnosis and follow-up of three patients with vasculitis. Am J Med 2004;116:50-53.
14 Bar-Shalom R, Valdivia AY, Blaufox MD. PET imaging in oncology. Semin Nucl Med 2000;30:150-185.
15 Kubota R, Yamada S, Kubota K et al. Intratumoral distribution of fluorine-18-fluorodeoxyglucose in vivo: high accumulation in macrophages and granulation tissues studied by microautoradiography. J Nucl Med 1992;33:1972-1980.

16 Brown RS, Leung JY, Fisher SJ et al. Intratumoral distribution of tritiated fluorodeoxyglucose in breast carcinoma: I. Are inflammatory cells important? J Nucl Med 1995;36:1854-1861.
17 Blockmans D, Maes A, Stroobants S et al. New arguments for a vasculitic nature of polymyalgia rheumatica using positron emission tomography. Rheumatology (Oxford) 1999;38:444-447.
18 Blockmans D, Stroobants S, Maes A, Mortelmans L. Positron emission tomography in giant cell arteritis and polymyalgia rheumatica: evidence for inflammation of the aortic arch. Am J Med 2000;108:246-249.
19 Turlakow A, Yeung HW, Pui J et al. Fludeoxyglucose positron emission tomography in the diagnosis of giant cell arteritis. Arch Intern Med 2001;161:1003-1007.
20 Meller J, Strutz F, Siefker U et al. Early diagnosis and follow-up of aortitis with [(18)F]FDG PET and MRI. Eur J Nucl Med Mol Imaging 2003;5:730-736.
21 Hara M, Goodman PC, Leder RA. FDG-PET finding in early-phase Takayasu arteritis. J Comput Assist Tomogr 1999;23: 16-18.
22 Meller J, Altenvoerde G, Munzel U et al. Fever of unknown origin: prospective comparison of [18F]FDG imaging with a double-head coincidence camera and gallium-67 citrate SPET. Eur J Nucl Med 2000;27:1617-1625.
23 Meller J, Grabbe E, Becker W, Vosshenrich R. Value of F-18 FDG hybrid camera PET and MRI in early takayasu aortitis. Eur Radiol 2003;13:400-405.
24 Malik IS, Harare O, AL Nahhas A, Beatt K, Mason J. Takayasu's arteritis: management of left main stem stenosis. Heart 2003;89:e9.
25 Blockmans D, Baeyens H, Van Loon R, Lauwers G, Bobbaers H. Periaortitis and aortic dissection due to Wegener's granulomatosis. Clin Rheumatol 2000;19:161-164.
26 Derdelinckx I, Maes A, Bogaert J, Mortelmans L, Blockmans D. Positron emission tomography scan in the diagnosis and follow-up of aortitis of the thoracic aorta. Acta Cardiol 2000;55:193-195.
27 Wiest R, Gluck T, Schonberger J et al. Clinical image: occult large vessel vasculitis diagnosed by PET imaging. Rheumatol Int 2001;20:250.
28 Wenger M, Gasser R, Donnemiller E et al. Images in cardiovascular medicine. Generalized large vessel arteritis visualized by 18fluorodeoxyglucose-positron emission tomography. Circulation 2003;107:923.
29 Hoogendoorn EH, Oyen WJ, van Dijk AP, van der Meer JW. Pneumococcal aortitis, report of a case with emphasis on the contribution to diagnosis of positron emission tomography using fluorinated deoxyglucose. Clin Microbiol Infect 2003;9:73-76.
30 Petersdorf RG. Fever of unknown origin. An old friend revisited. Arch Intern Med 1992;152:21-22.
31 Bleeker-Rovers CP, de Kleijn EM, Corstens FH, van der Meer JW, Oyen WJ. Clinical value of FDG PET in patients with fever of unknown origin and patients suspected of focal infection or inflammation. Eur J Nucl Med Mol Imaging 2004;3:29-37.
32 Lederman RJ, Raylman RR, Fisher SJ et al. Detection of atherosclerosis using a novel positron-sensitive probe and 18-fluorodeoxyglucose (FDG). Nucl Med Commun 2001;22:747-753.
33 Yun M, Jang S, Cucchiara A, Newberg AB, Alavi A. 18F FDG uptake in the large arteries: a correlation study with the atherogenic risk factors. Semin Nucl Med 2002;32:70-76.
34 Genereau T, Lortholary O, Guillevin L et al. Temporal 67gallium uptake is increased in temporal arteritis. Rheumatology (Oxford) 1999;38:709-713.
35 Reuter H, Wraight EP, Qasim FJ, Lockwood CM. Management of systemic vasculitis: contribution of scintigraphic imaging to evaluation of disease activity and classification. QJM 1995;88:509-516.
36 Chen CC, Kerr GS, Carter CS et al. Lack of sensitivity of indium-111 mixed leukocyte scans for active disease in Takayasu's arteritis. J Rheumatol 1995;22:478-481.
37 Sugawara Y, Braun DK, Kison PV et al. Rapid detection of human infections with fluorine-18 fluorodeoxyglucose and positron emission tomography: preliminary results. Eur J Nucl Med 1998;25:1238-1243.
38 Kalicke T, Schmitz A, Risse JH et al. Fluorine-18 fluorodeoxyglucose PET in infectious bone diseases: results of histologically confirmed cases. Eur J Nucl Med 2000;27:524-528.
39 Park JH, Chung JW, Im JG et al. Takayasu arteritis: evaluation of mural changes in the aorta and pulmonary artery with CT angiography. Radiology 1995;196:89-93.
40 Lefebvre C, Rance A, Paul JF et al. The role of B-mode ultrasonography and electron beam computed tomography in evaluation of Takayasu's arteritis: a study of 43 patients. Semin Arthritis Rheum 2000;30:25-32.
41 Tanigawa K, Eguchi K, Kitamura Y et al. Magnetic resonance imaging detection of aortic and pulmonary artery wall thickening in the acute stage of Takayasu arteritis. Improvement of clinical and radiologic findings after steroid therapy. Arthritis Rheum 1992;35:476-480.

42 Matsunaga N, Hayashi K, Sakamoto I et al. Takayasu arteritis: MR manifestations and diagnosis of acute and chronic phase. J Magn Reson Imaging 1998;8:406-414.
43 Flamm SD, White RD, Hoffman GS. The clinical application of 'edema-weighted' magnetic resonance imaging in the assessment of Takayasu's arteritis. Int J Cardiol 1998;66:S151-S159.
44 Harada S, Mitsunobu F, Kodama F et al. Giant cell arteritis associated with rheumatoid arthritis monitored by magnetic resonance angiography. Intern Med 1999;38:675-678.
45 Anders HJ, Sigl T, Sander A et al. Gadolinium contrast magnetic resonance imaging of the temporal artery in giant cell arteritis. J Rheumatol 1999;26:2287-2288.
46 Schmidt WA, Kraft HE, Vorpahl K, Volker L, Gromnica-Ihle EJ. Color duplex ultrasonography in the diagnosis of temporal arteritis. N Engl J Med 1997;337:1336-1342.
47 Schmidt WA, Nerenheim A, Seipelt E, Poehls C, Gromnica-Ihle E. Diagnosis of early Takayasu arteritis with sonography. Rheumatology (Oxford) 2002;41:496-502.
48 Taniguchi N, Itoh K, Honda M et al. Comparative ultrasonographic and angiographic study of carotid arterial lesions in Takayasu's arteritis. Angiology 1997;48:9-20.
49 Salvarani C, Silingardi M, Ghirarduzzi A et al. Is duplex ultrasonography useful for the diagnosis of giant-cell arteritis? Ann Intern Med 2002;137:232-238.

Chapter 4

^{18}F-fluorodeoxyglucose positron emission tomography for visualization of lipodystrophy in HIV-infected patients

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Abstract

Lipodystrophy is accompanied by increased adipose tissue inflammatory activity. Together with mitochondrial toxicity of nucleoside reverse transcriptase inhibitors, this induces metabolic stress causing increased glucose-uptake. We hypothesize that this can be visualized by FDG-PET. Markedly increased subcutaneous FDG-uptake was observed in 3 out of 4 HIV-infected patients with lipodystrophy treated by a stavudine-containing HAART-regimen. This phenomenon was absent in HIV-infected controls without lipodystrophy. In conclusion, markedly increased subcutaneous FDG-uptake on PET is an appropriate tool to visualize lipodystrophy.

Introduction

Treatment with highly active antiretroviral therapy (HAART) has dramatically reduced HIV-associated morbidity and mortality. However, an important side effect of HAART is lipodystrophy, a syndrome characterized by peripheral fat wasting (lipoatrophy), central adiposity and metabolic changes such as hyperlipidemia, hyperglycemia and insulin resistance.

The etiology of adipose tissue changes and metabolic disturbances in patients with HIV-associated lipodystrophy is unclear, but is likely to be multifactorial. Increased cytokine secretion from adipose tissue and increased systemic pro-inflammatory cytokine activity appears to play a significant role in adipose tissue remodeling in lipodystrophy [1]. As a consequence, metabolic demand of adipose tissue is increased. Stavudine-based regimens have the highest incidence of lipoatrophy and switching treatment to zidovudine or abacavir may reduce this adverse effect [2]. It is well known that stavudine, like other nucleoside reverse transcriptase inhibitors (NRTI), compromises mitochondrial function. In addition, stavudine suppresses the expression of adipocyte differentiation markers [3]. The combination of an increased metabolic demand and a compromised oxidative phosphorylation induces metabolic stress in adipose tissue. In general, metabolic stress is accompanied by increased glucose-uptake as a result of the translocation of the specific glucose-transporter GLUT-1 [4]. Therefore, we investigated whether active lipodystrophy can be monitored in vivo by visualizing glucose-uptake using ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET).

Methods

In this prospective study, the diagnosis of HIV-related lipodystrophy was based on the following criteria: clinical evidence by doctor's and patient's report of fat wasting of the face, arms, legs, or buttocks and/or fat accumulation in the abdomen or over the dorsocervical spine and fasting hyperlipidemia (cholesterol $\geq$ 5.5 mmol/L or triglyceride $\geq$ 2.0 mmol/L), fasting C-peptide >2.5 mmol/L or impaired fasting glucose or diabetes mellitus (fasting glucose >6.1 mmol/L) in the absence of an AIDS-defining event or other severe clinical illness or the use of anabolic steroids, glucocorticoids

or immune modulators within three months of assessment. FDG-PET was performed in 4 HIV-infected patients with early features of lipodystrophy (all fulfilling the clinical definition) treated by a stavudine-containing HAART regimen for a maximum of 3 years, in 4 HIV-infected patients never treated by HAART (control 1) and in 5 HIV-infected patients without lipodystrophy treated for a maximum of 3 years by HAART that never included stavudine (control 2). In lipodystrophy patients with markedly increased subcutaneous FDG-uptake, stavudine was replaced by zidovudine, abacavir or tenofovir and FDG-PET was repeated 3 to 6 months later. The protocol was approved by the local Research Ethics Committee. All patients provided written informed consent.

Whole body PET scanning was performed using a dedicated full ring PET scanner (ECAT-EXACT, Siemens/CTI, Knoxville, TN., USA). Prior to FDG injection patients had fasted for at least 6 hours, inducing a low insulin-state. Immediately prior to the procedure, the patients were hydrated with 500 ml of water. One hour after intravenous injection of 220 MBq FDG (Tyco Healthcare/Mallinckrodt Medical, Petten, The Netherlands) and 10 to 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). Images were reconstructed with segmented attenuation correction. Subcutaneous FDG-uptake was evaluated by two nuclear medicine specialists without information on the prescription of HAART or the presence or absence of the lipodystrophy syndrome. Disagreements were resolved by consensus.

Results

All patients were male with a median age of 48 years in the lipodystrophy group (range 38 to 56), 41 years in control group 1 (range 28 to 50) and 36 years in control group 2 (range 28 to 44). The median duration of HAART was 27 months in lipodystrophy patients (range 14 to 32) and 20 months in control group 2 (range 14 to 36). Lipodystrophy patients were treated by 2 NRTI and protease inhibitors (n=3) or 2 NRTI and nevirapine (n=1). In control group 2, HAART consisted of 2 NRTI and a protease inhibitor (n=1), of 2 NRTI and efavirenz (n=3) or of 2 NRTI and nevirapine (n=1). All of these patients had a favorable virological response (viral load <50 copies/ml) except for one control patient with a viral load of 100 copies/ml. Markedly increased subcutaneous FDG-uptake was observed in 3 out of 4 lipodystrophy patients (Figure 1A) and in none of the patients in both control groups. In all patients with markedly increased subcutaneous FDG-uptake, stavudine was replaced by zidovudine or abacavir. In these three patients, who reported a slight improvement of symptoms, FDG-PET, repeated 3 to 6 months later, showed normalization of subcutaneous FDG-uptake (Figure 1B).

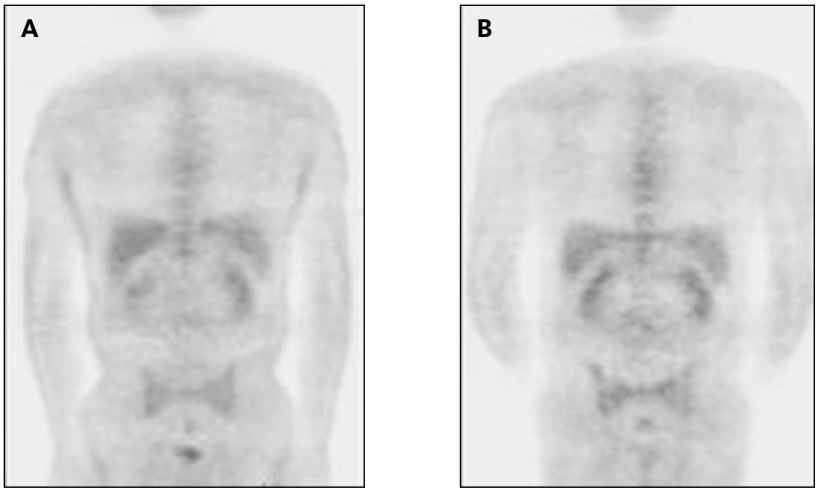

Figure 1 This 46-year-old HIV-positive man who had been treated with HAART for 30 months developed lipodystrophy. PET showed markedly increased subcutaneous FDG-uptake in the thoracic, abdominal and pelvic areas (Figure 1A). In this patient antiretroviral therapy was adjusted which resulted in a slight subjective improvement. FDG-PET 6 months after switching of therapy was completely normal without any evidence of increased subcutaneous FDG-uptake (Figure 1B).

Discussion

Markedly increased subcutaneous FDG-uptake in 3 out of 4 HIV-infected patients with lipodystrophy and absence of this phenomenon in HIV-infected controls without lipodystrophy supports the hypothesis that stavudine-related lipodystrophy is associated with increased glucose-uptake as a result of metabolic stress of adipose tissue in response to HAART. Because of the low insulin-state, glucose-uptake is probably mediated by GLUT-1. It is unlikely that increased subcutaneous FDG-uptake is mediated by translocation of the insulin-dependent GLUT-4-transporter, because lipodystrophy is associated with marked insulin resistance. In one study using FDG-PET in order to explain the mechanism of insulin resistance in HIV-infected patients with the lipodystrophy syndrome, a decreased cellular FDG-uptake in skeletal muscle was observed [5]. Our data show that FDG-PET is able to visualize lipodystrophy. As such, FDG-PET may become a promising tool to monitor lipodystrophy during the course of HIV-treatment. Moreover, in clinical trials, the lipodystrophy-inducing effect of newly developed antiretroviral regimens may be monitored objectively by this approach.

In conclusion, markedly increased subcutaneous FDG-uptake on PET-scanning is an objective tool to visualize stavudine-related lipodystrophy and supports the hypothesis that lipodystrophy is associated with increased glucose-uptake as a result of metabolic stress of adipose tissue in response to HAART. Reduction of subcutaneous FDG-uptake 3 to 6 months after replacement of stavudine suggests that this strategy is able to decrease HAART-related metabolic stress of adipose tissue.

References

1 Johnson JA, Albu JB, Engelson ES et al. Increased systemic and adipose tissue cytokines in patients with HIV-associated lipodystrophy. Am J Physiol Endocrinol Metab 2004;286:E261-E271.

2 McComsey GA, Ward DJ, Hessenthaler SM et al. Improvement in lipoatrophy associated with highly active antiretroviral therapy in human immunodeficiency virus-infected patients switched from stavudine to abacavir or zidovudine: the results of the TARHEEL study. Clin Infect Dis 2004;38:263-270.

3 Pace CS, Martin AM, Hammond EL et al. Mitochondrial proliferation, DNA depletion and adipocyte differentiation in subcutaneous adipose tissue of HIV-positive HAART recipients. Antivir Ther 2003;8:323-331.

4 Rudich A, Kozlovsky N, Potashnik R, Bashan N. Oxidant stress reduces insulin responsiveness in 3T3-L1 adipocytes. Am J Physiol 1997;272 1:E935-E940.

5 Behrens GM, Boerner AR, Weber K et al. Impaired glucose phosphorylation and transport in skeletal muscle cause insulin resistance in HIV-1-infected patients with lipodystrophy. J Clin Invest 2002;110:1319-1327.

Chapter 5

^{18}F-fluorodeoxyglucose positron emission tomography in detecting metastatic infectious disease

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Abstract

Timely identification of metastatic complications of blood stream infections due to spreading of the micro-organisms to distant sites, although critical, is often difficult. As ^{18}F-fluorodeoxyglucose (FDG) accumulates in activated leukocytes in infectious lesions, FDG-positron emission tomography (PET) represents a promising imaging technique in these patients. The aim of this study was to assess the value of FDG-PET in detecting infectious foci in patients at high risk of metastatic complications.

Methods: The results of all FDG-PET-scans ordered because of suspected metastatic infection from October 1998 to September 2004 were analyzed retrospectively. These results were compared to conventional investigation techniques and the final clinical diagnosis.

Results: The results of 40 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 four diagnostic procedures to search for metastatic infection had been performed before FDG-PET was ordered. FDG-PET diagnosed a clinically relevant new focus in 45% of cases and confirmed abnormalities already diagnosed in 30%. The positive predictive value of FDG-PET was 91% and the negative predictive value was 100%.

Conclusion: 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.

Introduction

One of the main complications of blood stream infections, especially in case of *S. aureus* bacteremia or candidemia, is secondary metastatic infection caused by spreading of the micro-organisms 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 micro-organisms 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 first symptoms and initiation of antibiotic therapy, the presence of prosthetic devices, persistent fever after 72 hours, and positive follow-up blood cultures at 24 to 96 hours [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 blood stream 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 computed tomography (CT), magnetic resonance imaging (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. Since activated inflammatory cells take up large amounts of glucose as a result of an increased metabolic rate [9], ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) represents a promising imaging technique in these patients. The aim of this study was to assess the value of 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 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: persisting fever or positive blood cultures for more than 48 hours after initiation of antibiotic therapy, clinical deterioration after initial improvement of symptoms, or metastatic infectious foci elsewhere. All patients were evaluated with other imaging modalities and laboratory tests as was considered clinically appropriate.

FDG-PET

A full ring PET scanner (ECAT-EXACT, Siemens/CTI, Knoxville, TN, USA) was used for data acquisition. Prior to FDG-injection patients had fasted for at least 6 hours. Immediately prior to the procedure, the patients were hydrated with 500 ml of water. One hour after intravenous injection of 200-220 MBq FDG (Tyco Healthcare/Mallinckrodt Medical, Petten, The Netherlands) and 10 to 15 mg furosemide, emission and transmission images of the area between the proximal femora and the base of the skull were acquired (10 minute 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. FDG-PET results were judged to be abnormal if focal accumulation of the tracer was detected outside areas of physiological 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 and/or culture of the vascular catheter tip was positive for the same micro-organism without clinical evidence of another source for infection. The infection was considered to be nosocomial if cultures obtained after >48 hours 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 hours after admission and/or signs of blood stream infection were present before admission.

Clinical assessment of test results and diagnosis

The results of FDG-PET were evaluated for their diagnostic contribution. A normal FDG-PET-scan was called true negative when no metastatic complications or relapse of infection were diagnosed during clinical follow-up of at least three months. A normal FDG-PET scan was considered false negative when a focal infection was diagnosed except for infection in the brain, the heart, the kidneys or the bladder (sites known for low sensitivity of FDG-PET due to physiological uptake of FDG) or the legs (not routinely imaged). Results were considered to be true positive when abnormal FDG-uptake pointed to the organ or tissue where the cause of the symptoms was eventually found. FDG-uptake in the source of the infection as well as in metastatic infectious foci were considered as true positive results. True positive FDG-PET results were further categorized as "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 "clinically irrelevant new finding" when the abnormality did not change treatment or as "already known" when FDG-PET only showed 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 FDG-PET results.

Follow-up

Medical charts were reviewed for follow-up data. After a minimum follow-up of three months, 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 micro-organism within 12 weeks of the initial episode.

Statistical analysis

Descriptive statistics for continuous variables are represented as medians $\pm$ standard deviations. Categorical 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 Fisher's exact tests for categorical variables. Differences were considered to be statistically significant at $P < 0.05$.

Results

From October 1998 to September 2004, 40 FDG-PET-scans were performed because of suspected metastatic infection. In two patients, FDG-PET was performed during two separate episodes of central venous catheter (CVC)-related blood stream 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 one day). 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.

Table 1 Patient characteristics of 40 patients suspected of infectious metastatic disease in whom FDG-PET was performed

Characteristic	Total	Metastatic Foci	
	(n=40)	Yes (n=30)	No (n=10)
Male	23 (58%)	17 (57%)	6 (60%)
Female	17 (42%)	13 (43%)	4 (40%)
Age (years)	60 ± 17	60 ± 17	60 ± 18
Community acquired infection	30 (75%)	23 (77%)	7 (70%)
Duration of symptoms until presentation (days)#†	1 ± 8	1 ± 7	1 ± 9
Duration of symptoms until adequate therapy (days)#†	2 ± 8	3 ± 8	2 ± 9
CVC present	13 (33%)	10 (33%)	3 (30%)
Duration of CVC present (weeks)†	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
Mechanic heart valve	2 (5%)	2 (7%)	0
Malignancy	1 (3%)	1 (3%)	0
Immunosuppressive drugs	8 (20%)	7 (23%)	1 (10%)
I.V. drug use	0	0	0
Positive blood cultures (number/patient)†	3 ± 3	4 ± 3‡	2 ± 1‡
Duration of positive blood cultures (days)†	2 ± 8	3 ± 8‡	1 ± 1‡

CVC=central venous catheter
# One patient was excluded from these calculations because she had suffered from lower back pain, periodic low-grade fever and fatigue for almost three years before she was diagnosed with a *S. aureus* psoas abscess and before FDG-PET was performed.
† median ± SD
‡ P <0.05

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 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 blood

stream infections, the CVC was removed before FDG-PET was requested. In 30 cases (75%), metastatic infectious foci were eventually diagnosed by conventional diagnostic techniques, FDG-PET or both. Metastatic infection was most often diagnosed in the cardiovascular system, the lungs and in bones or joints (Table 4). Of those with metastatic infection, 11 (37%) were diagnosed with metastatic foci in more than one organ system.

Table 2 Culture results

Category	Species	Total	Metastatic foci	
		(n=40)	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 one patient, blood cultures were positive for *Enterococcus faecium* as well as *Candida tropicalis*.

Table 3 Portal of entry: source of the bacteremia or fungemia

Diagnosis	Total	Metastatic foci	
	(n=40)	Yes (n=30)	No (n=10)
CVC-related blood stream infection	12	9	3
Soft tissue-/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
Not known	12	12	0

CVC=central venous catheter
CAPD=continuous ambulatory peritoneal dialysis

A median number of four diagnostic procedures to search for metastatic complications was performed before FDG-PET was requested (range 1 to 10). Chest X-ray was performed in 34 patients (85%), chest CT in seven patients (18%), abdominal ultrasound in 25 patients (63%), abdominal CT in 18 patients (45%), doppler ultrasonography of the subclavian and internal jugular veins in six patients (50% of all patients with CVC-related infection), and echocardiography was performed in 21 patients (53%).

Table 4 Localization of metastatic infectious foci in 30 patients eventually diagnosed with metastatic disease

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

In 11 patients, metastatic infectious foci were found in more than one organ system.

Results of FDG-PET were negative in six patients (Table 5). None of these patients were diagnosed with metastatic complications or relapse after a follow-up period of at least three months, so these results were considered true negative. FDG-PET results were true positive in 31 cases (78%). FDG-PET diagnosed a clinically relevant new focus (Figure 1) in 18 cases (45%), a clinically irrelevant new focus in one patient and confirmed already diagnosed abnormalities in 12 cases (30%). In 27 of these 31 episodes, FDG-PET results were fully confirmed by conventional diagnostic techniques. Results were partially confirmed in three cases. In the first patient, PET demonstrated increased 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 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 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 one patient with endocarditis, PET showed increased 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 deteriorated cardiovascular condition. The histories of three patients with *Candida* lung abscesses diagnosed with FDG-PET have been described in a research note [11]. In three other patients, 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 FDG-uptake in the thrombosed blood vessels, but also in several mediastinal lymph nodes. On chest CT, however, no pathologically enlarged lymph nodes were found. In the second patient, PET demonstrated increased FDG-uptake in the right hip and the left femur. Arthritis of the right hip was confirmed by ^{111}Indium-labeled polyclonal immunoglobulin G

(IgG)-scintigraphy, but no abnormal IgG-uptake in the left femur was found. In the third patient who was treated with azathioprine and prednisone because of a renal transplant, PET showed right-sided retroperitoneal FDG-uptake, but abdominal ultrasound was normal. In the remaining 7 patients treated with immunosuppressive drugs, FDG-PET was true positive. In the 40 cases studied, positive predictive value of FDG-PET was 91% and negative predictive value was 100%.

Table 5 FDG-PET results in 40 patients suspected of metastatic infectious disease

FDG-PET results			Number	Confirmation		
			(n=40)	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 one patient with *Staphylococcus aureus* bacteremia without metastatic infection, FDG-uptake was seen in the abscess of his right arm, which was the source of his bacteremia. FDG-PET was otherwise normal.

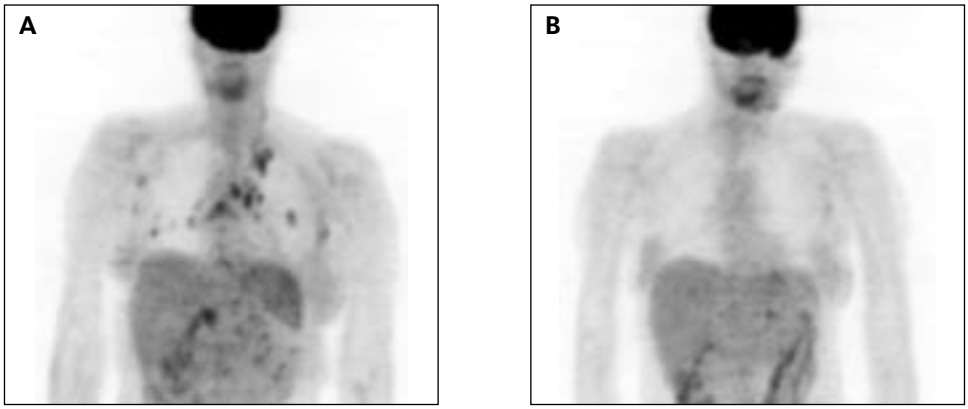

Figure 1 In a 45-year-old woman with *Staphylococcus aureus* septicemia and persistent fever during therapy, PET showed increased FDG-uptake in multiple lesions in both lungs, the mediastinum and in the upper abdomen (Figure 1A). Subsequently, chest CT also showed multiple lesions in both lungs and the mediastinum. Cholangitis caused by gallstones was confirmed by abdominal ultrasound and endoscopic retrograde cholangiopancreatography (ERCP). The fever disappeared within two days after ERCP. After three months, FDG-PET was normal (Figure 1B) and antibiotic therapy was discontinued.

The median duration of follow-up was 12 months (range 3 to 51 months). The duration of hospitalization was significantly longer in the patients with metastatic complications (median 47 vs. 23 days, Table 6). The patients with metastatic complications were also treated with antibiotics for a longer time period (median 75 vs. 35 days). The duration of fever, the percentage of patients

admitted to the ICU, and the duration of ICU stay, however, did not differ significantly between patients with and patients without metastatic complications. In the group with metastatic infection, five patients died of complicated infection and four patients had persisting infection (one patient with a mycotic aortic aneurysm with a follow-up of 36 months and three patients with infected vascular prostheses, who could not be treated surgically, with a follow-up of 3, 6, and 23 months, respectively). One patient, who had been treated because of 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%).

Table 6 Outcome of 40 patients suspected of metastatic infectious disease

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

median ± SD
† P <0.05

Discussion

In this study, the utility of FDG-PET in patients suspected of metastatic infectious disease was evaluated. Even after a median number of four conventional diagnostic tests, FDG-PET revealed clinically relevant new infectious foci in 45% of all patients. In these cases, the results of FDG-PET led to a change of treatment. This study represents the largest patient population ever screened for metastatic infectious foci by FDG-PET. No comparable studies are available at this time. In several previous studies, the accuracy of FDG-PET for diagnosing primary, mostly orthopedic, infections ranged from 80 to 100% [12-14]. Although 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 three prospective studies, FDG-PET enabled correct visualization of spondylodiscitis and proved to be superior to MRI, ^{67}gallium-citrate scintigraphy and bone scan [17-19]. In two studies, 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 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

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. The results of this study, therefore, should not be applied to all patients with blood stream infection. Furthermore, since 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 three months 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 FDG-PET in patients suspected of focal infection is difficult for several reasons. First, the interpretation of this procedure is hampered due to a lack of a gold standard, especially in case of a normal FDG-PET-scan. When additional diagnostic procedures were negative and a follow-up of at least three months 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, FDG-PET cannot exclude cerebral disease or meningitis, because physiologic uptake in the cerebral cortex in most cases obscures any pathological uptake. Besides physiologic uptake of FDG in the brain, normal activity in the heart, the kidneys and the bladder severely hampers the delineation of disease in these organs. Variable physiologic FDG-uptake in the bowel is possible [22] and can thus 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 lack of substantial anatomical changes at that time. Also, discrimination of active infectious lesions from residual changes due to cured processes or surgery remains difficult. FDG-PET shows functional changes caused by activation of inflammatory cells and does not depend on anatomical changes. In addition, advantages of FDG-PET in suspected metastatic infection, compared to 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 leucocytes 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]. Advantages of FDG-PET are early imaging (one hour vs. up to 48 hours), 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 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 FDG-PET may well become a clinically significant and also cost-effective modality, since adequate early diagnosis limits the number of non-contributing (invasive) tests required and the time to diagnosis and thus facilitates adequate antibiotic and/

or local (surgical) therapy. A further potential application, that needs to be investigated, is the contribution of FDG-PET in determining the duration of antimicrobial treatment in patients with metastatic infection.

Conclusion

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 FDG-PET for this indication and for determination of its exact position in the order of diagnostic tests, prospective studies in a larger number of patients are warranted.

References

1. Mylotte JM, McDermott C, Spooner JA. Prospective study of 114 consecutive episodes of Staphylococcus aureus bacteremia. *Rev Infect Dis.* 1987;9:891-907.
2. Fowler VG, Jr., Sanders LL, Sexton DJ, et al. Outcome of Staphylococcus aureus bacteremia according to compliance with recommendations of infectious diseases specialists: experience with 244 patients. *Clin Infect Dis.* 1998;27:478-486.
3. Oude Lashof AM, Donnelly JP, Meis JF, van der Meer JW, Kullberg BJ. Duration of antifungal treatment and development of delayed complications in patients with candidaemia. *Eur J Clin Microbiol Infect Dis.* 2003;22:43-48.
4. Nolan CM, Beaty HN. Staphylococcus aureus bacteremia. Current clinical patterns. *Am J Med.* 1976;60:495-500.
5. Fowler VG, Jr., Olsen MK, Corey GR, et al. Clinical identifiers of complicated Staphylococcus aureus bacteremia. *Arch Intern Med.* 2003;163:2066-2072.
6. Lautenschlager S, Herzog C, Zimmerli W. Course and outcome of bacteremia due to Staphylococcus aureus: evaluation of different clinical case definitions. *Clin Infect Dis.* 1993;16:567-573.
7. Lesens O, Hansmann Y, Storck D, Christmann D. Risk factors for metastatic infection in patients with Staphylococcus aureus bacteremia with and without endocarditis. *Eur J Intern Med.* 2003;14:227-231.
8. Lesens O, Hansmann Y, Brannigan E, et al. Positive surveillance blood culture is a predictive factor for secondary metastatic infection in patients with Staphylococcus aureus bacteraemia. *J Infect.* 2004;48:245-252.
9. Kubota R, Yamada S, Kubota K, et al. Intratumoral distribution of fluorine-18-fluorodeoxyglucose in vivo: high accumulation in macrophages and granulation tissues studied by microautoradiography. *J Nucl Med.* 1992;33:1972-1980.
10. Durack DT, Lukes AS, Bright DK. New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. Duke Endocarditis Service. *Am J Med.* 1994;96:200-209.
11. Bleeker-Rovers CP, Warris A, Drenth JPH, et al. Diagnosis of *Candida* lung abscesses by 18F-fluorodeoxyglucose positron emission tomography in three patients with catheter-related candidemia. *Clin Microbiol Infect.* 2005;11:493-495.
12. Sugawara Y, Braun DK, Kison PV, et al. Rapid detection of human infections with fluorine-18 fluorodeoxyglucose and positron emission tomography: preliminary results. *Eur J Nucl Med.* 1998;25:1238-1243.
13. Stumpe KD, Dazzi H, Schaffner A, von Schulthess GK. Infection imaging using whole-body FDG-PET. *Eur J Nucl Med.* 2000;27:822-832.
14. Chacko TK, Zhuang H, Nakhoda KZ, Moussavian B, Alavi A. Applications of fluorodeoxyglucose positron emission tomography in the diagnosis of infection. *Nucl Med Commun.* 2003;24:615-624.
15. Love C, Marwin SE, Tomas MB, et al. Diagnosing infection in the failed joint replacement: a comparison of coincidence detection 18F-FDG and 111In-labeled leukocyte/99mTc-sulfur colloid marrow imaging. *J Nucl Med.* 2004;45:1864-1871.
16. Oyen WJ, Claessens RA, van Horn JR, van der Meer JW, Corstens FH. Scintigraphic detection of bone and joint infections with indium-111- labeled nonspecific polyclonal human immunoglobulin G. *J Nucl Med.* 1990;31:403-12.

17. Schmitz A, Risse JH, Grunwald F, et al. Fluorine-18 fluorodeoxyglucose positron emission tomography findings in spondylodiscitis: preliminary results. *Eur Spine J*. 2001;10:534-539.
18. Gratz S, Dorner J, Fischer U, et al. 18F-FDG hybrid PET in patients with suspected spondylitis. *Eur J Nucl Med Mol Imaging*. 2002;29:516-524.
19. Stumpe KD, Zanetti M, Weishaupt D, et al. FDG positron emission tomography for differentiation of degenerative and infectious endplate abnormalities in the lumbar spine detected on MR imaging. *AJR Am J Roentgenol*. 2002;179: 1151-1157.
20. Miceli MH, Jones Jackson LB, Walker RC, et al. Diagnosis of infection of implantable central venous catheters by [18F]fluorodeoxyglucose positron emission tomography. *Nucl Med Commun*. 2004;25:813-818.
21. Miceli M, Atoui R, Walker R, et al. Diagnosis of deep septic thrombophlebitis in cancer patients by fluorine-18 fluorodeoxyglucose positron emission tomography scanning: a preliminary report. *J Clin Oncol*. 2004;22:1949-1956.
22. de Groot M, Meeuwis AP, Kok PJ, Corstens FH, Oyen WJ. Influence of blood glucose level, age and fasting period on non-pathological FDG uptake in heart and gut. *Eur J Nucl Med Mol Imaging*. 2005;32:98-101.
23. Bleeker-Rovers CP, Boerman OC, Rennen HJ, Corstens FH, Oyen WJ. Radiolabeled compounds in diagnosis of infectious and inflammatory disease. *Curr Pharm Des*. 2004;10:2935-2950.
24. Sugawara Y, Gutowski TD, Fisher SJ, Brown RS, Wahl RL. Uptake of positron emission tomography tracers in experimental bacterial infections: a comparative biodistribution study of radiolabeled FDG, thymidine, L-methionine, 67Ga-citrate, and 125I-HSA. *Eur J Nucl Med*. 1999;26:333-341.
25. Guhlmann A, Brecht-Krauss D, Suger G, et al. Fluorine-18-FDG PET and technetium-99m antigranulocyte antibody scintigraphy in chronic osteomyelitis. *J Nucl Med*. 1998;39:2145-2152.
26. De Winter F, van de WC, Vogelaers D, et al. Fluorine-18 fluorodeoxyglucose-position emission tomography: a highly accurate imaging modality for the diagnosis of chronic musculoskeletal infections. *J Bone Joint Surg Am*. 2001;83-A: 651-660.
27. Zhuang H, Duarte PS, Pourdehand M, Shnier D, Alavi A. Exclusion of chronic osteomyelitis with F-18 fluorodeoxyglucose positron emission tomographic imaging. *Clin Nucl Med*. 2000;25:281-284.

Chapter 6

Fever of unknown origin

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Abstract

Nowadays fever of unknown origin (FUO) is often defined as a fever higher than 38.3°C on several occasions during at least 3 weeks with uncertain diagnosis after a number of obligatory tests. Infection accounts for about one-third of cases of FUO, followed by neoplasm and non-infectious inflammatory diseases. No diagnosis is reached in 25 to 35% of cases. In patients with periodic fever, this percentage is even higher. A diagnostic algorithm is proposed in which the most important step is a history taking, physical examination and the obligatory investigations in a search for potentially diagnostic clues (PDCs). First, factitious fever and drug fever should be ruled out. Further diagnostic procedures should be guided by a list of most probable diagnoses. In patients without useful PDCs, certain diagnostic procedures, divided in first stage and second stage investigations should be performed. If no diagnosis is reached and the clinical condition is stable, waiting for new PDCs is recommended. In patients with recurrent fever, the diagnostic workup should consist only of the search for PDCs matching known recurrent syndromes. Scintigraphic methods, such as ^{67}gallium citrate, labeled leukocytes, and ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET), are often used in patients with FUO. Because of favorable characteristics of FDG-PET, conventional scintigraphic techniques may be replaced by FDG-PET in institutions where PET is available. If undiagnosed fever persists, supportive treatment with NSAIDs can be helpful. Most patients with undiagnosed FUO have benign self-limiting or recurrent fever. Only if patients deteriorate, other therapeutic trials should be considered.

Definition

Despite recent advances in diagnostic techniques, fever of unknown origin (FUO) remains a formidable diagnostic challenge. In 1961, FUO was defined by Petersdorf and Beeson as an illness of more than three weeks duration, fever higher than 38.3°C (101°F) on several occasions, and diagnosis uncertain after one week of study in the hospital [1]. This definition has been modified by removing the requirement that the evaluation must take place in the hospital and by excluding immunocompromized patients, because these patients need an entirely different diagnostic and therapeutic approach. Recently it has been proposed to change the quantitative criterion (diagnosis uncertain after one week of study) to a qualitative criterion that requires a list of certain investigations to be performed in order to reduce selection bias. Defining the necessary initial investigations will remain a matter of debate, but it is generally agreed that the initial diagnostic protocol required for a case to qualify as FUO should at least include the following tests: a comprehensive history and physical examination, routine blood tests, antinuclear antibodies, rheumatoid factor, microscopic urinalysis, three blood cultures, a urine culture and other cultures if clinically indicated, chest X-ray, abdominal ultrasonography and a tuberculin skin test (Table 1).

Table 1 Definition of fever of unknown origin

1.	Fever higher than 38.3°C (101°F) on two occasions
2.	More than three weeks duration
3.	Exclusion of immunocompromized patients: neutropenia (leukocyte count < 1.0 x 10^9/l and/or granulocyte count < 0,5 x 10^9/l) during at least 1 week within the 3 months preceding the fever, known HIV-infection, known hypogammaglobulinemia (IgG < 50% of the normal value), use of the equivalent of more than 10 mg prednisone during at least 2 weeks in the previous 3 months
4.	Diagnosis uncertain after thorough history-taking, physical examination and the following obligatory investigations: ESR or CRP, hemoglobulin, trombocyte count, leukocyte count and differentiation, electrolytes, kreatinine, total protein, protein electrophoresis, alkaline phosphatase, AST, ALT, LDH, creatine kinase, antinuclear antibodies, rheumatoid factor, urinalysis, blood cultures (n=3), urine culture, chest X-ray, abdominal ultrasonography and tuberculin skin test

Causes of FUO

Table 2 presents an overview of the differential diagnosis of FUO, which is probably the longest in medicine. In general, infection accounts for about one-third of cases of FUO, followed by neoplasm and non-infectious inflammatory diseases (NIID) [2]. The term NIID has replaced older terms such as rheumatic diseases, collagen diseases etc. The category NIID includes "collagen or rheumatic diseases", vasculitis syndromes and granulomatous disorders.

In recent series of FUO, no diagnosis could be reached in 25 to 35% of all cases. In patients with recurrent fever, often defined as repeated episodes of fever with fever-free intervals of at least two weeks and apparent remission of the underlying disease, the chance of reaching a diagnosis is less than 50%.

Table 2 Possible causes of FUO

Infections
Bacterial, non-specific
Endocarditis, abdominal abscesses, appendicitis, diverticulitis, adnexitis, endometritis, renal abscess, xanthogranulomatous pyelonephritis, cholecystitis, cholangitis, bacterial hepatitis, prostatitis, urinary tract infections, apical granuloma, sinusitis, mastoiditis, intracranial abscess, epidural abscess, lung abscess, mediastinitis, mycotic aneurysm, infected vascular catheter, infected vascular prosthesis, septic phlebitis, osteomyelitis, spondylodiscitis, infectious arthritis, infected joint prosthesis, infective myonecrosis
Bacterial, specific
Actinomycosis, bartonellosis, brucellosis, campylobacteriosis, *Chlamydia pneumoniae* infection, chronic meningococcemia, ehrlichiosis, febris recurrens (*Borrelia recurrentis*), gonococcemia, legionellosis, leptospirosis, listeriosis, Lyme disease, melioidosis (*Pseudomonas pseudomallei*), *Mycoplasma* infection, psittacosis, Q-fever (*Coxiella burnetii),* rickettsiosis, salmonellosis, *Spirillum minor* infection, *Streptobacillus moniliformis* infection, syphilis, tularemia, tuberculosis, Whipple's disease, yersiniosis
Viral
Cytomegalovirus infection, Coxsackievirus infection, dengue, Epstein Barr virus infection, hanta, hepatitis A, B or C, Herpes simplex, HIV infection, parvovirus infection
Fungal
Aspergillosis, candidiasis, cryptococcosis, histoplasmosis, malassezia furfur infection, Pneumocystis jiroveci pneumonia
Parasitic
Amoebiasis, babesiosis, schistosomiasis, echinococcosis, fascioliasis, leishmaniasis, malaria, toxocariasis, toxoplasmosis, trypanosomiasis, trichinosis

Neoplasia
Hematological Angio-immunoblastic lymphoma, Hodgkin's disease, non-Hodgkin's lymphoma, leukemia, malignant histiocytosis, multiple myeloma, myelodysplastic syndrome, myelofibrosis, lymphomatoid granulomatosis, systemic mastocytosis
Solid tumors Most solid tumors and metastases can cause fever, the most common causes of FUO are: breast carcinoma, colon carcinoma, hepatocellular carcinoma, lung carcinoma, pancreatic carcinoma and renal cell carcinoma
Benign tumors Angiomyolipoma, craniopharyngioma, cavernous hemangioma of the liver, necrosis in dermoid tumor in Gardner's syndrome
Non-infectious inflammatory diseases
"Collagen diseases" Acute rheumatic fever, ankylosing spondylitis, Behçet's disease, cryoglobulinemia, dermatomyositis, Felty syndrome, mixed connective tissue disease, polymyositis, Reiter's syndrome, rheumatoid arthritis, systemic lupus erythematosus, recurrent polychondritis, Sjögren's syndrome, Still's disease
Vasculitis syndromes Allergic vasculitis, Churge-Strauss syndrome, giant cell vasculitis/polymyalgia rheumatica, hypersensitivity vasculitis, polyarteritis nodosa, Takayasu arteritis, urticarial vasculitis, Wegener's granulomatosis
Granulomatous diseases Crohn's disease, granulomatous hepatitis, granulomatous myositis, sarcoidosis
Miscellaneous (in alphabetical order)
Adrenal insufficiency, amyloidosis, aneurysms, anhidrotic ectodermal dysplasia, anomalous thoracic duct, antiphospholipid syndrome, aortic dissection, aortic-enteral fistula, aseptic meningitis (Mollaret's syndrome), atrial myxoma, auto-immune hemolytic anemia, auto-immune hepatitis, brewer's yeast ingestion, Caroli's disease, Castleman's disease, cerebrovascular accident, cholesterol emboli, cirrhosis, complex partial status epilepticus, cyclic neutropenia, drug fever, Erdheim-Chester disease, erythema multiforme, erythema nodosum, extrinsic allergic alveolitis, Fabry's disease, factitious disease, familial Mediterranean fever, FAPA syndrome (fever, aphthous stomatitis, pharyngitis, adenitis), Gaucher's disease, gout, habitual hyperthermia, Hamman-Rich syndrome (acute interstitial pneumonia), Hashimoto's encephalopathy, hematoma, hemophagocytic syndrome, hyper IgD syndrome, hypersensitivity pneumonitis, hyperthyroidism, hypertriglyceridemia, hypothalamic hypopituitarism, idiopathic hypereosinophilic syndrome, idiopathic normal pressure hydrocephalus, inflammatory pseudotumour, Kawasaki's syndrome, Kikuchi's syndrome, linear IgA dermatosis, Loch Fyne fever, malacoplakia, mesenteric fibromatosis, metal fume fever, milk protein allergy, Muckle-Wells syndrome, myotonic dystrophy, pheochromocytoma, polymer fume fever, postmyocardial infarction syndrome, primary biliary cirrhosis, primary hyperpathyroidism, pseudogout, psychogenic fever, pulmonary embolism, retroperitoneal fibrosis, Schnitzler's syndrome, sclerosing mesenteritis, sickle cell disease vaso-occlusive crisis, silicone embolisation, subacute thyroiditis (de Quervain's), Sweet's syndrome, Teflon embolisation, thrombosis, TRAPS (tumor necrosis factor receptor-associated periodic syndrome, formerly known as familial Hibernian fever), ulcerative colitis, vitamin B12 deficiency, Vogt-Koyanagi-Harada syndrome, Weber-Christian disease

Diagnosis

Because of the diversity of causes of longstanding fever, it is difficult to construct algorithms that cover the complete spectrum of FUO. The algorithm we propose is shown in Figure 1. The most important step in the diagnostic workup is a complete and repeated history taking, physical examination and the obligatory investigations in a search for potentially diagnostic clues (PDCs). PDCs are defined as all localizing signs, symptoms and abnormalities potentially pointing toward a diagnosis. Although often misleading, only with help of these PDCs a limited list of probable diagnoses can be made.

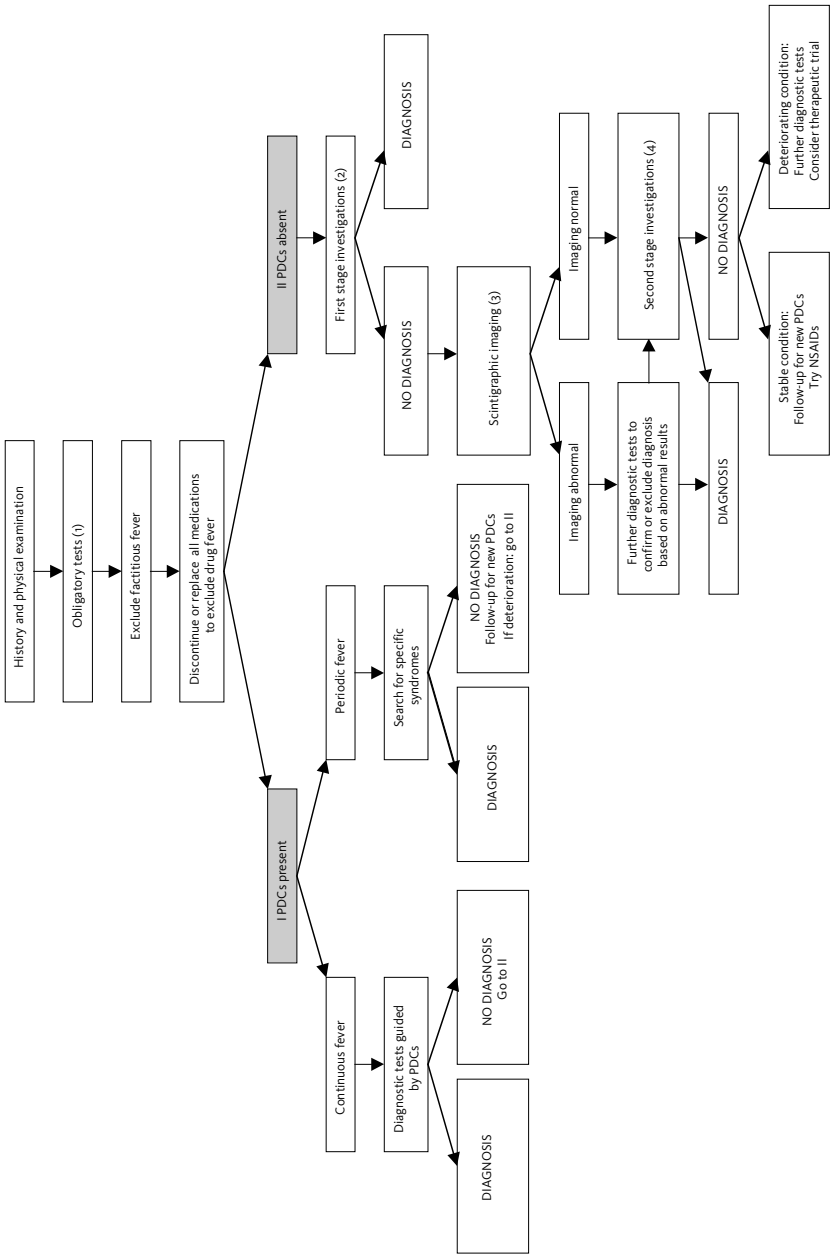

Figure 1 Diagnostic algorithm in patients with FUO

PDCs = potential diagnostic clues, NSAID = non-steroidal anti-inflammatory drug

(1) Obligatory tests for the definition of fever of unknown origin are shown in Table 1.

(2) First stage investigations are fundoscopy, serum for cryoglobulins, and temporal artery biopsy in patients older than 55 years

(3) ^{67}gallium citrate, ^{111}indium-labeled or ^{99m}technetium-labeled leukocytes or ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) can be used. Because of favorable characteristics of FDG-PET, we believe that conventional scintigraphic techniques may be replaced by FDG-PET in institutions where PET is available. In our hospital, FDG-PET is performed after the first stage investigations, but placing scintigraphic imaging after the second stage investigations is a common strategy.

(4) Second stage investigations are bone marrow biopsy, liver biopsy, abdominal CT and chest CT.

History

A thorough history should include information about alcohol intake, medications, occupational exposures, exposure to animals, travel, risk for venereal diseases, familial disorders, exposure to tuberculosis and previous illnesses. The most common PDCs are relevant past medical or social history, weight loss, headache, myalgia, arthralgia, skin lesions and diarrhea.

Physical examination

Clinicians should perform a complete physical examination with special attention to the lymph nodes, temporal arteries, sites of previous surgery, the entire skin surface and mucous membranes. Specific findings leading to a diagnosis in FUO are numerous and diverse, but can often be detected only by a very careful examination and may be missed the first time. In the absence of PDCs, the physical examination should therefore be repeated regularly.

Clinical features

One of the first steps should be to rule out factitious fever particularly in patients without signs of inflammation on laboratory tests. Also, all medications, including non-prescription drugs and nutritional supplements, should be discontinued early in the evaluation to exclude drug fever. The length of time of previous use is irrelevant since medications that a patient has consumed without problems for years can cause fever. If the fever persists beyond 72 hours after discontinuation of the suspected drug it is unlikely that this drug is causing the fever.

Investigations

Continuous fever

After identification of all PDCs retrieved from the history, physical examination and obligatory tests, a limited list of most probable diagnoses should be made. Since most investigations are helpful only when performed in patients with PDCs for the diagnoses searched for, further diagnostic procedures should be limited to specific investigations used to confirm or exclude diseases on this list. In patients without PDCs or only misleading PDCs, the following procedures were found to be useful in the early stage of the diagnostic workup: fundoscopy, cryoglobulins, and temporal artery biopsy in patients older than 55 years. In a later phase, bone marrow biopsy, liver biopsy, abdominal CT and chest CT are useful in patients without PDCs [3]. However, second stage investigations should also be determined by local epidemiological data and the diagnostic facilities available. In patients with unexplained fever at this point, the last step in the diagnostic workup comes at an extraordinary high cost and discomfort with a marginal diagnostic yield. Repeating a thorough history taking, physical examination and review laboratory results and imaging studies

including those from other hospitals is recommended. Delay often results from the failure to recognize helpful clues in available information. In these patients with persisting FUO, waiting for new PDCs to appear probably is better than ordering more screening investigations. Only in the rare patient who deteriorates without presenting new PDCs, a further diagnostic workup should be performed.

Recurrent or episodic fever

In patients with familial fever or recurrent fever for more than two years, it is very unlikely that the fever is being caused by infection or malignancy. In these patients, the diagnostic workup should consist only of the thorough history taking, physical examination and obligatory examinations. The search for PDCs should be directed to PDCs matching known recurrent syndromes (Table 3). Only when PDCs for infections, vasculitis syndromes or malignancy are present, or when the clinical condition is deteriorating, further diagnostic tests should be considered. Systemic examinations should only be performed during a symptomatic phase.

Table 3 Possible causes of periodic fever

Familial syndromes
Fabry's disease, familial Mediterranean fever, Gaucher's disease, hyper IgD syndrome, hypertriglyceridemia, Muckle-Wells syndrome, TRAPS (tumor necrosis factor receptor-associated periodic syndrome)
Infections
Bacterial, non-specific
Recurrent bacteremia caused by colonic neoplasia, prostatitis, apical granuloma, diverticulitis or other focal infections
Bacterial, specific
Brucellosis, chronic meningococcemia, febris recurrens (*Borrelia recurrentis*), melioidosis (*Pseudomonas pseudomallei*), Q-fever (*Coxiella burnetii),* salmonellosis, *Spirillum minor* infection, *Streptobacillus moniliformis* infection, syphilis, tularemia, Whipple's disease, yersiniosis
Parasitic
Babesiosis, malaria, toxoplasmosis, trypanosomiasis, visceral leishmaniasis (Kala Azar)
Neoplasia
Angio-immunoblastic lymphoma, Hodgkin's disease, non-Hodgkin lymphoma, malignant histiocytosis, colon carcinoma, craniopharyngioma
Non-infectious inflammatory diseases
Ankylosing spondylitis, mixed cryoglobulinemia, recurrent polychondritis, Reiter's syndrome, systemic lupus erythematosus, Still's disease, Crohn's disease, granulomatous hepatitis, sarcoidosis
Miscellaneous (in alphabetical order)
Aortic-enteral fistula, atrial myxoma, brewer's yeast ingestion, Castleman's disease, cholesterol emboli, cyclic neutropenia, drug fever, extrinsic allergic alveolitis, factitious disease, FAPA syndrome (fever, aphthous stomatitis, pharyngitis, adenitis), habitual hyperthermia, hypersensitivity pneumonitis, hypothalamic hypopituitarism, inflammatory pseudotumour, Loch Fyne fever, metal fume fever, milk protein allergy, polymer fume fever, psychogenic fever, pulmonary embolism, Schnitzler's syndrome, sclerosing mesenteritis

Scintigraphic imaging

Although the diagnostic yield and the exact place in the order of diagnostic procedures remain unclear, scintigraphic methods play an important role in the diagnostic process of patients with FUO in clinical practice. Opinions differ on the type of scintigraphic method that should be used. Conventional radiopharmaceuticals routinely used in patients suspected of infectious or inflammatory disease, such as ^{67}gallium citrate (^{67}Ga) and ^{111}indium-labelled or ^{99m}technetium-

labelled leukocytes (WBC), have disadvantages and limitations, such as handling of potentially infected blood products (WBC), high radiation burden (^{67}Ga), and the long time span between injection and diagnosis (^{67}Ga).

^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET)

FDG-PET detects malignant processes as well as infectious and inflammatory disorders, but is not able to differentiate between those disorders. As a screening procedure in the investigation of patients with FUO, however, this appears to be an advantage rather than a drawback. Compared to conventional nuclear medicine techniques, other advantages of FDG-PET are early imaging (one hour), higher resolution, and sensitivity in chronic low-grade infections, infections of the central skeleton and vasculitis. Based on several studies [4-6] and resulting from favorable characteristics of FDG-PET, conventional scintigraphic techniques may be replaced by FDG-PET in institutions where this technique is available. When ordered early in the diagnostic workup, FDG-PET enables identifying the organ or tissue where the cause of the fever is likely to be found. Abnormal FDG-PET results could then be used for guiding intelligent further testing. However, for determination of its exact position in the order of diagnostic tests, prospective studies of FDG-PET being part of a structured diagnostic protocol are needed.

Management

If the fever persists and the source remains elusive after completing the second stage investigations, supportive treatment with NSAIDs can be helpful. Therapeutic trials with antibiotics, steroids, or antituberculous agents should be avoided, except in patients whose condition is deteriorating.

Prognosis

The prognosis is determined primarily by the underlying disease and also by rapidity of diagnosis. Most patients with undiagnosed FUO, however, have benign self-limiting or recurrent fever. In two-thirds of cases, fever will resolve by two years with 3% mortality in this group at five years [7].

References

1 Petersdorf RG and Beeson PB. Fever of unexplained origin: report on 100 cases. Medicine 1961;40:1-30.
2 de Kleijn EM, Vandenbroucke JP, van der Meer JW. Fever of unknown origin (FUO). I A. prospective multicenter study of 167 patients with FUO, using fixed epidemiologic entry criteria. The Netherlands FUO Study Group. Medicine (Baltimore) 1997;76:392-400.
3 de Kleijn EM, van Lier HJ, van der Meer JW. Fever of unknown origin (FUO). II. Diagnostic procedures in a prospective multicenter study of 167 patients. The Netherlands FUO Study Group. Medicine (Baltimore) 1997;76:401-414.
4 Blockmans D, Knockaert D, Maes A et al. Clinical value of [(18)F]fluoro-deoxyglucose positron emission tomography for patients with fever of unknown origin. Clin Infect Dis 2001;32:191-196.

5 Meller J, Altenvoerde G, Munzel U et al. Fever of unknown origin: prospective comparison of [18F]FDG imaging with a double-head coincidence camera and gallium-67 citrate SPET. Eur J Nucl Med 2000;27:1617-1625.
6 Bleeker-Rovers CP, de Kleijn EM, Corstens FH, van der Meer JW, Oyen WJ. Clinical value of FDG PET in patients with fever of unknown origin and patients suspected of focal infection or inflammation. Eur J Nucl Med Mol Imaging 2004;31:29-37.
7 Knockaert DC, Dujardin KS, Bobbaers HJ. Long-term follow-up of patients with undiagnosed fever of unknown origin. Arch Intern Med 1996;156:618-620.

Chapter 7

Clinical value of ^{18}F-fluorodeoxyglucose positron emission tomography in patients with fever of unknown origin and patients suspected of focal infection or inflammation

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Abstract

Fever of unknown origin (FUO) and suspected focal infection or inflammation are challenging medical problems. The aim of this study was to assess the value of FDG-PET in patients with FUO and patients suspected of focal infection or inflammation. All FDG-PET scans ordered because of FUO or suspected focal infection or inflammation in the last four years were reviewed. These results were compared to the final diagnosis. Thirty-five FDG-PET scans were performed in 35 patients with FUO. A final diagnosis was established in 19 patients (54%). Of the total number of scans, 37% were clinically helpful. Positive predictive value of FDG-PET in these patients was 87% and negative predictive value was 95%. Fifty-five FDG-PET scans were performed in 48 patients with suspected focal infection or inflammation. A final diagnosis was established in 38 patients (82%). Of the total number of scans, 65% were clinically helpful. Positive predictive value of FDG-PET in these 55 episodes of suspected infection or inflammation was 95% and negative predictive value was 100%. It is concluded that FDG-PET appears to be a valuable imaging technique in evaluation of FUO and suspected focal infection or inflammation. Furthermore, FDG-PET could become a useful tool for evaluating the effect of treatment of infectious and inflammatory processes that cannot reliably be visualized by conventional techniques. However, to assess the additional diagnostic value of this technique, prospective studies of FDG-PET being part of a structured diagnostic protocol are warranted.

Introduction

Fever of unknown origin and suspected focal infection or inflammation are challenging medical problems. In 1961, fever of unknown origin was defined by Petersdorf and Beeson as an illness of more than three weeks duration, fever higher than 38.3°C (101°F) on several occasions, and diagnosis uncertain after one week of study in the hospital [1]. This definition has been modified by removing the requirement that the evaluation must take place in the hospital [2] and by excluding immunocompromized patients, because these patients need an entirely different diagnostic and therapeutic approach [2,3]. In general, infection accounts for about one-third of cases of FUO, followed by neoplasm and collagen vascular diseases, while in 25 to 36% of the cases no diagnosis can be made [2,4-6]. Timely identification and localization of infectious and inflammatory lesions is critical in appropriate treatment of patients. Focal infectious and inflammatory processes can be detected by several radiological techniques including computerized tomography (CT), magnetic resonance imaging (MRI) and ultrasonography. However, infectious and inflammatory foci cannot be detected by these techniques in an early phase because of the lack of substantial anatomical changes at this time. Also, discrimination of active infectious or inflammatory lesions from residual changes due to cured processes or surgery remains difficult.

Scintigraphic imaging is a non-invasive method allowing delineation of both localization and number of foci in all parts of the body, based on functional changes of tissues. ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) has become an established imaging tool in oncology and is now entering the field of clinical infectious diseases [7]. FDG accumulates in organ tissues with a high rate

of glycolysis [8], which not exclusively occurs in neoplastic cells. Lesions with a high concentration of activated inflammatory cells also show increased uptake of FDG [9,10]. Since the first report on high FDG-uptake in a human abdominal abscess [11], there have been many reports of FDG accumulation in different infections and inflammatory lesions. To assess the role of FDG-PET imaging in the evaluation of patients with FUO or suspected localized infection or inflammation, we evaluated the results of FDG-PET scans ordered because of FUO or suspected infection or inflammation.

Materials and methods

Patients

The results of all FDG-PET scans ordered for evaluation of FUO or suspected focal infection or inflammation from January 1999 to December 2002 in the Radboud University Nijmegen Medical Centre were analyzed retrospectively. The first group consisted of patients with FUO, which was defined as a febrile illness of >3 weeks duration, a temperature of >38.3°C on several occasions, and no diagnosis after one week of evaluation in the hospital or in the outpatient department. Recurrent fever was defined as repeated episodes of fever with fever-free intervals of at least two weeks and apparent remission of the underlying disease. A rigid investigation protocol for the diagnostic work-up of patients with FUO was not applied. First level diagnostic tests were defined as tests performed in almost every patient, such as routine laboratory tests, blood cultures, serology, chest radiograph and abdominal ultrasound. Second level tests were defined as tests performed after the first level tests proved to be normal, for example CT or MRI scans, endoscopy, biopsy, ^{67}gallium-citrate (^{67}Ga), ^{111}indium-leukocyte (^{111}In-WBC) or ^{111}In-human immunoglobulin G scintigraphy (^{111}In-HIG). Third level tests were defined as tests performed after a thorough diagnostic work-up including several second level tests, usually concerning patients referred to our hospital for a second opinion. The second group of patients was defined by suspected focal infection or inflammation being the reason for ordering FDG-PET. The suspicion of infection or inflammation was based on a combination of several of the following symptoms and signs: fever, localizing symptoms, leucocytosis, elevated CRP or positive blood cultures. Both patient groups were evaluated with other imaging modalities and laboratory tests as was considered clinically appropriate.

FDG-PET

A dedicated, full ring PET scanner (ECAT-EXACT, Siemens/CTI, Knoxville, TN., USA) was used for data acquisition. Prior to FDG injection patients had fasted for at least 6 hours. Intake of sugar-free liquids was permitted. Immediately prior to the procedure, the patients were hydrated with 500 ml of water. One hour after intravenous injection of 200-220 MBq FDG (Tyco Healthcare/ Mallinckrodt Medical, Petten, The Netherlands) and 10 to 15 mg furosemide, emission images or emission and transmission images of the area between the proximal femora and the base of the skull were acquired (10 minute per bed position). When only an emission study was recorded, the images were not corrected for attenuation and were reconstructed using filtered back-protection (Butterworth filter with a cut-off frequency of 0.4 Nyquist). When emission and transmission

studies were recorded, 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.

Interpretation

For this study, FDG-PET scans were interpreted by two staff members of the department of nuclear medicine without information of the results of the original interpretation of the FDG-PET scan, other diagnostic tests or the final diagnosis. Results were judged to be abnormal if focal accumulation of the tracer was detected outside of the areas of physiological uptake. Disagreements were resolved by consensus.

Clinical assessment of test results and diagnosis

The results of FDG-PET were evaluated for their diagnostic contribution. Abnormal FDG-PET scans were categorized as "helpful in diagnosis" or "non-contributory to diagnosis". They were regarded as helpful in diagnosis when abnormal FDG-uptake pointed to the organ or tissue where the cause of the symptoms was eventually found by additional conventional diagnostic techniques. Abnormal results were regarded as non-contributory to diagnosis when the detected abnormality was considered to be unrelated to the illness causing the symptoms or when no final diagnosis could be made. Results were considered to be true positive when abnormal FDG-uptake pointed to the organ or tissue where the cause of the symptoms was eventually found by additional conventional techniques, as mentioned above. Abnormal results were categorized as false positive when the abnormality was not related to the illness or when no final diagnosis could be made. A normal FDG-PET scan was called true negative when no cause of the symptoms was identified despite an extensive diagnostic work-up and clinical follow-up of at least six months. A normal FDG-PET scan was considered false negative when a focal infection, inflammation or neoplasm was diagnosed except for infection or inflammation in the brain (known low sensitivity of FDG-PET and brain not routinely imaged) or the legs (not routinely imaged). A final diagnosis was based on positive blood or tissue culture, biopsy, surgery or autopsy. When this was not possible, a probable diagnosis was made based on clinical follow up, serology, or conventional radiological studies. The final diagnosis was never based on FDG-PET results alone. This final or probable diagnosis served as a standard of reference and was used for the comparisons with the FDG-PET results.

Results

From January 1999 to December 2002, 84 patients were referred for a total of 91 FDG-PET scans because of FUO or suspected focal infection or inflammation. One patient had to be excluded because of insufficient clinical data other than FDG-PET results, so the results of 90 FDG-PET scans in 83 patients were evaluated. Thirty-five FDG-PET scans were performed in 35 patients with FUO and 55 FDG-PET scans were performed in 48 patients because of suspected focal infection or inflammation.

FUO

Of the total number of 35 patients with FUO, 15 were male and 20 were female with a median age of 51 years (range 18 to 82 years). Twenty patients (57%) had already been investigated by internists in other hospitals and were referred for a second opinion. The median duration of fever before an FDG-PET scan was performed was two months (range 3 weeks to 14 years). Six patients (17%) had recurrent fever.

An infectious disease was the cause of the fever in six patients (17%), a neoplasm in four patients (11%), non-infectious inflammatory diseases in six patients (17%), drug fever in one patient and "miscellaneous diseases" in two patients (6%) (Table 1). In 16 patients (46%), the cause of the fever was not found. In five of the 15 patients who were directly referred to our hospital (33%), no diagnosis could be reached. In 11 (55%) of the 20 patients who were referred for a second opinion, no cause of the fever was found. Six of 16 patients, in whom no diagnosis could be reached, had recurrent fever. In four patients, the fever subsided spontaneously after 3 months, 13 months, 3 years and 5 years, respectively. In one patient, the fever subsided after treatment with non-steroidal anti-inflammatory drugs after a duration of fourteen years and in two patients the fever disappeared upon treatment with prednisone after a duration of two and five years. One patient with a history of short bowel syndrome and chronic total parenteral nutrition recovered with antibiotic treatment after a total duration of fever of five weeks. In two patients the fever still persists for 18 months and 5 years.

Table 1 Final diagnoses in patients with FUO and classification of the results of FDG-PET for each category

Category	No. of cases	True positive	True negative	False positive	False negative
Infection	*6 (17%)*	*4*	*2*	-	-
Persistent Yersiniosis	1	1	-	-	-
Septic thrombophlebitis of the portal vein	1	1	-	-	-
Pelvic abscess	1	1	-	-	-
Prostatitis	1	1	-	-	-
Generalized Bartonella infection	1	-	1	-	-
Viral meningitis	1	-	1	-	-
Neoplasm	*4 (11%)*	*4*	-	-	-
Metastatic gastric carcinoma	1	1	-	-	-
Malignant lymphoma	2	2	-	-	-
Soft tissue leiomyoma	1	1	-	-	-
Non-infectious inflammatory disease	*6 (17%)*	*4*	*1*	-	*1*
Polymyalgia rheumatica	1	1	-	-	-
Cryoglobulinemia	1	-	1	-	-
Adult-onset Still's disease	1	1	-	-	-
Polyarteritis nodosa	1	1	-	-	-
Sarcoidosis	1	1	-	-	-
Crohn's disease	1	-	-	-	1
Drug fever	*1 (3%)*	-	-	*1*	-
Miscellaneous	*2 (6%)*	*1*	*1*	-	-
Hemophagocytic syndrome	1	1	-	-	-
Chronic non-infectious meningitis	1	-	1	-	-
No diagnosis	*16 (46%)*	-	*15*	*1*	-

Table 2 Second and third level diagnostic tests performed in 35 patients with FUO

Diagnostic method	No. of cases
Radiology	
Sinus radiography	13
Small bowel follow through	9
Barium enema	6
Mammography	2
Intravenous pyelography	3
Echocardiography	14
Thoracic CT	16
Abdominal CT	30
Cerebral CT	5
Other CT	3
Cerebral MRI	5
Other MRI	5
Endoscopy	
Gastroscopy	11
Colonoscopy	14
ERCP	1
Bronchoscopy	6
Scintigraphy	
^{99m}Tc-leukocyte scan	4
^{67}Ga-citrate scan	5
^{99m}Tc-human immunoglobulin scan	8
Ventilation/perfusion lung scan	6
Bone scan	7
Biopsy	
Bone marrow	15
Liver	4
Lymph node	6
Skin/muscle	9
Other	3
Surgery	
Mediastinoscopy	2
Laparotomy	5

ERCP = endoscopic retrograde cholangiopancreaticography.

In all of the patients with FUO, the following diagnostic procedures were performed: history, clinical examination, routine laboratory tests, blood cultures, chest radiograph and abdominal ultrasound. In most patients subsequent diagnostic studies were performed (Table 2). In some cases one or more of these studies were done to further evaluate the results of FDG-PET. When patients were directly referred to our hospital, an FDG-PET scan was ordered after a median duration of the fever of five weeks (range 3 weeks to 5 years) as a second level test after the basic diagnostic work-up in most cases. In the remaining patients, an FDG-PET scan was ordered after a median duration of fever of nine months (range one month to 14 years) as a third level test after a very extensive diagnostic work-up in the referring hospital. Fifteen (43%) of 35 FDG-PET scans were considered abnormal (Table 3). Of these abnormal FDG-PET scans, 13 correctly pointed to the source of the fever. In one patient, without evidence of colonic disease confirmed by colonoscopy and eventually diagnosed with drug fever, abnormal FDG-uptake in the colon was found. In

another patient, increased FDG-uptake in multiple lymph nodes was shown, but lymph node biopsy and two bone marrow biopsies were normal. Six months after FDG-PET, no diagnosis has been made and the fever has disappeared. The results of these two FDG-PET scans were considered false positive (Table 1). FDG-PET results were considered to be true negative in the patients with viral encephalitis, chronic meningitis, systemic Bartonella infection without focal infection, cryoglobulinemia without focal inflammation, and in 15 patients (94%) without a known cause of the fever. In one patient with Crohn's disease, FDG-PET was normal and this was considered to be false negative. Thus, 87% of the abnormal FDG-PET scans were clinically helpful and FDG-PET contributed to the eventual diagnosis in 37% of all patients with FUO in whom the probability of a diagnosis was only 54%. Sensitivity of FDG-PET in these FUO patients was 93%, specificity was 90%, positive predictive value was 87% and negative predictive value was 95%. Table 4 shows the diagnostic methods that established the cause of the fever in 19 patients with a final diagnosis. The abnormal FDG-PET results were confirmed by biopsy in 11 cases (85%).

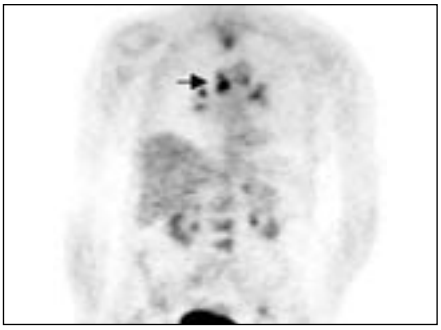

Figure 1 This 70-year-old female presented with fever, fatigue and weight loss of three weeks duration. Physical examination was normal. The erythrocyte sedimentation rate was 67 mm/h (normal 2-12 mm/h) with normal leukocytes, creatinine, liver function tests, and normal angiotensin converting enzyme. A chest X-ray, abdominal ultrasound and tuberculin skin test were normal. A temporal artery biopsy was also normal. PET revealed pathological FDG-uptake in pretracheal, hilar and mediastinal lymph nodes (arrow). Subsequent abdominal and thoracic CT showed slightly enlarged lymph nodes pretracheally and in the mediastinum. A lymph node biopsy obtained by mediastinoscopy demonstrated granulomatous inflammation confirming a diagnosis of sarcoidosis. Her symptoms resolved upon treatment with corticosteroids.

Table 3 Results of FDG-PET in patients with FUO

	FDG-PET abnormal		FDG-PET normal	No. of patients
	Contributory	Non-contributory		
Infection	4	0	2	6
Neoplasm	4	0	0	4
NIID	4	0	2	6
Drug fever	0	1	0	1
Miscellaneous	1	0	1	2
No diagnosis	0	1	15	16
Total	13 (37%)	2 (6%)	20 (57%)	35

NIID = non-infectious inflammatory diseases.

Table 4 Diagnostic methods establishing the final diagnosis in 19 patients with FUO in whom a cause of the fever was found

Diagnostic method	No. of patients	
	FDG-PET abnormal	FDG-PET normal
Non-invasive		
Culture or serology	0	2
Radiology	0	1
Clinical criteria or clinical course	3	2
Invasive		
Biopsy	11	0

Suspected focal infection or inflammation

Of the total number of 48 patients with suspected focal infection or inflammation, 20 were male and 28 were female with a median age of 61 years (range 18 to 85 years). In three patients, the second FDG-PET scan was ordered for follow-up of a known infection. In two patients with autosomal dominant polycystic kidney disease, multiple FDG-PET scans (2 and 4, respectively) were performed because of new episodes with complaints suggesting newly infected renal or hepatic cysts.

An infection was the cause of the symptoms in 32 episodes (58%), a neoplasm in three patients (5%), and non-infectious inflammatory diseases in four patients (7%). Three FDG-PET scans were performed for follow-up of a known infection and in three patients (5%) the final diagnosis was categorized as miscellaneous (Table 5). In 10 patients (18%) the cause of the symptoms was not found. In six of these patients the symptoms disappeared spontaneously after a median duration of six weeks. In the remaining four patients the symptoms persisted and no diagnosis could be made after a median follow-up of 22 months.

The median duration of the illness before the first FDG-PET scan in each patient was performed was three weeks (range 4 days to 30 months). Table 6 shows the results of FDG-PET in the different diagnostic categories of 55 episodes of suspected localized infection or inflammation in 48 patients. Of the total number of 55 FDG-PET scans, 38 (69%) were considered abnormal. Of these abnormal scans, 36 (95%) correctly pointed to the cause of the symptoms. In one patient, increased FDG-uptake in the upper lobe of the right lung was demonstrated. Subsequent chest X-ray and CT scanning were both normal and no diagnosis could be made, so the FDG-PET results were considered false positive (Table 5). In another patient with fever and abdominal pain with normal abdominal CT and colonoscopy, increased FDG-uptake in the entire colon was considered false positive. No diagnosis could be reached and her symptoms disappeared. FDG-PET was considered true negative in the patients with cerebral *Candida* abscess, *Candida* sepsis without focal infection (n=2), cystitis (n=2), myelodysplastic syndrome, non-infected hematoma, and in eight patients (80%) without a known cause of their symptoms. In two cases, FDG-PET performed for follow-up of a known infection was normal, which was supported by clinical follow-up, so these results were considered true negative. Persisting high FDG-uptake on FDG-PET performed for follow-up of a mycotic aortic aneurysm was in line with clinical follow-up and increasing wall thickness of

the aorta on CT, so the results were considered true positive. The history of this patient has been published as a case report [12]. Thus, 95% of the abnormal FDG-PET scans were clinically helpful and FDG-PET contributed to the final diagnosis in 65% of all 55 episodes of suspected localized infection or inflammation in which the probability of a diagnosis was 82%. Sensitivity of FDG-PET in these 55 episodes was 100%, specificity was 89%, positive predictive value was 95% and negative predictive value was 100%. Table 7 shows the diagnostic methods used to establish a final diagnosis in 45 episodes in which the cause of the symptoms was found.

Table 5 Final diagnoses in 55 episodes with symptoms suggesting a focal infection or inflammatory process in 48 patients and classification of the results of FDG-PET for each category

Category	No. of cases	True positive	True negative	False positive	False negative
Infection	*32 (58%)*	*27*	*5*	-	-
Soft tissue/skin infection	3	3	-	-	-
Septic arthritis	2	2	-	-	-
Spondylodiscitis	6	6	-	-	-
Infected vascular prosthesis	3	3	-	-	-
Mycotic aneurysm	2	2	-	-	-
Infected cyst in ADPKD	5	5	-	-	-
Abdominal abscess	2	2	-	-	-
Echinococcus infection liver	1	1	-	-	-
Prostatitis	1	1	-	-	-
Cystitis	2	-	2	-	-
Pneumonia	1	1	-	-	-
Cerebral abscess	1	-	1	-	-
Endophthalmitis	1	1	-	-	-
Candida sepsis without focus	2	-	2	-	-
Neoplasm	*3 (5%)*	*3*	-	-	-
ACUP	1	1	-	-	-
Pelvic squamous cell carcinoma	1	1	-	-	-
Malignant lymphoma	1	1	-	-	-
Non-infectious inflammatory disease	*4 (7%)*	*4*	-	-	-
Polymyalgia rheumatica	1	1	-	-	-
Giant-cell arteritis	1	1	-	-	-
Crohn's disease	1	1	-	-	-
Chronic granulomatous disease rectum	1	1	-	-	-
Follow-up of known infection	*3 (5%)*	*1*	*2*	-	-
Miscellaneous	*3 (5%)*	*1*	*2*	-	-
Amyloidosis	1	1	-	-	-
Hematoma	1	-	1	-	-
Myelodysplastic syndrome	1	-	1	-	-
No diagnosis	*10 (18%)*	-	*8*	*2*	-

ADPKD = autosomal dominant polycystic kidney disease, ACUP = adenocarcinoma with unknown primary.

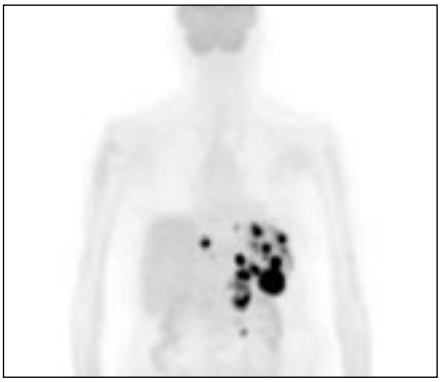

Figure 2 This 76-year-old woman presented with fever and weight loss. Physical examination was normal. The erythrocyte sedimentation rate was 143 mm/h (normal 2-12 mm/h), a severe microcytic anemia was present and alkaline phosphatase was 250 U/l (normal <120 U/l). A tuberculin skin test was positive. Blood, urine, bronchoalveolar lavage fluid and bone marrow cultures were negative. Chest X-ray, abdominal and thoracic CT-scans, MRI of the spine, bone scan, lung perfusion scintigraphy, ^{111}indium-leukocyte scan, gastroscopy, colonoscopy and bronchoscopy were all normal. Duodenum, liver, bone and temporal artery biopsies were normal. Her condition progressively deteriorated and she was referred to our hospital. PET demonstrated increased FDG-uptake in several areas in the spleen and para-aortal lymph nodes suggestive of malignant lymphoma. The patient refused further diagnostic tests or treatment and she died four weeks later. Autopsy revealed enlarged para-aortal lymph nodes and splenomegaly due to localization of malignant B-cell lymphoma.

Table 6 Results of FDG-PET in 55 episodes with symptoms suggesting a focal infection or inflammatory process in 48 patients

	FDG-PET abnormal		FDG-PET normal	No. of patients
	Contributory	Non-contributory		
Infection	27	0	5	32
Neoplasm	3	0	0	3
NIID	4	0	0	4
Follow-up	1	0	2	3
Miscellaneous	1	0	2	3
No diagnosis	0	2	8	10
Total (%)	36 (65)	2 (4)	17 (31)	55

NIID = non-infectious inflammatory diseases.

Table 7 Diagnostic methods establishing the final diagnosis in 45 episodes of suspected focal infection or inflammation in which a cause of the symptoms was found

Diagnostic method	No. of patients	
	FDG-PET abnormal	FDG-PET normal
Non-invasive		
Culture or serology	5	3
Radiology	10	4
Clinical criteria or clinical course	7	0
Invasive		
Biopsy	7	1
Surgery	4	1
Autopsy	3	0

Discussion

The utility of FDG-PET in patients with FUO and in patients suspected of focal infection or inflammation was retrospectively evaluated. In all patients with FUO, 37% of the FDG-PET scans were helpful in the diagnostic process while the probability of a diagnosis was only 54% in these patients. The percentage of FDG-PET scans helpful in the diagnostic process in patients with FUO, as reported in the literature, varied from 41% to 69% [6,13,14]. In a retrospective study of 16 patients with FUO in whom conventional diagnostics had not been conclusive, Lorenzen et al. found that FDG-PET was helpful in 69% [14]. Meller et al. prospectively studied the utility of FDG coincidence imaging in 20 patients with FUO. In 55% of these patients FDG-PET was helpful in establishing a final diagnosis. Positive predictive value was 90% and negative predictive value was 75% compared to a positive predictive value of ^{67}Ga scintigraphy in the same patients of 75% and a negative predictive value of 70% [13]. In a prospective study of 58 patients with FUO, Blockmans et al. demonstrated that FDG-PET was helpful in 41% of the patients. ^{67}Ga scintigraphy was only helpful in 25% of a subgroup of 40 patients in the same study [6]. Comparing these studies is difficult. The definition of FUO differed slightly, FDG-PET was performed at different stages of the diagnostic process, no structured diagnostic protocol was used and the FDG-PET technique differed between the studies, resulting in considerable selection bias. The percentage of patients in whom no diagnosis could be made varied from 10 to 36% and even 46% in our study, suggesting very different patient characteristics. The unusually high percentage of patients in whom no diagnosis could be made in our study can probably be explained by the high number of patients referred for a second opinion (57%) in whom the chance of finding a cause of the fever was only 45% compared to 67% in the patients who were directly referred to our clinic. The referred patients most probably represent a selected group of FUO cases, which have a lower chance of reaching a final diagnosis [5]. Furthermore, a high number of patients without a final diagnosis had recurrent fever (6/16). Infections, malignancies and inflammatory diseases represent only 20% of the causes of recurrent fever and in about half, the cause of the fever is never found [3,15].

In the patients suspected of focal infection or a localized inflammatory process, 65% of all FDG-PET scans were clinically helpful. In a prospective study of 11 patients suspected of various infections by Sugawara et al. [16], FDG-PET correctly diagnosed the presence or absence of active infection in 10 of 11 patients. Stumpe et al. [17] studied the results of 45 FDG-PET scans in 39 patients with suspected infectious foci, which were true positive in 40 cases, false positive in four and false negative in one patient. In a retrospective study, Chacko et al. [18] reviewed the results of 167 FDG-PET scans in patients suspected of various, but mostly orthopedic, infections. Accuracy of FDG-PET in 97 cases of suspected complicated orthopedic hardware was 96% for hip prosthesis, 81% for knee prosthesis, and 100% for other orthopedic devices. Accuracy of FDG-PET in 56 patients suspected of chronic osteomyelitis was 91%. FDG-PET was accurate in three out of six cases of FUO and in eight cases of vascular graft and soft tissue infections [18]. It is even more difficult to compare these studies because of different study designs and different patient characteristics, but the results of these three studies and our results suggest that FDG-PET is a very sensitive method to detect infectious and inflammatory foci with a reasonable specificity. Calculation of sensitivity

and specificity of FDG-PET in patients with FUO or suspected focal infection or inflammation is difficult for several reasons. First, since a final diagnosis is not established in all patients, the interpretation of this procedure is hampered due to a lack of a gold standard. When additional diagnostic procedures are negative and long-term follow-up does not reveal a diagnosis, it is probably legitimate to presume that focal infection or inflammation or malignancy is not the cause of the symptoms in these patients. Second, in patients with negative FDG-PET, a variety of diseases were found that could not be diagnosed with FDG-PET. FDG-PET cannot exclude cerebral disease or meningitis, because physiologic uptake in the cerebral cortex in most cases obscures any pathological uptake. Therefore, cerebral infection or meningitis was not scored as false negative. Besides physiologic uptake of FDG in the brain, normal activity in the kidneys and the bladder severely hamper the delineation of disease in these organs. Variable physiologic FDG-uptake in the bowel is possible and can thus lead to a false positive interpretation, as illustrated by two of our patients.

Conventional radiopharmaceuticals routinely used in clinical practice (^{67}Ga and ^{111}In-labeled or ^{99m}technetium-labeled leukocytes (WBC)) have disadvantages and limitations, such as handling of potentially infected blood products (WBC), high radiation burden (^{67}Ga), instability of the labeling (^{99m}Tc-WBC), and the long time span between injection and diagnosis (^{67}Ga) [19]. Compared to conventional nuclear medicine techniques, advantages of FDG-PET are early imaging (one hour) [16], higher resolution, high target-to-background ratio [20], sensitivity in chronic low-grade infections [21-23], high accuracy in the central skeleton [21,22,24], and high inter observer agreement [21,24]. Another major advantage of FDG-PET in the work-up of FUO is the vascular FDG-uptake in patients with vasculitis [13,25]. Obvious disadvantages are the relatively high cost and the currently limited availability. However, when 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 FDG-PET may very well become a clinically significant and also cost-effective modality, since adequate early diagnosis limits the number of other non-contributing (invasive) tests required and the time to diagnosis and thereby the duration of hospitalization for diagnostic purposes. Further positive aspects of FDG-PET imaging in FUO and suspected infectious or inflammatory diseases compared to CT and MRI are absence of disturbance by metallic implants, whole body screening and absence of contrast-related side effects. A negative aspect of FDG-PET when compared to CT is the limited anatomic information. In addition, differentiation between malignancy and infection or inflammation is not possible, but in the investigation of patients with FUO this appears to be an advantage rather than a drawback.

In conclusion, FDG-PET is a valuable new imaging technique in patients with FUO and patients suspected of focal infection or inflammation. Based on previous studies comparing ^{67}Ga and FDG-PET in patients with FUO [6,13] and resulting from favorable characteristics of FDG-PET, conventional scintigraphic techniques may be replaced by FDG-PET in institutions where PET is available. When ordered early in the diagnostic work-up, FDG-PET enables identifying the organ or tissue where the cause of the fever is likely to be found. Abnormal FDG-PET results could then be used for guiding intelligent further testing. Furthermore, FDG-PET could become a useful tool for

evaluating the effect of treatment of infectious and inflammatory processes that cannot reliably be visualized by conventional techniques. However, for a final validation of FDG-PET in patients with FUO and suspected infection or inflammation and for determination of its exact position in the order of diagnostic tests, especially in the work-up of FUO, prospective studies of FDG-PET being part of a structured diagnostic protocol are needed.

References

1 Petersdorf RG and Beeson PB. Fever of unexplained origin: report on 100 cases. Medicine 1961;40:1-30.
2 Petersdorf RG. Fever of unknown origin. An old friend revisited. Arch Intern Med 1992;152:21-22.
3 de Kleijn EM, Vandenbroucke JP, van der Meer JW. Fever of unknown origin (FUO). I A. prospective multicenter study of 167 patients with FUO, using fixed epidemiologic entry criteria. The Netherlands FUO Study Group. Medicine (Baltimore) 1997;76:392-400.
4 Knockaert DC, Vanneste LJ, Vanneste SB, Bobbaers HJ. Fever of unknown origin in the 1980s. An update of the diagnostic spectrum. Arch Intern Med 1992;152:51-55.
5 de Kleijn EM and van der Meer JW. Fever of unknown origin (FUO): report on 53 patients in a Dutch university hospital. Neth J Med 1995;47:54-60.
6 Blockmans D, Knockaert D, Maes A et al. Clinical value of [(18)F]fluoro-deoxyglucose positron emission tomography for patients with fever of unknown origin. Clin Infect Dis 2001;32:191-196.
7 De Winter F, Vogelaers D, Gemmel F, Dierckx RA. Promising role of 18-F-fluoro-D-deoxyglucose positron emission tomography in clinical infectious diseases. Eur J Clin Microbiol Infect Dis 2002;21:247-257.
8 Bar-Shalom R, Valdivia AY, Blaufox MD. PET imaging in oncology. Semin Nucl Med 2000;30:150-185.
9 Kubota R, Yamada S, Kubota K et al. Intratumoral distribution of fluorine-18-fluorodeoxyglucose in vivo: high accumulation in macrophages and granulation tissues studied by microautoradiography. J Nucl Med 1992;33:1972-1980.
10 Brown RS, Leung JY, Fisher SJ et al. Intratumoral distribution of tritiated fluorodeoxyglucose in breast carcinoma: I. Are inflammatory cells important? J Nucl Med 1995;36:1854-1861.
11 Tahara T, Ichiya Y, Kuwabara Y et al. High [18F]-fluorodeoxyglucose uptake in abdominal abscesses: a PET study. J Comput Assist Tomogr 1989;13:829-831.
12 Hoogendoorn EH, Oyen WJ, van Dijk AP, van der Meer JW. Pneumococcal aortitis, report of a case with emphasis on the contribution to diagnosis of positron emission tomography using fluorinated deoxyglucose. Clin Microbiol Infect 2003;9:73-76.
13 Meller J, Altenvoerde G, Munzel U et al. Fever of unknown origin: prospective comparison of [18F]FDG imaging with a double-head coincidence camera and gallium-67 citrate SPET. Eur J Nucl Med 2000;27:1617-1625.
14 Lorenzen J, Buchert R, Bohuslavizki KH. Value of FDG PET in patients with fever of unknown origin. Nucl Med Commun 2001;22:779-783.
15 Knockaert DC, Vanneste LJ, Bobbaers HJ. Recurrent or episodic fever of unknown origin. Review of 45 cases and survey of the literature. Medicine (Baltimore) 1993;72:184-196.
16 Sugawara Y, Braun DK, Kison PV et al. Rapid detection of human infections with fluorine-18 fluorodeoxyglucose and positron emission tomography: preliminary results. Eur J Nucl Med 1998;25:1238-1243.
17 Stumpe KD, Dazzi H, Schaffner A, von Schulthess GK. Infection imaging using whole-body FDG-PET. Eur J Nucl Med 2000;27:822-832.
18 Chacko TK, Zhuang H, Nakhoda KZ, Moussavian B, Alavi A. Applications of fluorodeoxyglucose positron emission tomography in the diagnosis of infection. Nucl Med Commun 2003;24:615-624.
19 Rennen HJ, Boerman OC, Oyen WJ, Corstens FH. Imaging infection/inflammation in the new millennium. Eur J Nucl Med 2001;28:241-252.
20 Sugawara Y, Gutowski TD, Fisher SJ, Brown RS, Wahl RL. Uptake of positron emission tomography tracers in experimental bacterial infections: a comparative biodistribution study of radiolabeled FDG, thymidine, L-methionine, 67Ga-citrate, and ^{125}I-HSA. Eur J Nucl Med 1999;26:333-341.
21 Guhlmann A, Brecht-Krauss D, Suger G et al. Fluorine-18-FDG PET and technetium-99m antigranulocyte antibody scintigraphy in chronic osteomyelitis. J Nucl Med 1998;39:2145-2152.

22 De Winter F, van de WC, Vogelaers D et al. Fluorine-18 fluorodeoxyglucose-position emission tomography: a highly accurate imaging modality for the diagnosis of chronic musculoskeletal infections. J Bone Joint Surg Am 2001;83-A: 651-660.
23 Zhuang H, Duarte PS, Pourdehand M, Shnier D, Alavi A. Exclusion of chronic osteomyelitis with F-18 fluorodeoxyglucose positron emission tomographic imaging. Clin Nucl Med 2000;25:281-284.
24 Kalicke T, Schmitz A, Risse JH et al. Fluorine-18 fluorodeoxyglucose PET in infectious bone diseases: results of histologically confirmed cases. Eur J Nucl Med 2000;27:524-528.
25 Blockmans D, Stroobants S, Maes A, Mortelmans L. Positron emission tomography in giant cell arteritis and polymyalgia rheumatica: evidence for inflammation of the aortic arch. Am J Med 2000;108:246-249.

Chapter 8

A prospective multi-center study of the value of ^{18}F-fluorodeoxyglucose positron emission tomography as part of a structured diagnostic protocol in patients with fever of unknown origin

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Abstract

Since ^{18}F-fluorodeoxyglucose (FDG) accumulates in neoplastic cells and in activated inflammatory cells, positron emission tomography (PET) with FDG could be valuable in diagnosing patients with fever of unknown origin (FUO). The aim of this study was to validate the use of FDG-PET as part of a structured diagnostic protocol in the general patient population with FUO.

Methods: From December 2003 to July 2005, 70 patients with FUO were recruited from one university hospital (n=38) and five community hospitals (n=32). A structured diagnostic protocol including FDG-PET was used. A dedicated, full ring PET-scanner was used for data acquisition. FDG-PET scans were interpreted by two staff members of the department of nuclear medicine without further clinical information. The final clinical diagnosis was used for comparison with the FDG-PET results.

Results: Of all scans, 33% were clinically helpful. Contribution of FDG-PET to the final diagnosis did not differ significantly between patients diagnosed in the university hospital and patients in the community hospitals. FDG-PET contributed significantly more often to the final diagnosis in patients with continuous fever than in patients with periodic fever. FDG-PET was not helpful in any of the patients with normal erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).

Conclusion: FDG-PET is a valuable imaging technique as part of a diagnostic protocol in the general patient population with FUO and a raised ESR or CRP.

Introduction

Despite modern diagnostic techniques, no diagnosis can be reached in up to 53% of all patients with fever of unknown origin (FUO) [1-9]. Since ^{18}F-fluorodeoxyglucose (FDG) accumulates in cells with a high rate of glycolysis [10], such as neoplastic cells and activated inflammatory cells [11,12], positron emission tomography (PET) with FDG could be valuable in diagnosing patients with FUO. In previous studies, the percentage of FDG-PET scans helpful in the diagnostic process in patients with FUO varied from 16% to 69% [13-18]. All previous studies have been performed in tertiary care or university hospitals and it is unknown whether these results can also be applied to FUO patients who are being diagnosed in community hospitals. Furthermore, in none of these studies a structured diagnostic protocol was used. The aim of this prospective multi-center study was to validate the use of FDG-PET as part of a structured diagnostic protocol in a general population of patients with FUO.

Materials and methods

Hospitals

From December 2003 to July 2005, patients with FUO were prospectively recruited from the Radboud University Nijmegen Medical Centre (RUNMC), a 950-bed university hospital and tertiary referral center for patients with classical FUO and periodic fever. Patients were also recruited from 5 community hospitals: Canisius Wilhelmina Hospital Nijmegen (650 beds), Jeroen Bosch Hospital 's-Hertogenbosch (450 beds), Rijnstate Hospital Arnhem (750 beds), Slingeland Hospital Doetinchem

(450 beds) and Maxima Medical Center Veldhoven (500 beds). The study was approved by all local ethical committees and all patients provided written informed consent.

Patients

FUO was defined as a febrile illness of >3 weeks duration, a temperature of >38.3°C on at least two occasions, and diagnosis uncertain after thorough history-taking, physical examination and certain obligatory investigations (Figure 1). Periodic fever was defined as repeated episodes of fever with fever-free intervals of at least two weeks and apparent remission of the underlying disease. Immunocompromized patients, defined as patients with neutropenia (leukocyte count <1.0 x 10^9/l and/or granulocyte count <0.5 x 10^9/l) during at least 1 week within 3 months preceding the fever, known HIV-infection, known hypogammaglobulinemia, use of the equivalent of more than 10 mg prednisone during at least 2 weeks in the previous 3 months, were excluded. All records of non-immunocompromized patients with fever on the internal medicine wards and out patient departments aged 18 years or older were reviewed at least weekly for the criteria for FUO by the first author or the local investigator. In a retrospective study of patients with FUO previously performed in our university hospital, it was observed that blood cultures were performed in all patients with FUO [4]. Because of the size of the university hospital, records of all patients in whom blood cultures were performed were reviewed weekly for the criteria of FUO by the first author as a second check.

Diagnostic work-up

In all patients primarily referred to one of the participating hospitals, a structured diagnostic protocol was used (Figure 1). The maximum time interval between the obligatory tests and the FDG-PET scan was one week in hospitalized patients and 2 weeks in the remaining patients. In patients with periodic fever, FDG-PET was performed during a symptomatic phase (within 3 days after the beginning of the fever). In these patients, second level diagnostic tests were only recommended when potential diagnostic clues for infectious diseases, vasculitis syndromes or malignancy were present, or when the clinical condition was deteriorating.

FDG-PET

A dedicated, full ring PET-scanner (Philips Allegro, Philips, Eindhoven, The Netherlands for patients recruited in Rijnstate Hospital in Arnhem, ECAT-EXACT, Siemens/CTI, Knoxville, TN, USA for all other patients) was used for data acquisition. Prior to FDG-injection, patients had fasted for at least 6 hours. Immediately prior to the procedure, the patients were hydrated with 500 ml of water. One hour after intravenous injection of 200-220 MBq FDG (Tyco Healthcare/Mallinckrodt Medical, Petten, The Netherlands) and 10 to 15 mg furosemide, emission and transmission images of the area between the proximal femora and the base of the skull were acquired (10 minute per bed position). Performing total body FDG-PET including the legs was not possible because of the long duration of the procedure expected to cause patient compliance problems and because this would have significantly decreased PET capacity. Scanning of the legs was performed when PDCs for diseases occurring in the legs were present. The images were corrected for attenuation and were reconstructed using the ordered subsets-expectation maximization (OSEM) algorithm. FDG-PET scans were interpreted by two staff members of the department of nuclear medicine without information of the results of other diagnostic tests or the final diagnosis. All abnormalities, no matter how subtle, were reported. Disagreements were resolved by consensus.

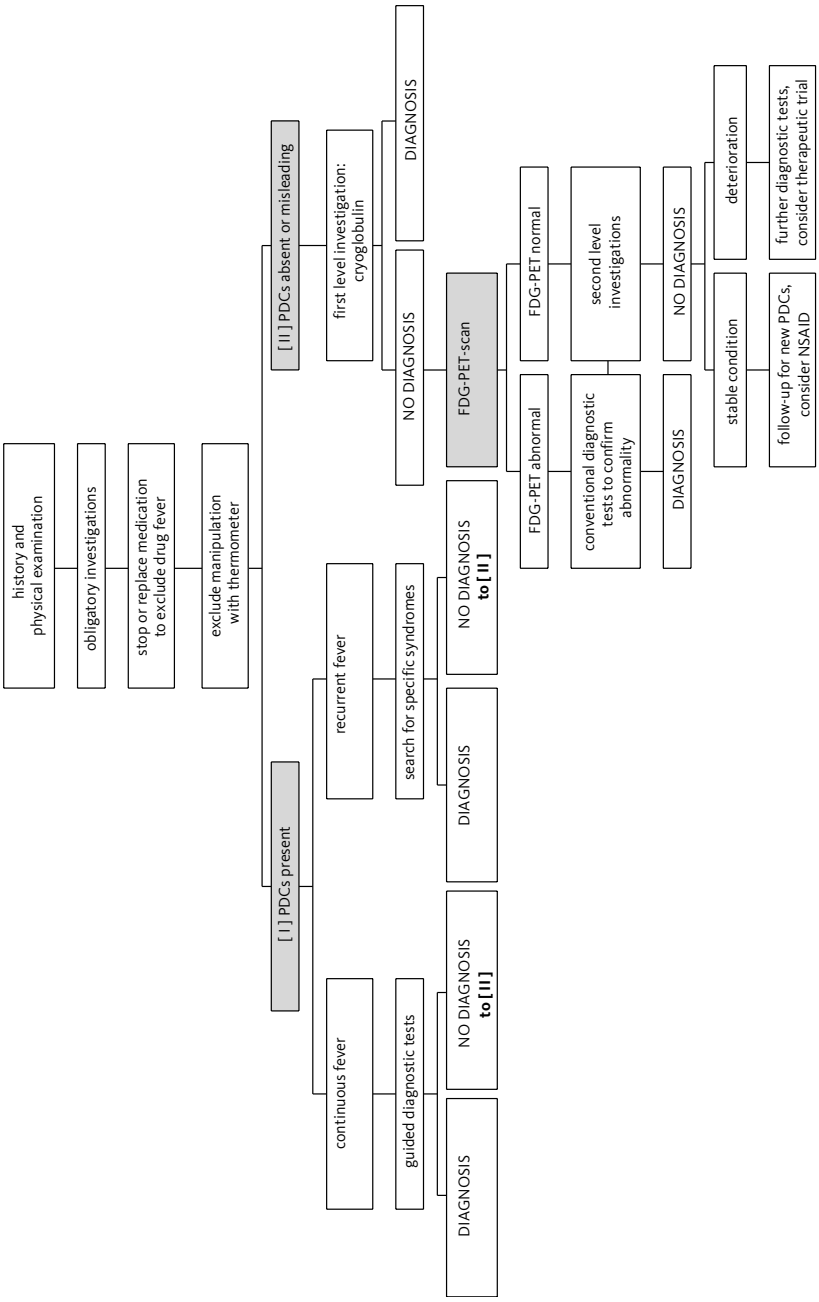

Figure 1 This figure shows the diagnostic protocol that was used in all participating patients.
PDCs = potentially diagnostic clues. Obligatory tests: erythrocyte sedimentation rate or C-reactive protein, hemoglobin, platelet count, leukocyte count and differentiation, electrolytes, creatinine, total protein, protein electrophoresis, alkaline phosphatase, ALAT, LDH, creatine kinase, antinuclear antibodies, rheumatoid factor, urinalysis, blood cultures (n=3), urine culture, chest X-ray, abdominal ultrasonography (or CT) and tuberculin skin test. Second level investigations: bone marrow biopsy, temporal artery biopsy in patients older than 55 years, fundoscopy, abdominal CT and chest CT

Diagnosis and assessment of FDG-PET results

The final diagnosis, established by the attending physician and the first author, was used for comparison with FDG-PET results. A definite diagnosis was based on biopsy, positive serology, or positive cultures. *Yersinia* serology was considered positive in case both IgA and IgG immunoblots were repeatedly positive for at least 2 bands and other diagnoses were excluded. When patients fulfilled generally accepted clinical criteria, the diagnosis was also considered definite. In this study, the following criteria were used: American College of Rheumatology revised criteria (ARA-criteria) for systemic lupus erythematosus (SLE) [19], American College of Rheumatology criteria for giant cell vasculitis [20], American College of Rheumatology criteria for Henoch Schonlein purpura [21], criteria by Fautrel et al. for adult onset Still's disease [22], and the Moll and Wright criteria for psoriatic arthritis [23]. Polymyalgia rheumatica was diagnosed in case the patient (1) was 50 years or older at onset, (2) had bilateral aching and morning stiffness (lasting 30 minutes or more) persisting for at least one month, with involvement of at least two of the following three areas: neck or torso, shoulders or proximal regions of the arms, and hips or proximal aspects of the thighs, and (3) when erythrocyte sedimentation rate (ESR) was elevated to 40 mm/h or more. A diagnosis was never based on the FDG-PET results alone. Abnormal FDG-PET scans were considered helpful in establishing the diagnosis or true positive when abnormal FDG-uptake pointed to the organ or tissue where the cause of the fever was found by additional diagnostic techniques. Abnormal results were regarded as non-contributory to diagnosis or false positive when the detected abnormality was considered to be unrelated to the illness causing the fever or when no final diagnosis could be made. A normal FDG-PET scan was considered true negative when no cause of the symptoms was identified despite an extensive diagnostic work-up and clinical follow-up of at least 3 months after FDG-PET. A normal FDG-PET scan was considered false negative when a focal infection, a focal inflammatory process or neoplasm was diagnosed.

Statistical analysis

Descriptive statistics for continuous variables are represented as means ± standard deviations. Categorical variables are reported in terms of the number and percentage of patients affected. Differences between the patient groups were tested with Fisher's exact tests for categorical variables. Differences were considered to be statistically significant at $P < 0.05$.

Results

Between December 2003 and July 2005, 75 patients with FUO were identified. No additional patients were identified through review of the records of all patients in whom blood cultures were requested. Two patients refused participation and 3 patients had to be excluded (Figure 2). The results of 70 patients (32 males and 38 females) with a mean age of 53 years (range 26 to 87 years) were evaluated: 38 patients were recruited from RUNMC and 32 from the other hospitals. Twenty-four patients (34% of all patients, 63% of patients recruited from RUNMC) were referred to RUNMC for a second opinion after previous extensive investigation elsewhere. All patients recruited from the community hospitals were referred by their general practitioner. Twenty-six patients (37%) had periodic fever: 20 of these patients (77%) were enrolled in RUNMC and 6 in other hospitals ($P < 0.01$).

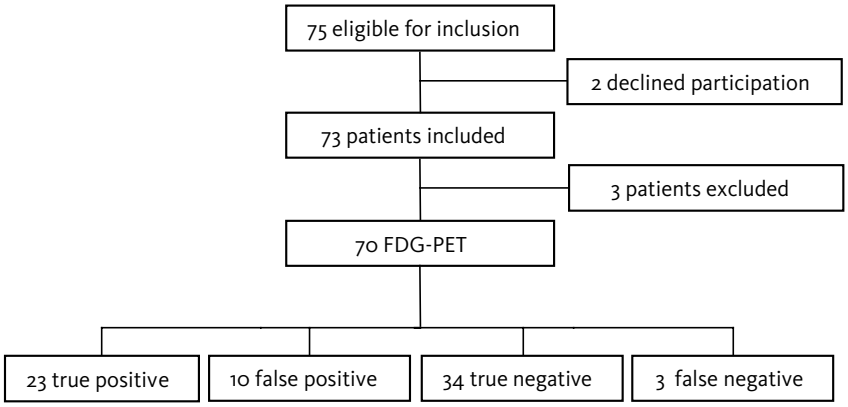

Figure 2 Three patients had to be excluded: all symptoms resolved before FDG-PET was performed in one patient, in another patient, it proved to be impossible to obtain a reliable FDG-PET scan due to severe contractures of the extremities, and one patient died before FDG-PET was performed.

An infectious disease was the cause of the fever in 12 patients (17%), a neoplasm in 5 patients (7%), non-infectious inflammatory diseases (NIID) in 16 patients (23%), and hypertriglyceridemia and drug fever in one patient each (Table 1). In 35 patients (50%), the cause of the fever was not found. Obligatory laboratory tests, other chemical tests, immunological serology, and endocrinological investigations never directly revealed the diagnosis. The presence of antinuclear antibodies was helpful in diagnosing SLE in all 4 patients diagnosed with this disease, but showed false positive results in 8 patients. In one patient with microscopic polyangiitis, the presence of anti neutrophil cytoplasmic antibodies (ANCA) was helpful while ANCA were also present in 5 patients without vasculitis. In 53 patients, 509 microbiological serologic tests were performed (repeated measurements of the same parameter were not counted). Except for *Yersinia enterocolitica* serology, these tests were never helpful in establishing a diagnosis. Positive results (IgA and IgG repeatedly positive for at least 2 bands) were obtained in 4 patients who were diagnosed with chronic persistent yersiniosis as cause of the fever. In three patients, all symptoms disappeared after antibiotic treatment and in one patient, symptoms disappeared and inguinal lymphadenopathy markedly decreased without treatment. Except for *Yersinia* serology there were no significant differences in the number of abnormal results of biochemical or serological tests between the different diagnostic categories and patients without a final diagnosis. In none of the 11 patients with normal C-reactive protein (CRP) and normal ESR, FDG-PET contributed to the final diagnosis compared to 39% in patients with either elevated CRP or ESR (P=0.01). None of the other biochemical or serological tests were helpful in predicting whether FDG-PET would be helpful in establishing a final diagnosis.

Thirty-three (47%) of 70 FDG-PET scans were considered abnormal (Table 2). Of these abnormal FDG-PET scans, 23 correctly pointed to the source of the fever and were thus true positive (Figures 2-4). FDG-PET was considered true negative in 7 patients with NIID (polymyalgia rheumatica, adult onset Still's disease, Henoch Schonlein and microscopic polyangiitis, respectively) without any focal symptoms of disease, arthritis or signs of large vessel vasculitis (Table 1, in the patient with

adult onset Still's disease with palpable lymphadenopathy, abnormal FDG-uptake in multiple lymph nodes was considered true positive). Normal FDG-PET results were also considered true negative in one patient with hypertriglyceridemia. In 26 patients without a final diagnosis, a normal FDG-PET scan was classified as true negative, so in total there were 34 true negative FDG-PET-scans. FDG-PET was considered false negative in two patients with small pleural effusions who were eventually diagnosed with SLE and one patient with pyelonephritis. FDG-PET was classified as false positive in 10 cases (Table 3). In these patients, 12 diagnostic procedures were performed as a result of FDG-PET. Following the diagnostic protocol, 5 of these diagnostic tests would also have been performed in case the FDG-PET results had been negative. So false positive FDG-PET results generated 7 unnecessary diagnostic procedures: 3 invasive procedures (2 lymph node biopsies and 1 gastroscopy) and 4 non-invasive procedures (consultation of another specialty: n=3 and 1 MRI). In comparison, 16 false positive abdominal CT scans (performed in a total of 60 patients) generated 22 unnecessary investigations: 15 non-invasive procedures and 7 invasive procedures. In all patients, a total of 997 diagnostic procedures not including laboratory tests or cultures were performed before a cause of the fever was found or until the end of follow-up in patients with unexplained fever. So false-positive FDG-PET results were responsible for only 0.7% of all diagnostic procedures.

Table 1 Final diagnoses in patients with FUO and classification of the results of FDG-PET for each category

Category	No. of cases	True positive	True negative	False positive	False negative
Infection	*12 (17%)*	*11*	-	-	1
Bronchiectasia/pneumonia	2	2	-	-	-
Diverticulitis	1	1	-	-	-
Pyelonephritis	1	-	-	-	1
Abdominal abscesses	1	1	-	-	-
Osteomyelitis	2	2	-	-	-
Tonsillitis	1	1	-	-	-
Chronic persistent Yersiniosis	4	4	-	-	-
Neoplasm	*5 (7%)*	*5*	-	-	-
Non-Hodgkin's lymphoma	3	3	-	-	-
Metastatic breast cancer	1	1	-	-	-
Adenocarcinoma with unknown primary	1	1	-	-	-
Non-infectious inflammatory disease	*16 (23%)*	*6*	*7*	*1*	*2*
Large vessel vasculitis	2	2	-	-	-
Polymyalgia rheumatica	3	-	3	-	-
Henoch Schonlein purpura	1	-	1	-	-
Microscopic polyangiitis	1	-	1	-	-
Psoriatic arthritis	1	1	-	-	-
Adult onset Still's disease	3	1	2	-	-
Systemic lupus erythematosus	4	2	-	-	2
Cryoglobulinemia	1	-	-	1	-
Miscellaneous	*2 (3%)*	*1*	*1*	-	-
Drug fever	1	1	-	-	-
Hypertriglyceridemia	1	-	1	-	-
No diagnosis	*35 (50%)*	-	*26*	*9*	-

Table 2 Results of FDG-PET in patients with FUO

	FDG-PET abnormal		FDG-PET normal
	Contributory	Non-contributory	
Infection	11	-	1
Neoplasm	5	-	-
NIID	6	1	9
Miscellaneous	1	-	1
No diagnosis	-	9	26
Total	23 (33%)	10 (14%)	37 (53%)

NIID = non-infectious inflammatory diseases.

Table 3 Final diagnosis in patients with false-positive FDG-PET results (n=10)

Patient	FDG-PET result	Investigation guided by FDG-PET	Final diagnosis	Follow-up (duration months)
F, 29 yr	Right lower quadrant abdomen	Gynecological examination: normal	No diagnosis	Persisting FUO (20)
M, 61 yr	Supraclavicular lymph node	Lymph node biopsy: reactive	No diagnosis	Persisting FUO (10)
M, 45 yr	Supraclavicular lymph node	Lymph node biopsy: reactive	No diagnosis	Persisting FUO (13)
M, 29 yr	Vertebra Th10	MRI: impression fracture Th10	No diagnosis	Recovery (6)
F, 27 yr	Focal mediastinal FDG-uptake	Thoracic CT: normal	No diagnosis	Persisting FUO (7)
F, 26 yr	FDG-uptake above bladder	Abdominal CT, gynecological examination: normal	No diagnosis	Persisting FUO (11)
M, 60 yr	Focal mediastinal FDG-uptake	Thoracic CT: enlarged subcarinal lymph node (no biopsy)	No diagnosis	Recovery (6)
M, 71 yr	Large vessel vasculitis	-	No diagnosis	Recovery (7)
M, 42 yr	FDG-uptake upper abdomen	Abdominal CT/gastroscopy: normal	No diagnosis	Recovery (6)
M, 69 yr	Right lung, both hips	Thoracic CT: previous bilobectomy, Consultation pulmonary medicine: recurrence of lung cancer unlikely	Cryoglobulinemia	Recovery (4)

Thus, 70% of the abnormal FDG-PET scans were clinically helpful and FDG-PET contributed to the ultimate diagnosis in 33% of all patients. FDG-PET was considered helpful in 66% of all patients with a final diagnosis. Sensitivity of FDG-PET was 88%, specificity was 77%, positive predictive value was 70% and negative predictive value was 92%. In a subgroup of 43 patients, both abdominal and chest CT was performed. In these 43 patients, a combination of abdominal and chest CT had a positive predictive value of 48% and a negative predictive value of 86%. In the same 43 patients, positive predictive value of FDG-PET was 65% with a negative predictive value of 90%.

True positive FDG-PET results were definitely confirmed by biopsy (n=8), culture (n=3), serology (n=4) or generally accepted clinical criteria (n=16) [19-23] in 31 cases (89%) and a probable confirmation was reached in the remaining 4 cases (11%) through radiology (n=3) or the clinical course (n=1). Median duration of follow-up was 10 months (range 4 to 22 months, >6 months in 93% of all patients). Contribution of FDG-PET to the final diagnosis did not differ significantly between

patients referred after investigation in another hospital and patients who were directly referred (25% vs. 39%) or between patients diagnosed in RUNMC and patients in the other hospitals (26% vs. 41%). FDG-PET contributed significantly more often to the final diagnosis in patients with continuous fever than in patients with periodic fever (45 vs. 12%, P <0.005). Although a diagnosis was reached in only 6 out of 26 patients with periodic fever, FDG-PET contributed to the diagnosis in 3 of these cases (50%) and was considered true negative in the other 3 patients with adult onset Still's disease without localizing symptoms or focal abnormalities, Henoch Schonlein purpura and hypertriglyceridemia. In none of the 3 cases with true positive FDG-PET results, the final diagnosis was suspected before FDG-PET was performed despite extensive previous diagnostic tests.

Discussion

In this multi-center prospective clinical study, 33% of all FDG-PET scans contributed to the final diagnosis while the probability of reaching a diagnosis was only 50%. Since significant differences in the contribution of FDG-PET between patients diagnosed in the university hospital and the community hospitals or between patients who were directly referred and patients referred after investigation in another hospital were absent, FDG-PET as part of the structured diagnostic protocol used in this study is valuable in the general population of patients with FUO. The contribution of FDG-PET in patients with periodic fever was low. It is very unlikely, however, that any of the conditions diagnosed after abnormal FDG-PET results in these patients would have been found without FDG-PET since these diagnoses were not suspected after a previous very extensive diagnostic workup. In none of the patients with periodic fever, a diagnosis with focal abnormalities was reached in case FDG-PET was normal (negative predictive value 100%) and FDG-PET was helpful in 50% of patients with a final diagnosis. We believe that by adding FDG-PET to the diagnostic protocol in these patients and by avoiding any follow-up tests in case of normal FDG-PET results in the absence of potential diagnostic clues or clinical deterioration, the number of unnecessary tests can be significantly reduced. In patients with periodic fever, sensitivity of FDG-PET is probably highest when performed during a fever episode (Figure 3). Since FDG-PET did not contribute in any of the patients with normal CRP and ESR, it is not indicated in these patients.

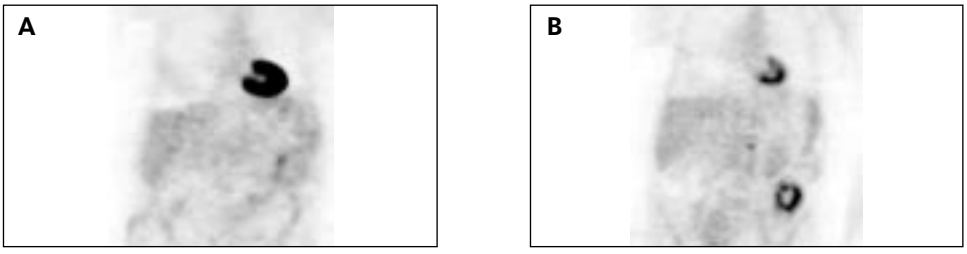

Figure 3 This 61-year-old woman with periodic fever was referred after a very extensive diagnostic workup in another university hospital. A previous abdominal CT, performed at the end of a fever episode, was normal. Her first FDG-PET scan, performed in another hospital before inclusion in the present study between fever episodes, was normal (Figure 3A). When FDG-PET was repeated during a fever episode after inclusion, however, clearly abnormal FDG-uptake was seen in the left lower abdomen (Figure 3B). The next day abdominal CT showed diverticulitis.

Including the patients in the present study, the value of FDG-PET has been studied in 2 retrospective and 5 prospective studies in 292 patients with FUO [13-18] (Table 4) showing an overall helpfulness of FDG-PET corrected for study population of 36%. Comparing these studies, however, is difficult. First of all, the definition of FUO was different in each study. In 3 studies, patients were not recruited from all patients with FUO presenting at the hospital, but from patients referred to the nuclear medicine department [14], from patients referred for ^{111}In-granulocyte scintigraphy because of FUO by the department of infectious diseases [24] and from patients referred for FDG-PET because of FUO by the department of internal medicine [18], respectively. Second, the FDG-PET technique in the study by Meller et al. [14] is inferior to the FDG-PET technique in the other studies. Furthermore, FDG-PET was performed at different stages of the diagnostic process and a structured diagnostic protocol was never used. The use of a structured diagnostic protocol including FDG-PET has reduced the chance of selection bias in our study. To further reduce the chance of unintended selection bias, a broad initial selection criterion was used: reviewing of all records of non-immunocompromized patients with fever on the internal medicine wards and out patient clinics in all hospitals for the criteria for FUO. No further patients were identified by checking the records of patients in whom blood cultures were ordered during the study period. Since blood cultures were ordered in all patients with FUO in previous studies in the Netherlands [4,16], this indicates that all patients with FUO were identified by the first selection criterion.

Calculation of sensitivity and specificity of FDG-PET in patients with FUO is difficult, because a final diagnosis is not established in all patients. When additional diagnostic procedures, performed according to the diagnostic protocol, are negative and long-term follow-up does not reveal a diagnosis, it is probably legitimate to presume that focal infectious disease, inflammation or malignancy is not the cause of the symptoms in these patients. Second, in patients with negative FDG-PET, a variety of diseases were found that could not be diagnosed with FDG-PET. The way we perform FDG-PET does not allow to draw conclusions about the lower legs. Besides physiological uptake of FDG in the brain and the heart, physiological activity in the kidneys and the bladder severely hampers the delineation of disease in these organs. This hampers the classification of PET-scans as true negative. However, in our series we have obtained no evidence of infectious or inflammatory foci in the brain, the heart, or the bladder despite intensive searching. In one patient, pyelonephritis was diagnosed. This patient's normal FDG-PET scan has been categorized as false negative. Variable physiologic FDG-uptake in the bowel is possible [25] and may lead to a false positive interpretation, although this problem was not encountered in the present study. Also, diseases without focal abnormalities (for example polymyalgia rheumatica without signs of large vessel vasculitis) or diseases with focal abnormalities smaller than 0.5 cm (for example microscopic polyangiitis) cannot be detected by FDG-PET. Therefore, normal FDG-PET results were not scored as false negative when such diseases were diagnosed. In all large series of FUO patients, simple diagnoses will eventually be established in a few patients when symptoms and signs are not specific as is illustrated in this study in the patients with tonsillitis and pyelonephritis, for example, and in the patient with diverticulitis described in Figure 3.

Table 4 Review of the literature on the utility of FDG-PET in patients with FUO and comparison to the present study

First author (year)	Study design	FUO-definition	FDG-PET technique	Conclusions
Meller (2000) [14]	Prospective (n=20): comparison FDG-PET and ^{67}Ga-citrate (n=18)	- Temp. >38.3°C during >3 weeks - no diagnosis after 1 week of diagnostic work-up - AND referral to nuclear medicine department	Dual-headed coincedence camera	FDG-PET helpful in 55%, PPV* 92%, †NPV 75%, FDG-PET superior to ^{67}Ga-citrate
Blockmans (2001) [13]	Prospective (n=58): comparison to ^{67}Ga-citrate (n=40)	- Temp. >38.3°C during >3 weeks - no diagnosis after 3 days in-hospital investigation	Full ring PET scanner	FDG-PET helpful in 41%, FDG-PET superior to ^{67}Ga-citrate
Lorenzen (2001) [15]	Retrospective (n=16)	- Temp. >38.0°C during >3 weeks - increased ‡ESR and §CRP - inconclusive diagnostic tests	Full ring PET scanner	FDG-PET helpful in 69%, PPV 92%, NPV 100%
Bleeker-Rovers (2004) [16]	Retrospective (n=35)	- Temp. >38.3°C during >3 weeks - no diagnosis after one week of evaluation in the hospital or in the outpatient department	Full ring PET scanner	FDG-PET helpful in 37%, PPV 87%, NPV 95%
Kjaer (2004) [17]	Prospective (n=19): comparison to ^{111}In-granulocyte	- Temp. >38.3°C during >3 weeks - no diagnosis after one week of evaluation in the hospital or in the outpatient department - AND referral for ^{111}In-granulocyte scintigraphy	Full ring PET scanner	FDG-PET helpful in 16%, PPV 30%, NPV 67%, ^{111}In-granulocyte scintigraphy helpful in 26%,
Buysschaert (2004) [18]	Prospective (n=74)	- Temp. >38.3°C during >3 weeks - no diagnosis after 3 days in hospital or 3 outpatient visits - AND referral for FDG-PET	Full ring PET scanner	FDG-PET helpful in 26%
Bleeker-Rovers (present study)	Prospective, multicenter (n=70)	- Temp. >38.3°C during >3 weeks - no diagnosis after certain obligated initial investigations	Full ring PET scanner	FDG-PET helpful in 33%, PPV 70%, NPV 92%

*PPV = positive predictive value, †NPV = negative predictive value, ‡ESR = erythrocyte sedimentation rate, §CRP = C-reactive protein

No systematic research studying the use of CT or magnetic resonance imaging (MRI) in patients with FUO is available. Advantages of FDG-PET are absence of disturbance by metallic implants, whole body screening and absence of contrast-related side effects. The more limited anatomic

information will be overcome in the future as integrated PET-CT scanners become increasingly available. In a subgroup in our study in whom both abdominal and chest CT were performed as well as FDG-PET, positive and negative predictive values of FDG-PET were higher than those of abdominal and chest CT combined.

The conventional radiopharmaceuticals routinely used in clinical practice, ^{67}Ga and ^{111}In-labelled or ^{99m}Tc-labeled leukocytes, have disadvantages, such as handling of potentially infected blood products, high radiation burden, and the long time span between injection and diagnosis. Advantages of FDG-PET are higher resolution, sensitivity in chronic low-grade infections, and high accuracy in the central skeleton [26]. Another major advantage of FDG-PET in the work-up of FUO is the vascular FDG-uptake in patients with vasculitis [14,27]. 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 anyhow. Obvious disadvantages are the relatively high cost and the currently limited availability. However, when 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 thereby the duration of hospitalization for diagnostic purposes.

From two prospective studies comparing FDG-PET with ^{67}Ga-citrate scintigraphy in a total of 58 patients with FUO, it was concluded that FDG-PET was superior to ^{67}Ga-citrate scintigraphy because the diagnostic yield is at least comparable to that of ^{67}Ga-citrate scintigraphy and the results are available within hours instead of days [13,14]. Kjaer et al. [17] conclude in their prospective study comparing FDG-PET with ^{111}In-granulocyte scintigraphy in 19 patients with FUO that ^{111}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 if a relatively high percentage of false positive results is sufficient reason to reject FDG-PET as a valuable diagnostic method in patients with FUO. In our study, despite the fact that FDG-PET was read very sensitive with the inherent risk of over reporting, false positive FDG-PET results were responsible for less than 1% of all diagnostic studies performed in these patients. On the other hand, an abnormal FDG-PET scan leading to the underlying cause of the fever, prevents at least the tests that are advised in the diagnostic protocol as second level investigations. Furthermore, FDG-PET has a very high sensitivity for most malignant tumours while ^{111}In-granulocyte scintigraphy does not have a similar sensitivity. In addition, the therapeutic and prognostic consequences of a delay in diagnosing malignancy, responsible for FUO in 7 to 28% of cases [1-9], are clinically very important. Therefore, we believe that high accuracy in diagnosing malignant disease should be an important characteristic of the recommended nuclear medicine technique in FUO patients.

Conclusion

FDG-PET is a valuable imaging technique as part of a structured diagnostic protocol in patients with FUO with a raised ESR or CRP, either referred to a university hospital or to a community hospital. Because reaching a diagnosis is extremely difficult in patients with periodic fever and FDG-PET offers a contribution (albeit small) and a very high negative predictive value, it is advised that FDG-PET is also added to the diagnostic protocol in these patients.

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References

1 Barbado FJ, Vazquez JJ, Pena JM, Arnalich F, Ortiz-Vazquez J. Pyrexia of unknown origin: changing spectrum of diseases in two consecutive series. Postgrad Med J 1992;68:884-887.
2 Kazanjian PH. Fever of unknown origin: review of 86 patients treated in community hospitals. Clin Infect Dis 1992;15: 968-973.
3 Knockaert DC, Vanneste LJ, Vanneste SB, Bobbaers HJ. Fever of unknown origin in the 1980s. An update of the diagnostic spectrum. Arch Intern Med 1992;152:51-55.
4 de Kleijn EM, van der Meer JW. Fever of unknown origin (FUO): report on 53 patients in a Dutch university hospital. Neth J Med 1995;47:54-60.
5 de Kleijn EM, Vandenbroucke JP, van der Meer JW. Fever of unknown origin (FUO). I A. prospective multicenter study of 167 patients with FUO, using fixed epidemiologic entry criteria. The Netherlands FUO Study Group. Medicine (Baltimore) 1997;76:392-400.
6 Tabak F, Mert A, Celik AD, Ozaras R, Altiparmak MR, Ozturk R, et al. Fever of unknown origin in Turkey. Infection 2003;31:417-420.
7 Vanderschueren S, Knockaert D, Adriaenssens T, Demey W, Dumez A, Blockmans D, et al. From prolonged febrile illness to fever of unknown origin: the challenge continues. Arch Intern Med 2003;163:1033-1041.
8 Saltoglu N, Tasova Y, Midikli D, Aksu HS, Sanli A, Dundar IH. Fever of unknown origin in Turkey: evaluation of 87 cases during a nine-year-period of study. J Infect 2004;48:81-85.
9 Ergonul O, Willke A, Azap A, Tekeli E. Revised definition of 'fever of unknown origin': limitations and opportunities. J Infect 2005;50:1-5.
10 Bar-Shalom R, Valdivia AY, Blaufox MD. PET imaging in oncology. Semin Nucl Med 2000;30:150-185.
11 Kubota R, Yamada S, Kubota K, Ishiwata K, Tamahashi N, Ido T. Intratumoral distribution of fluorine-18-fluorodeoxyglucose in vivo: high accumulation in macrophages and granulation tissues studied by microautoradiography. J Nucl Med 1992;33:1972-1980.
12 Brown RS, Leung JY, Fisher SJ, Frey KA, Ethier SP, Wahl RL. Intratumoral distribution of tritiated fluorodeoxyglucose in breast carcinoma: I. Are inflammatory cells important? J Nucl Med 1995;36:1854-1861.
13 Blockmans D, Knockaert D, Maes A, De Caestecker J, Stroobants S, Bobbaers H, et al. Clinical value of [(18)F]fluoro-deoxyglucose positron emission tomography for patients with fever of unknown origin. Clin Infect Dis 2001;32:191-196.
14 Meller J, Altenvoerde G, Munzel U, Jauho A, Behe M, Gratz S, et al. Fever of unknown origin: prospective comparison of [18F]FDG imaging with a double-head coincidence camera and gallium-67 citrate SPET. Eur J Nucl Med 2000;27: 1617-1625.

15 Lorenzen J, Buchert R, Bohuslavizki KH. Value of FDG PET in patients with fever of unknown origin. Nucl Med Commun 2001;22:779-783.
16 Bleeker-Rovers CP, de Kleijn EM, Corstens FH, van der Meer JW, Oyen WJ. Clinical value of FDG PET in patients with fever of unknown origin and patients suspected of focal infection or inflammation. Eur J Nucl Med Mol Imaging 2004;31:29-37.
17 Kjaer A, Lebech AM, Eigtved A, Hojgaard L. Fever of unknown origin: prospective comparison of diagnostic value of 18F-FDG PET and 111In-granulocyte scintigraphy. Eur J Nucl Med Mol Imaging 2004;31:622-626.
18 Buysschaert I, Vanderschueren S, Blockmans D, Mortelmans L, Knockaert D. Contribution of (18)fluoro-deoxyglucose positron emission tomography to the work-up of patients with fever of unknown origin. Eur J Intern Med 2004;15: 151-156.
19 Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997;40:1725.
20 Hunder GG, Bloch DA, Michel BA, Stevens MB, Arend WP, Calabrese LH, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum 1990;33:1122-1128.
21 Mills JA, Michel BA, Bloch DA, Calabrese LH, Hunder GG, Arend WP, et al. The American College of Rheumatology 1990 criteria for the classification of Henoch-Schonlein purpura. Arthritis Rheum 1990;33:1114-1121.
22 Fautrel B, Zing E, Golmard JL, Le Moel G, Bissery A, Rioux C, Rozenberg S, Piette JC, Bourgeois P. Proposal for a new set of classification criteria for adult-onset still disease. Medicine (Baltimore) 2002;81:194-200.
23 Moll JM, Wright V. Psoriatic arthritis. Semin Arthritis Rheum 1973;3:55-78.
24 Kjaer A, Lebech AM. Diagnostic value of (111)In-granulocyte scintigraphy in patients with fever of unknown origin. J Nucl Med 2002;43:140-144.
25 de Groot M, Meeuwis AP, Kok PJ, Corstens FH, Oyen WJ. Influence of blood glucose level, age and fasting period on non-pathological FDG uptake in heart and gut. Eur J Nucl Med Mol Imaging 2005;32:98-101.
26 Bleeker-Rovers CP, Boerman OC, Rennen HJ, Corstens FH, Oyen WJ. Radiolabeled compounds in diagnosis of infectious and inflammatory disease. Curr Pharm Des 2004;10:2935-2950.
27 Blockmans D, Stroobants S, Maes A, Mortelmans L. Positron emission tomography in giant cell arteritis and polymyalgia rheumatica: evidence for inflammation of the aortic arch. Am J Med 2000;108:246-249.

Chapter 9

A prospective multi-center study on fever of unknown origin: the yield of a structured diagnostic protocol

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Abstract

This prospective study was performed to update our knowledge of FUO and to explore the utility of a structured diagnostic protocol. From December 2003 to July 2005, 73 patients with FUO were recruited from one university hospital (n=40) and 5 general hospitals (n=33) in the same region in The Netherlands. FUO was defined as a febrile illness of >3 weeks duration, a temperature of >38.3°C on several occasions without a diagnosis after standardized history-taking and physical examination and certain obligatory investigations. Immunocompromized patients were excluded. A structured diagnostic protocol was used. Patients from the university hospital were characterized by more secondary referrals and a higher percentage of periodic fever than those referred to general hospitals. Infection was the cause in 16%, a neoplasm in 7%, non-infectious inflammatory diseases in 22%, miscellaneous causes in 4%, and in 51%, the cause of fever was not found (no differences between university and general hospitals). There were no differences regarding the number and type of investigations between university and general hospitals. Significant predictors for reaching a diagnosis included: continuous fever, fever present for <180 days, elevated ESR, CRP, or LDH, leucopenia, thrombocytosis, abnormal chest CT and abnormal ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET). For future FUO studies, inclusion of out-patients and the use of a set of obligated investigations instead of a time-related criterion are recommended. Except for tests from the obligatory part of our protocol and cryoglobulins in an early stage, followed by FDG-PET, and in a later stage by abdominal and chest CT, temporal artery biopsy in patients of 55 years or older and possibly bone marrow biopsy, other tests should not be used as screening investigations.

Introduction

Despite recent advances in diagnostic techniques, fever of unknown origin (FUO) remains a formidable challenge. Since the 1961 definition of FUO as an illness of more than three weeks duration, fever >38.3°C (101°F) on at least two occasions, and diagnosis uncertain after one week of hospitalization [1], this definition has been modified by removing the requirement that the evaluation must take place in the hospital [2]. Also, immunocompromized patients have been excluded, because these patients require an entirely different approach [2-4]. To reduce selection bias, it has been proposed to change the quantitative criterion (diagnosis uncertain after one week of study) to the qualitative requirement that certain investigations have to be performed [2,4,5].

The differential diagnosis of FUO is the most extensive in medicine and construction of algorithms covering all possible causes is difficult. In general, infectious diseases explain about one-third of cases of FUO, followed by neoplasms and non-infectious inflammatory diseases (NIID) [6]. In the vast literature on FUO, no controlled trials or meta-analyses are available. In recent series from Europe and the USA, the percentage of patients with unexplained FUO varied from 7 to 53% [4,7-14]. This variation is partly due to geographical factors and different definitions of FUO used. In addition, few studies have used uniform epidemiological entry criteria or a structured diagnostic protocol, which causes unintended selection bias and differences in diagnostic work-up. Moreover, results of those studies cannot easily be extrapolated to an individual patient presenting with FUO.

This prospective study of patients with FUO recruited from one university hospital and 5 general hospitals in The Netherlands was performed to update information on FUO using the revised definition of FUO. Since there are only two older studies that included patients from general hospitals [15,8], the second aim was to compare the number and sort of additional diagnostic tests that were used and causes of fever between patients with FUO referred to a university hospital and patients referred to general hospitals. To minimize diversity in diagnostic management, a standardized diagnostic protocol was used, which was based on a previously performed in-depth inquiry into diagnostic management of FUO among Dutch internists [16], on retrospective analysis of diagnostic management of patients with FUO in our university hospital [10,17] and, most importantly, on the large prospective Dutch FUO studies of De Kleijn et al. [4,18]. Based on previous studies, showing that ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) contributed to the final diagnosis in 16 to 69% of all patients with FUO [17,19-23], FDG-PET was added to this protocol.

Patients and methods

Hospitals

From December 2003 to July 2005, patients with FUO were recruited from the Radboud University Nijmegen Medical Center (RUNMC), a 950-bed university hospital and tertiary referral center for patients with classical FUO and periodic fever. Patients were also recruited from five general hospitals: Canisius Wilhelmina Hospital Nijmegen (CWH, 650 beds), Jeroen Bosch Hospital 's-Hertogenbosch (JBH, 450 beds), Rijnstate Hospital Arnhem (RH, 750 beds), Slingeland Hospital Doetinchem (SH, 450 beds) en Maxima Medical Center Veldhoven (MMC, 500 beds). The study was approved by all local ethic committees.

Patients

FUO was defined as a febrile illness of >3 weeks duration, a temperature >38.3°C on at least two occasions, without a diagnosis after standardized history-taking, standardized physical examination and the following obligatory diagnostic investigations: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), hemoglobin, platelet count, leukocyte count and differentiation, electrolytes, creatinine, total protein, protein electrophoresis, alkaline phosphatase, AST, ALT, LDH, creatine kinase, antinuclear antibodies, rheumatoid factor, urinalysis, at least 3 blood cultures, urine culture, chest X-ray, abdominal ultrasonography (or CT) and tuberculin skin test. Periodic fever was defined as repeated episodes of fever with fever-free intervals of at least two weeks and apparent remission of the underlying disease. Immunocompromized patients, defined as patients with neutropenia (leukocyte count <1.0 x 10^9/l and/or granulocyte count <0.5 x 10^9/l) during at least 1 week within the 3 months preceding the fever, known HIV-infection, known hypogammaglobulinemia (IgG <50% of the normal value), use of the equivalent of more than 10 mg prednisone during at least 2 weeks in the previous 3 months, were excluded. All patients with FUO aged 18 years or older in the participating hospitals were eligible for inclusion. To minimize the chance of unintended selection bias, broad initial selection criteria were used. All records of non-immunocompromized patients with fever on the internal medicine wards and out-patient clinics in all hospitals were reviewed for

the criteria for FUO by either the first author or the local investigator. In a retrospective study of patients with FUO previously performed in our university hospital, it was found that blood cultures were performed in all patients with FUO [10]. Therefore, in the university hospital, records of all patients in whom blood cultures were performed were reviewed weekly for the criteria of FUO by the first author. All patients provided written informed consent.

Diagnostic work-up

In all patients primarily referred to one of the participating hospitals, a structured diagnostic protocol was used (Figure 1). In patients referred after investigations in another hospital, this diagnostic protocol was followed directly after referral. First, a complete and repeated history was taken, a complete physical examination was performed followed by the obligatory investigations in a search for potentially diagnostic clues (PDCs). PDCs are defined as all localizing signs, symptoms and abnormalities potentially pointing toward a diagnosis [4]. With help of these PDCs a limited list of probable diagnoses was made. After identification of all PDCs retrieved from the history, physical examination and obligatory tests, further diagnostic procedures were recommended to be guided by this list. Misleading PDCs are defined as PDCs not leading to the eventual diagnosis. In patients without PDCs or only misleading PDCs, cryoglobulins were determined. When diagnosis was still uncertain, FDG-PET was performed. In patients with continuous fever with normal or false positive FDG-PET results, bone marrow biopsy, temporal artery biopsy in patients older than 55 years, fundoscopy, abdominal CT and chest CT were performed. In patients with periodic fever, FDG-PET was performed during a symptomatic phase. In these patients, second level diagnostic tests were only recommended when PDCs for infections, vasculitis syndromes or malignancy were present, or when the clinical condition was deteriorating. In all patients with unexplained fever at this point, repeating a thorough history taking, physical examination and reviewing laboratory results and imaging studies including those from other hospitals was recommended. Only in patients deteriorating without presenting new PDCs, a further diagnostic workup or therapeutic trial with antibiotics, steroids, or antituberculous agents was recommended.

Assessment of diagnostic results

The results of diagnostic investigations were evaluated for their diagnostic contribution. Abnormal test results were categorized as “helpful in diagnosis” or “non-contributory to diagnosis”. They were regarded as helpful in diagnosis or true positive when abnormal test results pointed to the cause of the fever. Abnormal results were regarded as non-contributory to diagnosis or false positive when the detected abnormality was considered to be unrelated to the illness causing the fever or when no final diagnosis could be made. Since in most cases a gold standard is not available, specificity and sensitivity could only be calculated assuming that negative results were true negative when further investigations or the final diagnosis did not contradict these results. Normal test results were categorized as true negative when no cause of the symptoms was identified despite an extensive diagnostic work-up and clinical follow-up of at least 3 months. Normal test results were considered false negative when a disease was diagnosed that would usually cause positive test results. Most investigations were performed in each hospital according to local standards, because the scale of this study did not allow us to centralize these measurements and investigations.

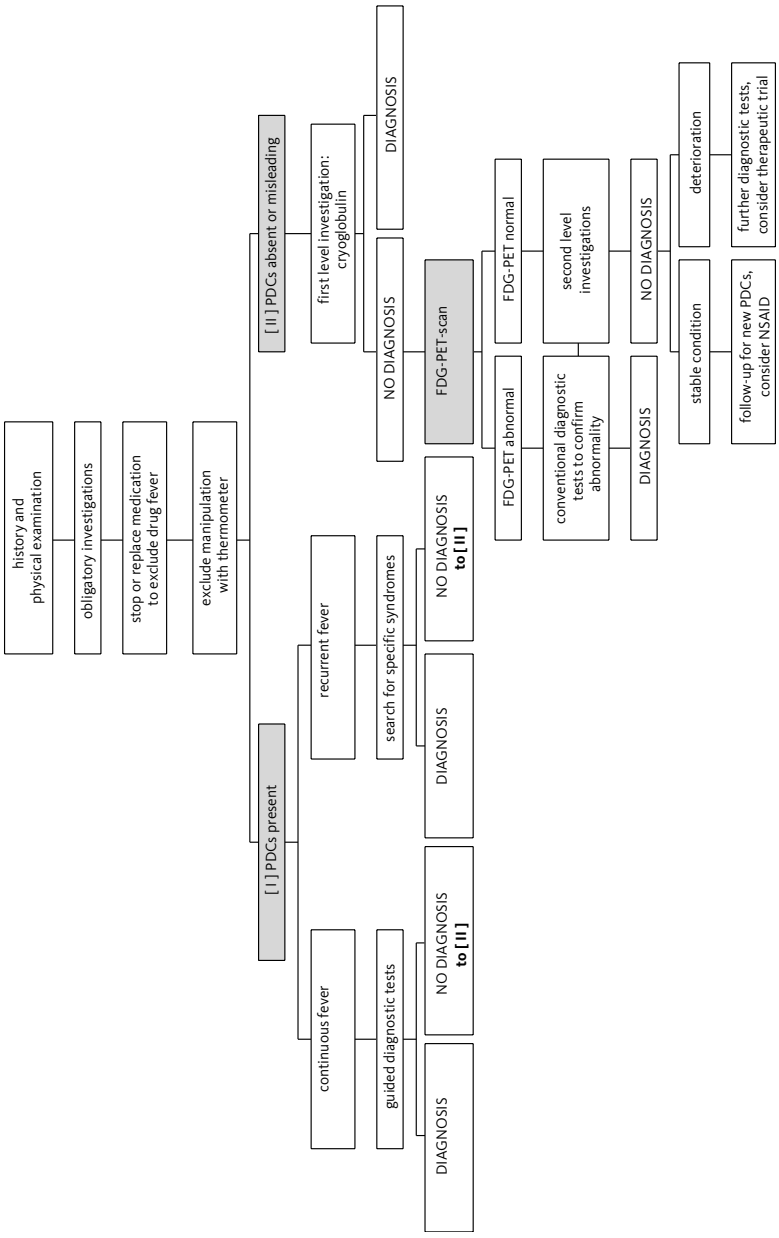

Figure 1 This figure shows the diagnostic protocol that was used in all participating patients.
PDCs = potentially diagnostic clues
Obligatory tests: erythrocyte sedimentation rate or C-reactive protein, hemoglobin, platelet count, leukocyte count and differentiation, electrolytes, creatinine, total protein, protein electrophoresis, alkaline phosphatase, ALAT, LDH, creatine kinase, antinuclear antibodies, rheumatoid factor, urinalysis, blood cultures (n=3), urine culture, chest X-ray, abdominal ultrasonography (or CT) and tuberculin skin test.
Second level investigations: bone marrow biopsy, temporal artery biopsy in patients older than 55 years, fundoscopy, abdominal CT and chest CT

Diagnosis and follow up

The final diagnosis was established by the attending physician and the first author. A definite diagnosis was based on positive cultures, serology, histology, or internationally accepted criteria for certain diseases. When this was not possible, a probable diagnosis was made based on a combination of clinical follow-up, response to specific therapy and conventional imaging studies. Follow up was performed by the first author by analysis of the patient's record, and, in case no diagnosis was reached at the end of the study, also by telephone calls to the attending physicians and, in some cases, to the patients after a follow-up of at least 3 months, and again after at least 6 months.

Data collection and statistical analysis

Of all patients, epidemiological data, number, sort and results of all diagnostic tests that were performed, the final diagnosis, treatment data, and follow-up data were registered in a structured database. Descriptive statistics for continuous variables are represented as means ± standard deviations. Categorical variables are reported in terms of the number and percentage of patients affected. Differences between the patient groups were tested with unpaired student t-tests for continuous variables and with Fisher's exact tests for categorical variables. Differences were considered to be statistically significant at $P < 0.05$. Sensitivity and specificity were calculated with 95% confidence intervals. All potential predicting factors for reaching a diagnosis (all parameters derived from the standardized history and physical examination and the obligatory diagnostic tests and also for results of FDG-PET, abdominal and chest CT) were dichotomized. Patients with a final diagnosis were compared to patients without a final diagnosis using a Fisher's exact test. Relative risks were calculated with 95% confidence intervals. A parameter was considered as a significant predicting factor when the 95% confidence interval of the relative risk was >1.

Results

Clinical features

Between December 2003 and July 2005, 75 patients with FUO were identified by review of patient records or through direct report by treating physicians (Figure 2). No additional patients were identified through review of the records of all patients in whom blood cultures were performed during the study period. Two patients refused participation, so a total number of 73 patients were enrolled. The results of 73 patients (33 males and 40 females) with a mean age of 54 years (range 26 to 87 years) were evaluated: 40 patients were recruited from the university hospital (RUNMC) and 33 from the other hospitals (Table 1). Twenty-five patients (34% of all patients, 63% of patients recruited from RUNMC) were referred to RUNMC after extensive investigation in another hospital.

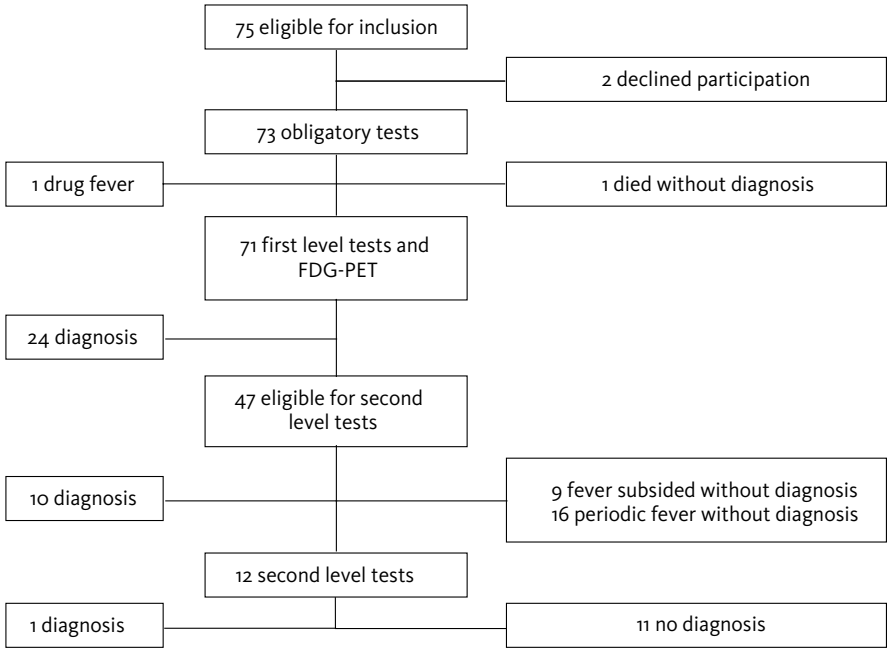

Figure 2 This figure shows the numbers of patients that were included in the different stages of the diagnostic protocol. It also shows the numbers of patients in whom a diagnosis was reached after every level of diagnostic tests and, for the remaining patients, the reasons for not participating in the next step of the diagnostic protocol.

Table 1 Epidemiological data of all patients with FUO

Characteristic	Total (n=73)	University hospital (n=40)	General hospitals (n=33)
Patients per hospital – No. (%)			
RUNMC	40 (55%)	40	-
CWH	11 (15%)	-	11 (33%)
JBH	5 (7%)	-	5 (15%)
RH	4 (5%)	-	4 (12%)
SH	11 (15%)	-	11 (33%)
MMC	2 (3%)	-	2 (6%)
Age – yr			
Mean ± SD	54 ± 16	51 ± 16	57 ± 16
Range	26-87	26-82	31-87
Male sex – No. (%)	33 (45%)	16 (40%)	17 (52%)
Secondary referral – No. (%)	15 (21%)	15 (38%)‡	0‡
Periodic fever	25 (34%)	20 (50%)‡	5 (15%)‡
Duration of fever before present analysis - days			
Median ± SD	53 ± 890	348 ± 1106‡	15 ± 200‡
Range	1-4197	1-4197	1-1144
Hospitalization – No. (%)	62 (85%)	33 (83%)	29 (88%)
Median duration ± SD	29 ± 32	32 ± 40	28 ± 18
Range	3-177	3-177	3-77

‡P <0.05

All patients recruited from the general hospitals were referred by a general practitioner (P <0.0001). Twenty-five patients (34%) had periodic fever: 20 of these patients (80%) were enrolled in RUNMC and 5 in general hospitals (P <0.005). The patient group from RUNMC was thus characterized by a higher percentage of secondary referrals and significantly more patients with periodic fever when compared to the patient group recruited from the general hospitals. Of all FUO patients, 85% were hospitalized for a median duration of 32 days (range 3-177 days). Significant differences between the university hospital and the general hospitals regarding the percentage of patients hospitalized or duration of hospitalization were absent.

Diagnosis and outcome

An infectious disease was the cause of the fever in 12 patients (16%), a neoplasm in 5 patients (7%), non-infectious inflammatory diseases (NIID) in 16 patients (22%), and miscellaneous causes in 3 patients (4%) (Table 2). The proportion of patients in each diagnostic category did not differ significantly between RUNMC and the general hospitals. In patients who were directly referred, NIID were significantly more often diagnosed than in patients referred for a second opinion (41% vs. 9%, P=0.04). Diagnoses were definitely confirmed by biopsy, microbiology or generally accepted clinical criteria [24-27] in 31 cases (86%). A probable confirmation was reached in the remaining 5 cases (14%) through radiology and clinical follow-up. In 37 patients (51%), the cause of the fever was not found. The percentage of patients without a final diagnosis did not differ significantly between RUNMC and the general hospitals (55% vs. 45%). In 19 of all 25 patients with periodic fever (76%), no cause of the fever was found. Of the remaining 48 patients with continuous fever, no diagnosis was established in 15 cases (31%, P <0.005). In patients referred for a second opinion, no diagnosis was reached in 17 of 25 patients (68%) compared to no diagnosis in 20 of 48 patients (42%) who were directly referred (P=0.05).

After a median follow-up of 12 months (range 6 to 23 months), the fever subsided spontaneously in 16 of all 37 patients without a final diagnosis, in 5 patients the fever subsided after empirical treatment with a non-steroidal anti-inflammatory drug (NSAID) or corticosteroids, and in 15 patients, the fever persisted. Of these 15 patients with persisting fever after a median follow-up of 15 months (7 to 23 months), 10 had periodic fever. One patient died before a diagnosis was reached. Duration of follow-up exceeded 6 months in all surviving patients without a diagnosis. In 36 patients with an explanation for the fever and a median follow-up of 11 months (range 4 to 23 months for surviving patients, >6 months in 88%), the fever subsided either spontaneously or after specific treatment in 22 patients and in 10 patients the fever persisted. Despite appropriate treatment, 4 patients died due to the underlying disease causing the fever (pulmonary infection with bronchiectasis, abdominal abscesses, non-Hodgkin's lymphoma (NHL) and metastatic adenocarcinoma).

Table 2 Final diagnoses in 73 patients with FUO

Category	Total (n=73)	University hospital (n=40)	General hospitals (n=33)
Infection	*12 (16%)*	*7 (18%)*	*5 (15%)*
Bronchiectasia/pneumonia	2	1	1
Diverticulitis	1	1	-
Pyelonephritis	1	-	1
Abdominal abscesses	1	1	-
Osteomyelitis	2	1	1
Tonsillitis	1	-	1
Chronic persistent Yersiniosis	4	3	1
Neoplasm	*5 (7%)*	*2 (5%)*	*3 (9%)*
Non-Hodgkin's lymphoma	3	2	1
Breast carcinoma with metastases	1	-	1
Adenocarcinoma with unknown primary	1	-	1
Non-infectious inflammatory disease	*16 (22%)*	8 (20%)	8 (24%)
Large vessel vasculitis	2	-	2
Polymyalgia rheumatica	3	1	2
Henoch Schonlein purpura	1	1	-
Microscopic polyangiitis	1	1	-
Psoriatic arthritis	1	-	1
Adult onset Still's disease	3	2	1
Systemic lupus erythematosus	4	2	2
Cryoglobulinemia	1	1	-
Miscellaneous	*3 (4%)*	*0*	*3 (9%)*
Drug fever	2	-	2
Hypertriglyceridemia	1	-	1
No diagnosis	*37 (51%)*	*22 (55%)*	*15 (45%)*
Spontaneous recovery	16	6	10
Recovery with NSAID or corticosteroids	5	3	2
Persistent fever	15	12	3
Death	1	1	-

Potentially diagnostic clues (PDCs)

After the standardized history, physical examination, and obligatory tests, PDCs were present in all patients (Table 3). On average, 15 PDCs were identified per patient of which 81% proved to be misleading. In the remaining 19%, PDCs contributed to the final diagnosis, but in none of these patients, PDCs alone directly led to a diagnosis. In all patients with PDCs contributing to the final diagnosis, misleading PDCs were also present. The PDCs most often leading to a diagnosis (<75% misleading, present in at least 10 patients) were weight loss, muscle weakness, skin changes, previous medical history, shortness of breath, chest pain, abdominal pain, arthralgia, morning stiffness, abnormal pulmonary auscultation, elevated lactate dehydrogenase (LDH), anemia, leukocytosis, abnormal urinalysis and abnormal chest X-ray. There was no significant difference between patients with a diagnosis and patients without a diagnosis or between patients from RUNMC and patients from the general hospitals regarding the number of PDCs present.

Table 3 Numbers of PDCs derived from the standardized history, physical examination and obligatory tests in 73 patients with FUO

PDCs – Total No. (%)	Total (n=73)	University hospital (n=40)	General hospitals (n=33)
History	649	354	295
Misleading	540 (83%)	297 (84%)	243 (82%)
Physical examination	128	64	64
Misleading	92 (72%)	45 (70%)	47 (73%)
Obligatory tests	287	140	147
Misleading	225 (78%)	108 (77%)	117 (80%)
Total	1064	558	506
Misleading	857 (81%)	450 (81)	407 (80%)

PDCs = potentially diagnostic clues

Adherence to the diagnostic protocol

A total number of 5331 investigations were performed in these 73 patients. Adherence to the diagnostic protocol did not differ significantly between the university hospital and the general hospitals except for measurement of cryoglobulins, which was significantly more often performed in the university hospital than in the general hospitals (95% vs. 52%). The obligatory investigations were performed in more than 95% of cases except for creatine phosphokinase (n=66, 90%) and tuberculin skin test (n=58, 79%). After the obligatory tests, one patient was diagnosed with drug fever (Figure 2). After performing FDG-PET and testing for cryoglobulins, a diagnosis was reached in 24 patients. In 10 patients, new PDCs leading to the final diagnosis (SLE in 2 patients, polymyalgia rheumatica in 3 patients, adult onset Still's disease in 2 patients, microscopic poly-angiitis, Henoch Schonlein purpura, and hypertriglyceridemia each in one patient) developed before second level tests were completed. In 9 patients, the fever subsided spontaneously and 16 patients had periodic fever, so only 12 patients with continuous fever qualified for second level tests. In one of these 12 patients, pyelonephritis was diagnosed with abdominal CT whereafter no further tests were performed. Abdominal CT was performed in 9 of the remaining 11 patients (82%), thoracic CT in 7 patients (64%), fundoscopy in 4 patients (36%), and bone marrow biopsy each in only one patient (9%). In 2 out of 4 patients older than 55 years, temporal artery biopsy was performed. In none of these 11 patients, an explanation for the fever was found.

Utility of investigations in the diagnostic process

Laboratory investigations

Including obligatory laboratory tests, other chemical tests, immunological serology, and endocrinological investigations, a total number of 3124 laboratory tests were performed (repeated measurements of the same parameter in one patient were not counted). None of these tests directly revealed the diagnosis. Abnormal liver tests, present in 20 patients (27%), contributed to the final diagnosis in only 3 patients (4%). The presence of antinuclear antibodies was helpful in diagnosing SLE in all 4 patients diagnosed with this disease, but showed false positive results in 8 patients. In one patient with microscopic polyangiitis, the presence of anti neutrophil cytoplasmic antibodies (ANCA) was helpful while ANCA were also present in 5 patients without vasculitis. Endocrinological investigations did not contribute to the final diagnosis in any of the patients.

Microbiology

In 53 patients, 509 microbiological serologic tests were performed (repeated measurements of the same parameter were not counted). Except for *Yersinia enterocolitica* serology, these tests were never helpful in establishing a diagnosis. Serology for cytomegalovirus (n=37), Epstein Barr virus (n=34), hepatitis B virus (n=21), hepatitis C virus (n=23), HIV (n=22), *Borrelia burgdorferi* (n=22), *Brucella spp.* (n=25), *Coxiella burnetii* (n=22), *Toxoplasma gondii* (n=25), and syphilis (n=21) were most often requested. In 29 patients (40%), serology for *Yersinia enterocolitica* was performed. *Yersinia* serology was negative in 15 patients and in 10 patients the results were considered equivocal (IgA negative and IgG positive for at least 2 bands, IgA and IgG positive for 1 band, or IgA and IgG weakly positive for 1 or more bands). Positive results (IgA and IgG repeatedly positive for at least 2 bands) were obtained in 4 patients who were diagnosed with chronic persistent yersiniosis as cause of the fever. In three patients, all symptoms disappeared after antibiotic treatment and in one patient, symptoms disappeared and inguinal lymphadenopathy markedly decreased without treatment.

A total of 743 blood cultures, 170 urine cultures, and 280 other cultures were performed. In none of these patients, however, blood or urine cultures led to the cause of the fever. In 10 patients, positive blood cultures were found (1.2% of all blood cultures). In one patient treated with continuous ambulatory peritoneal dialysis (CAPD) who was diagnosed with abdominal abscesses, *Escherichia coli*, *Proteus mirabilis*, and *Enterococcus spp.* were repeatedly cultured from the CAPD fluid, which proved to be the micro-organisms causing the abscesses after surgical drainage. In 6 patients, blood cultures grew coagulase-negative *Staphylococci* (n=3), *Corynebacterium* (n=1), diphteroid rods (n=1), and *Propionibacterium* (n=1), which were all considered to be contamination by the treating physician. In the remaining 3 patients with blood cultures growing *Streptococcus viridans*, *Stenotrophomonas maltophilia,* and *Enterococci* combined with coagulase-negative *Staphylococci* each in one patient, the fever persisted after appropriate antibiotic treatment followed by negative blood cultures and was considered to be unrelated to the bacteremia. In 9 patients who did not have convincing symptoms or signs of a urinary tract infection, urinary culture results were considered to be false positive (5% of all urine cultures), because after adequate treatment of the assumed urinary tract infection, bacteriuria disappeared while the fever remained unchanged. In one patient eventually diagnosed with pyelonephritis, urinary culture (obtained after 2 days of antibiotic treatment) was considered false negative. With regard to the number of cultures performed per patient, no difference was found between the university hospital and the general hospitals.

Imaging techniques (Table 4)

Chest X-ray was considered false negative in 4 patients with pulmonary NHL, mediastinal NHL, and SLE pleuritis (n=2). Abdominal ultrasound was performed in 58 patients (79%). An abdominal CT had been performed in 6 of the remaining patients before inclusion or referral to the university hospital. In the other 9 patients, abdominal CT was preferred by the treating physician, usually because of a longer waiting time for abdominal ultrasound. In 18 patients, abnormal abdominal ultrasound did not lead to the diagnosis and caused unnecessary investigations, so these were considered false positive. In one patient with diverticulitis, abdominal ultrasound was classified as false negative because FDG-PET and subsequent abdominal CT revealed the diagnosis. Assuming

all other normal chest X-rays and abdominal ultrasounds were true negative, sensitivity and specificity were calculated (Table 4).

Table 4 Diagnostic utility of imaging techniques, endoscopy, histological investigations, and laparotomy in 73 patients with FUO

Investigation	No. of patients	Helpful	False positive	Sensitivity (95% CI)	Specificity (95% CI)
Chest X-ray	73 (100%)	6 (8%)	8 (11%)	60% (26-88%)	87% (77-94%)
Sinus X-ray	32 (44%)	0	2 (6%)	NC	NC
Orthopantomogram	22 (30%)	0	2 (9%)	NC	NC
Barium enema	10 (14%)	0	1 (10%)	NC	NC
Enteroclysis	6 (8%)	0	0	NC	NC
Abdominal ultrasound	58 (79%)	6 (10%)	18 (31%)	86% (42-100%)	65% (50-78%)
Abdominal CT	60 (82%)	12 (20%)	17 (29%)	92% (64-100%)	63% (48-77%)
Chest CT	46 (63%)	9 (20%)	8 (17%)	82% (48-98%)	77% (60-90%)
FDG-PET	70 (96%)	23 (33%)	10 (14%)	88% (74-99%)	77% (63-89%)
Echocardiography	19 (26%)	0	4 (22%)	NC	NC
Bronchoscopy	5 (7%)	1 (20%)	0	NC	NC
Gastroscopy	21 (29%)	0	3 (14%)	NC	NC
Colonoscopy	19 (26%)	1 (5%)	2 (10%)	NC	NC
Temporal artery biopsy	14 (19%)	1 (7%)	0	NC	NC
Bone marrow biopsy	19 (26%)	2 (11%)	1 (5%)	NC	NC
Liver biopsy	7 (10%)	1 (14%)	3 (43%)	NC	NC
Duodenal biopsy	12 (16%)	0	1 (8%)	NC	NC
Colonic biopsy	13 (18%)	0	2 (15%)	NC	NC
Lymph node biopsy	11 (15%)	5 (46%)	3 (27%)	NC	NC
Skin biopsy	8 (11%)	5 (63%)	0	NC	NC
Laparotomy	4 (6%)	2 (50%)	1 (25%)	NC	NC

CT = computer tomography
FDG-PET = ^{18}F-fluorodeoxyglucose positron emission tomography
NC = not calculated

Sinus X-rays and orthopantomograms were not helpful in our patient population. The results of 2 sinus X-rays and 2 orthopantomograms were considered false positive. Also, barium enemas or enteroclysis never helped revealing a final diagnosis in this study. In one patient, barium enema showed diverticulosis and could not rule out diverticulitis, but abdominal CT and colonoscopy did not reveal any signs of diverticulitis, so barium enema was considered false positive. In this population of patients with FUO, echocardiography was never helpful. In 4 patients without cardiac causes explaining the fever, abnormal echocardiography showing a small pericardial effusion in the patient with diverticulitis, dubious vegetations of the mitral or aortic valve without endocarditis according to the Duke criteria (n=2), and thickened septum was considered false positive.

Abdominal CT, performed in 60 patients, was helpful in establishing a diagnosis in 12 patients (20%). Results of abdominal CT were considered false positive in 17 patients (28%, 12 patients without a final diagnosis and 5 patients with a diagnosis not explaining the abnormality). Abdominal CT was considered false negative in one patient who was eventually diagnosed with diverticulitis in whom only the last of 3 abdominal CT-scans was considered abnormal after comparison to the FDG-PET

results. In 46 patients, chest CT was performed, which was helpful in 9 (20%). False positive results were found in 8 patients without evidence of pulmonary disease (17%). Chest CT was considered false negative in a patient with NHL and in a patient with aortitis of the thoracic aorta. FDG-PET, performed in 70 patients, contributed to the final diagnosis in 23 patients (33%) and results were categorized as false positive in 10 patients (14%, 9 patients without a diagnosis). FDG-PET was considered false negative in 2 patients (3%) with small pleural effusions who were eventually diagnosed with SLE and one patient with pyelonephritis. The results of FDG-PET will be discussed in detail elsewhere. Assuming all other abdominal and chest CT-scans and FDG-PET-scans were true negative, sensitivity and specificity were calculated (Table 4).

Histological investigations (Table 4)

Bone marrow aspiration was performed in 21 patients, but never contributed to the diagnosis. Bone marrow biopsy, performed in 19 patients, was helpful in establishing a diagnosis in one patient with NHL and one patient with bone metastases of an adenocarcinoma with an unknown primary tumor. In both patients, bone marrow aspiration had not revealed the diagnosis. Temporal artery biopsy was performed in 14 patients (10 with PDCs for vasculitis, 2 with FDG-PET results suggesting vasculitis, and 2 as part of the second level tests), but in only one patient in whom FDG-PET already pointed to large vessel vasculitis, temporal artery biopsy was useful to confirm the diagnosis of temporal arteritis. Liver biopsy was performed in 7 patients. In one patient, lobular hepatitis supported the suspected diagnosis of persistent yersiniosis and thus contributed somewhat to the diagnosis. In 3 patients, the results were considered false positive: hepatitis suggestive of a drug reaction in the patient with diverticulitis and non-specific hepatitis and steatosis in two patient without a diagnosis and no signs of progressive liver disease or viral hepatitis after follow-up of 8 and 11 months, respectively. Lymph node biopsy was performed in 11 patients with lymphadenopathy. Lymph node biopsy supported persistent yersiniosis in 3 patients. Reactive changes were found in 3 patients without a final diagnosis (considered to be false positive) and in 2 patients with Still's disease (true positive). Skin biopsy, performed in 8 patients with skin changes, was helpful in 5 patients diagnosed with drug fever (n=2), Henoch Schonlein purpura, SLE, and Still's disease. Other successful histological investigations performed because PDCs were present or because of abnormal FDG-PET results were pulmonary wedge excision, confirming infection of known bronchiectasis, SLE, and NHL, each in one patient, histological examination of an excised tonsil confirming tonsillitis in one patient, and biopsy of the peritoneum showing a granulomatous infiltrate with necrosis supporting the diagnosis of persistent yersiniosis in one patient. Autopsy confirmed the presence of NHL in one patient.

Endoscopy and laparotomy or laparoscopy (Table 4)

Bronchoscopy was performed in only 5 patients and supported the diagnosis in one patient eventually diagnosed with acute infection of bronchiectasis after pulmonary wedge excision. Gastroscopy, performed in 21 patients, and colonoscopy, performed in 19 patients, were never useful. Gastroscopy showed false positive results in 3 patients (ischemic changes, duodenal ulceration and bulbitis, polyp suspected for malignancy). Colonoscopy was false positive in 2 patients (rectal ulceration and local redness with normal biopsy results). Laparotomy or laparoscopy

was performed in 4 patients with PDCs for abdominal pathology: in one patient, lymphadenopathy caused by persistent yersiniosis was confirmed and in one patient peritonitis was found, which was later diagnosed as SLE peritonitis. In one patient, laparotomy showed lymphadenopathy, but biopsy showed only reactive changes and follow-up of almost one year has not revealed a diagnosis, so laparotomy was considered as false positive.

Factors predicting the likelihood of reaching a diagnosis

Statistically significant predictors for reaching a diagnosis are shown in Table 5. The chance of establishing a diagnosis was higher in patients with continuous fever and in patients in whom the fever persisted for less than 180 days before inclusion. Foreign descent appeared to be a significant predictor of reaching a diagnosis although these patients were diagnosed with diseases (SLE and large vessel vasculitis), which do not appear to relate to their ethnicity. Surprisingly, also otalgia was a significant predictor. Two of these patients were diagnosed with large vessel vasculitis, which could explain the otalgia, but the 5 remaining patients were diagnosed with diseases not explaining the otalgia (adult onset Still's disease, hypertriglyceridemia, pneumonia, NHL, and psoriatic arthritis, respectively). In none of 11 patients with normal C-reactive protein (CRP) and normal erythrocyte sedimentation rate (ESR), a diagnosis could be reached compared to 36 of 62 patients with elevated CRP and/or ESR (58%, P <0.0005), so elevated ESR or CRP is also an important factor in predicting the likelihood of reaching a diagnosis. Abnormal results of either chest X-ray, abdominal ultrasound, or abdominal CT were not predictive of reaching a diagnosis. Abnormal chest CT (performed in 46 patients) and abnormal FDG-PET (performed in 70 patients), however, were significant predicting factors.

Table 5 Predictors of the likelihood of reaching a diagnosis in 73 patients with FUO

Parameter	No diagnosis (n=37) No./Total No. (%)	Diagnosis (n=36) No./Total No. (%)	RR (95%CI)
Continuous fever	18/37 (49%)	30/36 (83%)	2.6 (1.3-5.4)
Fever present <180 days[A]	18/37 (49%)	31/36 (86%)	3.0 (1.4-6.8)
Foreign descent[B]	0/37	2/36 (6%)	2.6 (1.1-6.4)
Otalgia	1/37 (3%)	7/36 (19%)	2.0 (1.3-2.9)
Elevated CRP or ESR[C]	26/37 (70%)	36/36 (100%)	-
Elevated LDH	2/37 (5%)	9/36 (25%)	1.9 (1.3-2.8)
Leukopenia	0/37	2/36 (6%)	2.1 (1.6-2.7)
Thrombocytosis	2/37	7/36 (19%)	1.7 (1.1-2.7)
Chest CT abnormal	6/26 (23%)	12/20 (60%)	2.3 (1.2-4.6)
FDG-PET abnormal	9/35 (26%)	24/35 (69%)	2.4 (1.4-4.2)

[A] Fever present less than 180 days before inclusion in the study
[B] Either the patient or one or both parents were not born in The Netherlands
[C] Calculation of relative risk not possible because all patients with a diagnosis had an elevated CRP or ESR
CRP = C-reactive protein
ESR = erythrocyte sedimentation rate
LDH = lactate dehydrogenase
FDG-PET = ^{18}F-fluorodeoxyglucose positron emission tomography

Discussion

In this prospective multi-center study of 73 patients recruited from one university hospital and 5 community hospitals, the proportion of undiagnosed cases (51%) seems high, but the percentage of undiagnosed cases tends to increase in more recent studies. In the only two series of patients with classical FUO studied after 1990 in northwestern Europe, no diagnosis was reached in 30% [4] and 53% [12], respectively. There are several possible explanations. First, 35% of all patients were referred after extensive investigations elsewhere and it has been speculated that more difficult-to-diagnose cases are referred. The percentage of referred patients in this study, however, is similar to other recent studies (Table 6) reporting percentages of undiagnosed cases from 11 to 53% [4,7,9,10,12,14]. Furthermore, in the present study, secondary referral was not a significant factor predicting the likelihood of reaching a diagnosis.

Table 6 Comparison of previous FUO series with inclusion of patients from Europe and the USA since 1980

First author (country)	Design	Patients (recr. period)	Secondary referral	Periodic fever	Cause of the fever (%)				
					inf.	neopl.	NIID	misc.	unknown
Knockaert [9] (Belgium)	Prospective 1 UH	199 (1980-1989)	28%		23	7	25	20	26
Barbado [7] (Spain)	Prospective 1 UH	85 (1982-1989)	45%		11	28	34	12	15
Kazanjian [8] (US)	Prospective 3 GH	86 (1984-1990)			33	24	26	5	9
De Kleijn [10] (NL)	Retrospective 1 UH	53 (1988-1992)	53%	34%	21	19	23	8	30
Tabak [11] (Turkey)	Retrospective 1 UH	117 (1984-2001)			34	19	29	4	14
De Kleijn [4,18] (NL)	Prospective 8 UH	167 (1992-1994)	38%	34%	26	13	24	8	30
Ergonul [14] (Turkey)	Prospective 1 UH	80 (1993-1999)	33%		52	18	16	3	11
Vanderschueren [12] (Belgium)	Prospective 1 UH	185 (1990-1999)	32%	42%	11	10	18	8	53
Saltoglu [13] (Turkey)	Prospective 1 UH	87 (1994-2002)			59	14	18	2	7
Present study (NL)	Prospective 1 UH/5 GH	73 (2003-2005)	34%	34%	16	7	22	4	51

recr. period = recruitment period
UH= university hospital, GH = general hospital
US = United States, NL = The Netherlands
Inf. = infection, neopl. = neoplasm, NIID = non-infectious inflammatory disease, misc. = miscellaneous

A more probable explanation is the diagnostic strictness we, and also others with relatively high percentages of undiagnosed cases [4,9,10,12], have applied. Diagnoses lacking persuasive confirmatory tests (e.g., adult-onset Still's disease, polymyalgia rheumatica) were only accepted

if sufficient standard criteria were met and follow-up allowed exclusion of other diseases. Since periodic fever was strongly related to a reduced chance of reaching a diagnosis in this study and the chance of reaching a diagnosis in these patients is known to be significantly smaller than in patients with continuous fever [4,12,28], the high percentage of patients with periodic fever (34%) appears to be an important factor explaining the high number of undiagnosed cases. Another factor contributing to the seemingly high diagnostic failure rate might be that a diagnosis is more frequently reached before 3 weeks have elapsed because patients with fever tend to seek medical advice earlier and because better diagnostic techniques, such as CT or MRI, are widely available resulting in more hard-to-diagnose cases meeting the definition of FUO. Another contributing factor, as suggested by Vanderschueren et al. [12], could be the observation that most patients with FUO without a diagnosis do well [4,29], which may lead to a less aggressive diagnostic approach in clinically stable patients once diseases with immediate therapeutic or prognostic consequences have been ruled out to a reasonable extent. This could be especially true for patients with periodic fever who are asymptomatic in between febrile episodes. In the present study, the outcome of patients without a diagnosis was as favorable as in previous studies [4,12,29].

The spectrum of diseases causing FUO has changed as a result of changes in the broad spectrum of diseases causing FUO and the availability of new diagnostic techniques. The proportion of abdominal abscesses and tumors, for example, has decreased in recent series because of earlier detection by ultrasound. Also, infective endocarditis has decreased in frequency as blood culture techniques have improved. In addition, some diagnoses in recent series, such as Lyme disease, acute HIV infection, and Sweet's syndrome, were unknown four decades ago. The percentage of patients diagnosed with infection in our study is similar to the results of other recent studies performed in northwestern Europe [4,9,10,12] (Table 6). In most studies from southern Europe [11,13,14], infections account for a much larger proportion of diagnoses (34 to 59%), which can be explained by the high incidence of tuberculosis (29 to 70% of all infections). In the only study from southern Europe with a lower percentage of infections [7], 8 of 9 infections were caused by tuberculosis also. In one study from the US [8], the percentage of infections was also higher, which could possibly be explained by not excluding HIV-patients and by selection of FUO cases from all infectious disease consultations instead of from the general patient population. The patients in our study did not suffer from rare infections but exhibited rather atypical manifestations of common illnesses, which has already been emphasized as an important factor in patients with FUO by Petersdorf and Beeson [1]. The number of patients eventually diagnosed with NIID will probably not decrease in the near future, because fever may precede more typical manifestations or serological evidence by months in these diseases. Moreover, many of NIID can only be diagnosed after prolonged observation and exclusion of other diseases. In other recent series, the proportion of patients diagnosed with malignancy roughly varies between 10 and 20%. In two studies, a higher incidence of malignancy was found, but both of these studies had a remarkably low percentage of patients without a diagnosis suggesting different patient characteristics [7,8]. The widespread early use of diagnostic techniques such as ultrasound and CT have resulted in a steady decline of malignancy explaining FUO.

To enable adequate comparison between FUO studies, using a uniform definition and uniform entry criteria is very important. Selection bias increases when patients presenting to the outpatient department are included, because prospective case finding is harder and standardized diagnostic protocols are more difficult to implement. However, inclusion of these patients in future studies, as we did in the present study, is essential. Since Petersdorf and Beeson first defined FUO, health care has shifted from the inpatient to the ambulatory setting. Nowadays, most patients with FUO will be hospitalized if this is required by their clinical condition, but not for diagnostic purposes only. A vast proportion of patients who met the definition of FUO in the past would be omitted from future studies if the requirement of study in the hospital is maintained (11 patients in our study, for example). Also, the criterion no diagnosis after admission to the hospital for 1 week (or 3 days as was previously suggested by others) is a time-related criterion, which may cause important differences, as it is dependent on the experience of the physician. Furthermore, many differences in management and diagnostic facilities exist between hospitals or countries. We strongly recommend that, in future FUO studies, this criterion is changed to a quality-related criterion requiring a minimum list of certain investigations to be performed. Defining the necessary initial investigations will remain a matter of debate, but it is generally agreed that the initial diagnostic protocol required for a case to qualify as FUO should at least include the tests that were obligatory in our study. Further tests should be based on the local prevalence of certain diseases.

Classic test characteristics are difficult to apply in FUO studies since there is no diagnostic gold standard against which diagnostic tests may be measured. Determining the denominator for calculation of sensitivity and specificity is difficult since a significant proportion of all cases remain undiagnosed. Therefore, it seems more appropriate to rate diagnostic tests as useful-positive or helpful. The use of diagnostic tests in our patient population proved to be abundant. Although obligatory tests, the first stage investigations, and FDG-PET were performed in more than 95% of patients, the second stage screening tests (Figure 1) were completed in only one out of 12 patients qualifying for this part of the protocol. Therefore, this study does allow us to draw conclusions on the overall diagnostic value of many diagnostic techniques, but not, or to a lesser extent, on the screening diagnostic value of some of these techniques.

Only rarely do biochemical tests directly lead to a certain diagnosis. In our study, nonspecific liver test abnormalities, present in 27% of all patients, only rarely contributed to the final diagnosis, which is in agreement with data from previous studies showing that abnormal liver tests are not predictive of a diagnostic liver biopsy in FUO [30,31]. The diagnostic yield of immunologic serology is also relatively low. Although antinuclear antibodies and ANCA sometimes contributed to the diagnosis, these tests were more often false positive and are of little use without PDCs pointing to specific immunologic disorders. Based on results from a larger prospective study [18], the absence of specific symptoms in many patients, and the relatively low cost of the test, investigation of cryoglobulins appears to be a valuable screening test in patients with FUO although in our current population, cryoglobulinemia was diagnosed in only one patient who was not suspected of this disease.

De Kleijn et al. [18] studied the screening diagnostic value of microbiologic serology in 167 patients with FUO and concluded that these investigations should not be performed early in the diagnostic work-up in patients without PDCs for specific infections. In the present study, serologic tests, although abundantly performed, contributed to the final diagnosis in only four patients with chronic yersiniosis, which supports this conclusion.

Although on average 16 cultures were performed in each patient, culture results supported the final diagnosis in only one patient. Of course, the obligation of the diagnosis being uncertain after performing at least three blood cultures and a urine culture before meeting the definition of FUO is an important reason for this. What physicians should learn from this, however, is that performing more than three blood cultures or more than one urine culture is useless in patients with FUO in the absence of PDCs (i.e. a high clinical suspicion of endocarditis). In the present study, only one patient used antibiotics at the time of inclusion when blood and urine cultures were performed, which might explain why additional blood cultures never contributed to the diagnosis in contrast to the study by De Kleijn et al. [18].

The diagnostic yield of imaging techniques is often difficult to establish, because it is dependent on the imaging techniques that are used in an earlier stage. We tried to minimize this problem by including chest X-ray and abdominal ultrasound in the obligatory part of the diagnostic protocol and by dividing the protocol in several stages. Abdominal ultrasound was chosen as obligatory test above abdominal CT, because of the relatively low cost, no radiation burden, and the absence of side effects. Of course, none of the patients in whom abdominal ultrasound or chest X-ray directly led to the diagnosis were included in this study. In several patients meeting the criteria for FUO, however, abdominal ultrasound or chest X-ray contributed to the diagnosis. Despite the high number of false positive ultrasounds and the relatively low sensitivity of chest X-rays, we believe that these simple low-cost diagnostic tests remain obligatory in all patients with FUO in order to separate diseases that can be easily diagnosed from the real FUO cases.

In the present study, FDG-PET proved to be helpful in 33% of all patients. The value of FDG-PET in this patient population is discussed in greater detail in a separate article concluding that FDG-PET as part of a structured diagnostic protocol is valuable in the general population of FUO-patients. The diagnostic yield of abdominal CT in our study (20%) is similar to results from two previous studies investigating the usefulness of abdominal CT in FUO [18,32]. Specificity of chest CT was similar to the results from the study by De Kleijn et al. [18], but specificity of abdominal CT appeared to be lower (63 vs. 80%). As stated above, this might be explained by the imaging techniques already used (FDG-PET in most patients in the present study vs. no FDG-PET in the previous study). Despite the limited specificity of abdominal CT and the probably limited additional value of chest CT after normal FDG-PET, chest and abdominal CT may be used as screening procedures at a later stage of the diagnostic protocol due to their non-invasive nature and high sensitivity. In our study as well as in the study by De Kleijn et al. [18], the diagnostic yield of echocardiography, X-rays of the sinuses, radiological or endoscopic evaluation of the gastrointestinal tract, and bronchoscopy were very low when PDCs were absent, so these tests should not be performed as screening procedures.

Bone marrow aspiration was of no use in the absence of PDCs for bone marrow disorders in both the present study and the study by De Kleijn et al. [18] and is thus not recommended as a screening procedure. Bone marrow biopsy was useful in 2 patients without PDCs for bone marrow disorders in our study, but in both patients FDG-PET already pointed to the diagnosis. With addition of FDG-PET, which is very sensitive in detecting lymphoma, carcinoma, and osteomyelitis, the value of bone marrow biopsy as a screening procedure is probably less than in the study by De Kleijn et al. [18]. Some studies have shown a high prevalence of temporal arteritis among patients with FUO [9,12], up to 17% in elderly patients [33]. In the present study, temporal artery biopsy was useful in only one patient in whom vasculitis was already suspected after FDG-PET. Since temporal arteritis often starts with non-specific symptoms such as fever, diagnosis can be very difficult. Early diagnosis, however, is important to enable adequate treatment to prevent complications. Temporal artery biopsy can still be recommended for patients of 55 years or older in a later stage of the diagnostic protocol, because FDG-PET will not be useful if the vasculitis is limited to the temporal arteries due to the small diameter of these vessels and because of high FDG-uptake in the overlying brain. In the past, liver biopsies have often been performed as a screening procedure in patients with FUO. In one retrospective analysis of 24 patients with FUO, liver biopsy revealed 3 cases of histoplasmosis and one case of tuberculosis [30], all very uncommon causes of FUO in Europe and the USA. In another study, liver biopsy was performed in 43 patients (14% diagnostic), but these cases represented only 10% of the FUO patients seen in that hospital [31], indicating considerable selection bias. Furthermore, in both our study and the study by De Kleijn et al. [18], liver biopsy as part of the later stage of a screening diagnostic protocol was helpful in only one patient each. Liver biopsy is an invasive procedure with the possibility of complications and even death. Therefore, we believe that liver biopsy should not be performed as a screening procedure in all patients with FUO.

In many reviews of FUO since the 1970s, the importance of PDCs has been emphasized by advising the physician to observe Sutton's law "to go where the money is" [5,34,35]. Two retrospective studies showed significantly lower chances of reaching a diagnosis when PDCs were absent [10,36]. The value of PDCs was investigated in only one prospective study [18], however, which showed that the presence of PDCs does not increase the likelihood of reaching a diagnosis. Because of the low percentage of patients without PDCs in that study and the absence of patients without PDCs in our study, these findings should be interpreted carefully. We have no doubt that the search for PDCs is the physician's most important tool to unravel the cause of the fever, but both the present study and the study by De Kleijn et al. show that the majority of PDCs is misleading. In univariate analysis of patients with and patients without a diagnosis, significant predictive factors for reaching a diagnosis were continuous fever, duration of fever for less than 180 days, foreign descent, otalgia, elevated ESR, CRP, or LDH, leucopenia, thrombocytosis, abnormal chest CT and abnormal FDG-PET. Of most of these factors, it is understandable why reaching a diagnosis is more likely, but especially in case of "otalgia" and "foreign descent", this is much more difficult or even impossible, raising questions about the usefulness of these factors.

The vast majority of FUO studies have been performed in university hospitals. Patients with FUO are often referred to those institutions because of the local expertise, which is also true for RUNMC. It is questionable whether the results from such studies can be applied to the general population of patients with FUO. Two prospective studies were performed in general hospitals in the 1970s [15] and the 1980s [8], but, as far as we know, this is the first study directly comparing patients with FUO referred to one university hospital and several general hospitals in the same region during the same time period. Gleckman et al. [15] studied 34 patients referred to one small general hospital (180 beds) in the Boston area. In 35% of these patients, no diagnosis was reached. In 18% of all cases, infection was causing the fever, in 9% malignancy, in 12 % NIID, and in 26% the cause could be categorized as miscellaneous. In the more recent study by Kazanjian [8], 86 patients with FUO were recruited from 3 general hospitals in Rhode Island (Table 6). Diagnostic techniques have improved remarkably since Gleckman's study and FDG-PET was added to the diagnostic possibilities since Kazanjian's study. In our study, significantly more patients with periodic fever were found in the university hospital. Since diagnosis is more difficult in this patient population and our university hospital has specialized in periodic fever, this was to be expected. The fact that half of all patients were referred to RUNMC after extensive investigation elsewhere while in the general hospitals all patients were directly referred explains the significantly longer duration of fever before the present analysis. There were, however, no significant differences between the causes of FUO or the percentage of patients in whom no diagnosis was reached, so conclusions about the structured diagnostic protocol used in this study are applicable to the general population of FUO patients.

In conclusion, the proportions of patients with FUO that are eventually diagnosed with infection or malignancy have decreased in recent years while the percentage of undiagnosed cases has increased significantly. In patients with FUO, empiric testing should be based on the relative frequencies of the different causes and their importance to the health of the patient. In the absence of PDCs for certain infectious diseases, serologic tests are nearly always useless. Except for tests from the obligatory part of our protocol and measurement of cryoglobulins in an early stage, followed by FDG-PET, and in a later stage by abdominal and chest CT, temporal artery biopsy in patients of 55 years or older and possibly bone marrow biopsy, other tests should not be used as screening procedures in the hope that something abnormal will be found. Ordering other screening tests has many disadvantages, such as false positive results, the possibility of adverse reactions or complications, increasing costs of testing, and as stated before by De Kleijn [18] "a soporific effect on the doctor's diagnostic mental activities". Repeating a thorough history-taking and physical examination and waiting for new PDCs to appear seems to be preferable to ordering more screening tests. If the fever persists and the source remains elusive after completing the later stage investigations, supportive treatment with NSAIDs can be helpful. Empirical therapeutic trials with antibiotics, steroids, or antituberculous agents should be avoided, except in patients whose condition is deteriorating.

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References

1 Petersdorf RG and Beeson PB. Fever of unexplained origin: report on 100 cases. Medicine 1961;40:1-30.
2 Petersdorf RG. Fever of unknown origin. An old friend revisited. Arch Intern Med 1992;152:21-22.
3 Durack DT and Street AC. Fever of unknown origin--reexamined and redefined. Curr Clin Top Infect Dis 1991;11:35-51.
4 de Kleijn EM, Vandenbroucke JP, van der Meer JW. Fever of unknown origin (FUO). I A. prospective multicenter study of 167 patients with FUO, using fixed epidemiologic entry criteria. The Netherlands FUO Study Group. Medicine (Baltimore) 1997;76:392-400.
5 Knockaert DC, Vanderschueren S, Blockmans D. Fever of unknown origin in adults: 40 years on. J Intern Med 2003;253:263-275.
6 Arnow PM and Flaherty JP. Fever of unknown origin. Lancet 1997;350:575-580.
7 Barbado FJ, Vazquez JJ, Pena JM, Arnalich F, Ortiz-Vazquez J. Pyrexia of unknown origin: changing spectrum of diseases in two consecutive series. Postgrad Med J 1992;68:884-887.
8 Kazanjian PH. Fever of unknown origin: review of 86 patients treated in community hospitals. Clin Infect Dis 1992;15: 968-973.
9 Knockaert DC, Vanneste LJ, Vanneste SB, Bobbaers HJ. Fever of unknown origin in the 1980s. An update of the diagnostic spectrum. Arch Intern Med 1992;152:51-55.
10 de Kleijn EM and van der Meer JW. Fever of unknown origin (FUO): report on 53 patients in a Dutch university hospital. Neth J Med 1995;47:54-60.
11 Tabak F, Mert A, Celik AD et al. Fever of unknown origin in Turkey. Infection 2003;31:417-420.
12 Vanderschueren S, Knockaert D, Adriaenssens T et al. From prolonged febrile illness to fever of unknown origin: the challenge continues. Arch Intern Med 2003;163:1033-1041.
13 Saltoglu N, Tasova Y, Midikli D et al. Fever of unknown origin in Turkey: evaluation of 87 cases during a nine-year-period of study. J Infect 2004;48:81-85.
14 Ergonul O, Willke A, Azap A, Tekeli E. Revised definition of 'fever of unknown origin': limitations and opportunities. J Infect 2005;50:1-5.
15 Gleckman R, Crowley M, Esposito A. Fever of unknown origin: a view from the community hospital. Am J Med Sci 1977;274:21-25.
16 de Kleijn EM and van der Meer JW. Inquiry into the diagnostic workup of patients with fever of unknown origin. Neth J Med 1997;50:69-74.
17 Bleeker-Rovers CP, de Kleijn EM, Corstens FH, van der Meer JW, Oyen WJ. Clinical value of FDG PET in patients with fever of unknown origin and patients suspected of focal infection or inflammation. Eur J Nucl Med Mol Imaging 2004;31:29-37.
18 de Kleijn EM, van Lier HJ, van der Meer JW. Fever of unknown origin (FUO). II. Diagnostic procedures in a prospective multicenter study of 167 patients. The Netherlands FUO Study Group. Medicine (Baltimore) 1997;76:401-414.
19 Meller J, Altenvoerde G, Munzel U et al. Fever of unknown origin: prospective comparison of [18F]FDG imaging with a double-head coincidence camera and gallium-67 citrate SPET. Eur J Nucl Med 2000;27:1617-1625.
20 Blockmans D, Knockaert D, Maes A et al. Clinical value of [(18)F]fluoro-deoxyglucose positron emission tomography for patients with fever of unknown origin. Clin Infect Dis 2001;32:191-196.
21 Lorenzen J, Buchert R, Bohuslavizki KH. Value of FDG PET in patients with fever of unknown origin. Nucl Med Commun 2001;22:779-783.
22 Kjaer A, Lebech AM, Eigtved A, Hojgaard L. Fever of unknown origin: prospective comparison of diagnostic value of 18F-FDG PET and 111In-granulocyte scintigraphy. Eur J Nucl Med Mol Imaging 2004;31:622-626.
23 Buysschaert I, Vanderschueren S, Blockmans D, Mortelmans L, Knockaert D. Contribution of (18)fluoro-deoxyglucose positron emission tomography to the work-up of patients with fever of unknown origin. Eur J Intern Med 2004;15: 151-156.

24 Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997;40:1725-
25 Hunder GG, Bloch DA, Michel BA et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum 1990;33:1122-1128.
26 Fautrel B, Zing E, Golmard JL et al. Proposal for a new set of classification criteria for adult-onset still disease. Medicine (Baltimore) 2002;81:194-200.
27 Moll JM and Wright V. Psoriatic arthritis. Semin Arthritis Rheum 1973;3:55-78.
28 Knockaert DC, Vanneste LJ, Bobbaers HJ. Recurrent or episodic fever of unknown origin. Review of 45 cases and survey of the literature. Medicine (Baltimore) 1993;72:184-196.
29 Knockaert DC, Dujardin KS, Bobbaers HJ. Long-term follow-up of patients with undiagnosed fever of unknown origin. Arch Intern Med 1996;156:618-620.
30 Holtz T, Moseley RH, Scheiman JM. Liver biopsy in fever of unknown origin. A reappraisal. J Clin Gastroenterol 1993;17:29-32.
31 Mitchell DP, Hanes TE, Hoyumpa AM, Jr., Schenker S. Fever of unknown origin. Assessment of the value of percutaneous liver biopsy. Arch Intern Med 1977;137:1001-1004.
32 Quinn MJ, Sheedy PF, Stephens DH, Hattery RR. Computed tomography of the abdomen in evaluation of patients with fever of unknown origin. Radiology 1980;136:407-411.
33 Knockaert DC, Vanneste LJ, Bobbaers HJ. Fever of unknown origin in elderly patients. J Am Geriatr Soc 1993;41:1187-1192.
34 Esposito AL and Gleckman RA. A diagnostic approach to the adult with fever of unknown origin. Arch Intern Med 1979;139:575-579.
35 Brusch JL and Weinstein L. Fever of unknown origin. Med Clin North Am 1988;72:1247-1261.
36 Wanvarie S, Tanphaichitra D, Limsuwan A. Fever of unknown origin: a review of 25 cases in Ramathibodi Hospital. J Med Assoc Thai 1981;64:155-158.

Chapter 10

General discussion

General discussion

In this thesis, the results of several retrospective and three prospective clinical studies in patients with fever of unknown origin (FUO) and patients with various infectious and inflammatory diseases are described. Although ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) has become an established imaging tool in oncology, it has only recently entered the field of infectious and non-infectious inflammatory diseases. Over the past years, a variety of other radiopharmaceuticals have been used for the scintigraphic visualization of infectious and inflammatory diseases and the number of these compounds is still increasing. General characteristics of an ideal infection-imaging agent should include efficient accumulation and good retention in inflammatory foci, rapid clearance from the background, easy low-hazard preparation and wide availability at low cost. Absence of accumulation in non-target organs, specifically in the blood pool and the bowel is also important. Early diagnostic imaging and a one-day protocol are generally preferred especially in case of severe and acute illnesses. Delivering high radiation doses or using radiolabeled compounds with possible side effects is in general unwanted and should be considered only when significant clinical benefit is to be expected.

Conventional radiopharmaceuticals routinely used in clinical practice (^{67}Ga and ^{111}In-labeled or ^{99m}Tc-labeled leukocytes (WBC)) have disadvantages and limitations, such as handling of potentially infected blood products (WBC), high radiation burden (^{67}Ga), instability of the labeling (^{99m}Tc-WBC), and the long time span between injection and diagnosis (^{67}Ga). FDG rapidly accumulates in infectious and inflammatory foci and it is cleared very rapidly from almost all other sites of the body, including the blood compartment. Variable physiologic FDG-uptake in the bowel is possible and can thus lead to false positive results, although this problem was not frequently encountered in our studies. Another advantage of FDG-PET is that completion of the protocol only takes 2 to 3 hours. Side effects of FDG have never been encountered thus far, nor have adverse effects been described in literature. One FDG-PET scan results in a very acceptable radiation exposure of approximately 5 mSv as compared to for example the radiation exposure of an abdominal CT scan (8-15 mSv), a ^{67}Ga-scan (16.5 mSv) or ^{111}In-leukocyte-scan (11 mSv). In many cases, differentiation between infection and non-infectious inflammation is preferred, which is not possible by using FDG-PET. However, this is not true for patients with FUO. In these patients scintigraphic imaging is most often used to evaluate the presence of focal abnormalities, which can subsequently be further evaluated by specific diagnostic procedures. The fact that FDG-PET detects infectious and inflammatory diseases as well as malignancy can even be considered as an advantage in FUO patients. Another obvious disadvantage of FDG-PET is the relatively high cost and the currently limited availability. However, when FDG-PET performance for infection and inflammation is confirmed in larger prospective studies and the number of PET systems further increases, the high diagnostic yield of FDG-PET may very well become a clinically significant and also cost-effective modality, since adequate early diagnosis limits the number of other non-contributing (invasive) tests required and the time to diagnosis and thereby the duration of hospitalization for diagnostic purposes.

From the case reports presented in chapter 2 and a review of previous clinical studies using FDG-PET in the diagnosis of infection and inflammation described in chapter 1, it was concluded that FDG-PET is a promising new imaging technique in patients with various infectious and inflammatory disorders warranting further studies. Our retrospective study of the value of FDG-PET in patients with various types of vasculitis in chapter 3 shows that FDG-PET is useful in diagnosing and determining the extent of various forms of vasculitis. In this study, it was concluded that FDG-PET might become a useful tool for evaluating the effect of treatment of vasculitis that cannot reliably be visualized by conventional techniques. Previous clinical studies focused only on diagnosis of giant cell arteritis and Takayasu arteritis, while we also found increased FDG-uptake in polyarteritis nodosa, Wegener's granulomatosis and Churge-Strauss syndrome. Thus FDG-PET is also possibly valuable in the latter patients. However, for a validation of FDG-PET in patients with suspected vasculitis and for determination of its value in the follow-up of response to treatment, prospective studies in a larger number of patients are needed.

In the pilot study of FDG-PET for visualization of lipodystrophy in HIV-infected patients described in chapter 4, markedly increased FDG-uptake in patients with lipodystrophy and absence of this phenomenon in patients without lipodystrophy provided support for one of the hypotheses of the cause of lipodystrophy: increased glucose-uptake as a result of metabolic stress of adipose tissue in response to highly active antiretroviral therapy. We have shown that FDG-PET is able to visualize lipodystrophy. As such, FDG-PET may become a tool to monitor lipodystrophy during the course of HIV-treatment. Moreover, in clinical trials, the lipodystrophy-inducing effect of newly developed antiretroviral regimens may be monitored objectively by this approach. However, widespread use of FDG-PET in HIV-infected patients suspected of lipodystrophy cannot be recommended in clinical practice before these results are confirmed by larger clinical trials.

In a retrospective study in a highly selected patient population, the results of FDG-PET in patients suspected of metastatic infection described in chapter 5 are very promising. Even though several conventional imaging techniques were used in most patients, a new infectious focus that changed treatment strategy was found in 45%. A larger prospective study in an unselected patient population has been initiated to investigate if the addition of FDG-PET to the diagnostic strategy in patients with Gram-positive bacteremia is superior to the standard diagnostic strategy not including FDG-PET by evaluating the effects on patient outcome and costs. Based on the results described in chapter 5, it is hypothesized that FDG-PET enables early diagnosis of metastatic complications, resulting in a reduction of the number of unnecessary days in hospital for diagnostic purposes and a reduced number of relapses, because fewer metastatic lesions are missed when compared to conventional diagnostic techniques, which is expected to result in a reduction of the number of days in hospital due to relapse.

From previous clinical studies and our retrospective study described in chapter 7, it can be concluded that FDG-PET is a valuable imaging technique in patients with FUO. However, for a final validation of FDG-PET in patients with FUO and for better determination of its position in the order of diagnostic tests, a prospective multicenter study of FDG-PET being part of a structured

diagnostic protocol was performed (chapters 8 and 9). The results from this prospective study confirmed that FDG-PET is a valuable imaging technique as part of a diagnostic protocol in the general patient population with FUO. Despite the low contribution of FDG-PET in periodic fever, it is advised that FDG-PET should also be added to the diagnostic protocol in these patients, because it has a very high negative predictive value and it can thus prevent further unnecessary diagnostic tests. Based on previous studies comparing ^{67}Ga and FDG-PET in patients with FUO and resulting from favorable characteristics of FDG-PET, conventional scintigraphic techniques may be replaced by FDG-PET in institutions where PET is available. In the future, integrated PET-CT scanners will become increasingly available, which is expected to improve the value of FDG-PET for these patients further due to better anatomical detail. The yield of a structured diagnostic protocol including FDG-PET was further studied in chapter 9. Based on these results, a recommendation is provided on such a diagnostic protocol for all patients with FUO.

The studies described in this thesis represent an overview of infectious and inflammatory diseases in which FDG-PET can be of diagnostic value. It should be noted that at present, the diagnostic value of FDG-PET is only sufficiently studied in patients with FUO to recommend its use as part of a structured diagnostic protocol in clinical practice. Although results were invariably promising, in most other cases results of larger prospective studies should be awaited before widespread clinical use can be recommended. Although the use of FDG-labeled leukocytes has shown promising results in small clinical studies, handling of potentially infected blood products and the laborious preparation remain important problems that need to be solved. At present, neither FDG nor any other radiolabeled compound perfectly meets all of the characteristics of an ideal infection-imaging agent. In clinical practice, the choice of the imaging agent should be based on careful evaluation of each individual case, local availability of the radiopharmaceutical and of a PET-facility until the results of larger clinical studies are available.

Summary

Summary

In management of patients with fever of unknown origin (FUO) or suspected infectious or inflammatory disease, timely identification and localization of infectious and inflammatory lesions is essential for optimal treatment. Often symptoms and signs guide the clinician towards the possible localization of the infection or the inflammatory focus, but in many cases further diagnostic imaging is necessary. Nuclear medicine offers powerful noninvasive techniques for visualization of infectious and inflammatory disorders using whole body imaging enabling the determination of both localization and number of inflammatory foci. Over the past decades, several radiopharmaceuticals have been developed for this purpose. Nowadays, radiopharmaceuticals such as ^{67}Ga-citrate, labeled leukocytes, labeled IgG and labeled antigranulocyte monoclonal antibodies are routinely used for evaluation of infectious and inflammatory disorders. Each of these techniques, however, has its limitations with regard to radiation exposure, biodistribution, preparation, or safety, so there is still need for a more suitable agent. Since activated inflammatory cells take up large amounts of glucose as a result of an increased metabolic rate, ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) represents a promising imaging technique in patients suspected of infectious or inflammatory disorders. Initial studies of FDG-PET in diagnosis of FUO, orthopedic infections and vasculitis have provided encouraging results. The aim of the studies presented in this thesis was to further investigate the clinical value of FDG-PET in diagnosis of FUO and several infectious and inflammatory diseases.

In **chapter 1**, the different approaches to scintigraphic imaging of infection and inflammation, already in use or under investigation, are reviewed. A wide variety of approaches depicting the different stages of the inflammatory response have been developed: non-specific radiolabeled compounds, such as ^{67}Ga-citrate and radiolabeled polyclonal human immunoglobulin, which accumulate in inflammatory foci due to enhanced vascular permeability and radiolabeled compounds with specific accumulation in inflammatory lesions resulting from binding to activated endothelium, the enhanced influx of leukocytes (e.g. radiolabeled autologous leukocytes or anti-granulocyte antibodies), the enhanced glucose-uptake by activated leukocytes (FDG) or direct binding to micro-organisms. Scintigraphy using autologous leukocytes, labeled with ^{111}In or ^{99m}Tc, is still considered the ”gold standard” nuclear medicine technique for the imaging of infection and inflammation, but a gradual shift from non-specific, cumbersome or even hazardous approaches to more sophisticated, specific approaches is ongoing. Recently, FDG-PET has been shown to delineate various infectious and inflammatory disorders with high sensitivity. Previous studies examining the value of FDG-PET in FUO, osteomyelitis and spondylodiscitis, prosthetic joint infection, vasculitis, inflammatory bowel disease, sarcoidosis, and rheumatoid arthritis are briefly reviewed.

In **chapter 2.1**, three patients are described in whom FDG-PET led to the diagnosis of polyarteritis nodosa, aortitis due to Wegener’s granulomatosis, and giant cell arteritis, respectively. These three cases illustrate the promising role of FDG-PET in imaging vascular inflammation. In addition, an overview of all previous studies investigating the use of FDG-PET in patients with vasculitis is provided.

In **chapter 2.2**, the results of seven FDG-PET scans in three patients with autosomal dominant polycystic kidney disease (ADPKD) suspected of renal or hepatic cyst infection are presented. FDG-PET identified the infected cysts in two episodes of renal cyst infection, two episodes of hepatic cyst infection and one episode of both renal and hepatic cyst infection. In one case, FDG-PET was normal after antibiotic treatment for hepatic cyst infection and again at a time when hepatic cyst infection was suspected, but eventually excluded. It is concluded that FDG-PET is a promising new imaging technique enabling early identification of renal and hepatic cyst infections in ADPKD patients.

In **chapter 2.3**, the history of a patient with FUO in whom extensive diagnostic tests including ^{111}In-leukocyte scintigraphy did not reveal the cause of the fever is reported. FDG-PET subsequently pointed to the diagnosis of septic thrombophlebitis of the portal vein (pylephlebitis). Also, a review of the literature on pylephlebitis is provided.

In **chapter 2.4**, three patients with catheter-associated candidemia are described. In these patients, FDG-PET led to the unexpected diagnosis of *Candida* lung abscesses, which was confirmed by computed tomography and favorable response to antifungal therapy. It is concluded that FDG-PET enables early identification of sites of disseminated candidiasis and that it can be used in the evaluation of therapy.

In **chapter 3**, the results of all FDG-PET-scans performed because of suspected vasculitis (n=20), because of follow-up of vasculitis (n=5) or because of fever of unknown origin with results indicating vasculitis (n=2) between January 1999 and April 2003 were reviewed. These results were compared to the final diagnosis, based on the "American College of Rheumatology 1990 criteria". FDG-PET results were considered to be true positive in 10 patients, true negative in 14 patients and false negative in three patients resulting in a positive predictive value of 100% and a negative predictive value of 82%. Therefore, FDG-PET is a promising new imaging technique in diagnosing and determining the extent of various forms of vasculitis, including giant cell arteritis, polyarteritis nodosa, Takayasu arteritis, Churge-Strauss syndrome, and Wegener's granulomatosis. Furthermore, FDG-PET may become a useful tool for evaluating the effect of treatment of vasculitis.

In **chapter 4**, the results of a pilot study investigating FDG-PET for visualization of lipodystrophy in HIV-infected patients are presented. Lipodystrophy is accompanied by increased adipose tissue inflammatory activity. Together with mitochondrial toxicity of nucleoside reverse transcriptase inhibitors, this induces metabolic stress causing increased glucose-uptake. Markedly increased subcutaneous FDG-uptake was observed in 3 out of 4 HIV-infected patients with lipodystrophy treated by a stavudine-containing treatment-regimen. This phenomenon was absent in HIV-infected controls without lipodystrophy. Our data show that FDG-PET is able to visualize lipodystrophy. In addition, this supports the hypothesis that stavudine-related lipodystrophy is associated with increased glucose-uptake as a result of metabolic stress of adipose tissue in response to antiretroviral therapy.

In **chapter 5**, the results of all FDG-PET-scans ordered because of suspected metastatic infection (n=40) between October 1998 and September 2004 were analyzed retrospectively. These results were compared to conventional investigation techniques and the final clinical diagnosis. Metastatic complications were eventually diagnosed in 75% of all episodes. Although a median number of four diagnostic procedures to search for metastatic infection had been performed before FDG-PET was ordered, FDG-PET diagnosed a clinically relevant new focus resulting in a change of therapy in 45% of cases. The positive predictive value of FDG-PET was 91% and the negative predictive value was 100%. These results suggested that 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.

In **chapter 6**, a review is provided describing the adjusted definition of FUO and possible causes of continuous and periodic FUO. A diagnostic algorithm is proposed in which the most important step is a history taking, physical examination and the obligatory investigations in a search for potentially diagnostic clues (PDCs). First, factitious fever and drug fever should be ruled out. Further diagnostic procedures should be guided by a list of most probable diagnoses. In patients without useful PDCs, certain diagnostic procedures, divided in first stage and second stage investigations should be performed. If no diagnosis is reached and the clinical condition is stable, waiting for new PDCs is recommended. In patients with recurrent fever, the diagnostic work-up should consist only of the search for PDCs matching known recurrent syndromes. If undiagnosed fever persists, supportive treatment with NSAIDs can be helpful. Most patients with undiagnosed FUO have benign self-limiting or recurrent fever. It is concluded that only if patients deteriorate, other therapeutic trials should be considered.

In **chapter 7**, all FDG-PET scans ordered because of FUO (n=35) or suspected focal infection or inflammation (n=55) between January 1999 and December 2002 were reviewed. These results were compared to the final diagnosis. Of 35 patients with FUO, a final diagnosis was established in 19 patients (54%). Of the total number of scans, 37% were clinically helpful. Positive predictive value of FDG-PET in these patients was 87% and negative predictive value was 95%. In the patients with suspected focal infection or inflammation, positive predictive value of FDG-PET was 95% and negative predictive value was 100%. It is concluded that FDG-PET appears to be a valuable imaging technique in evaluation of FUO and suspected focal infection or inflammation. Furthermore, FDG-PET could become a useful tool for evaluating the effect of treatment of infectious and inflammatory processes that cannot reliably be visualized by conventional techniques.

In none of the previous studies examining the role of FDG-PET in patients with FUO, a structured diagnostic protocol was used nor were patients from general hospitals included. In **chapter 8**, the results of a prospective multi-center study designed to validate the use of FDG-PET as part of a structured diagnostic protocol in the general population of patients with FUO are described. From December 2003 to July 2005, 70 patients with FUO were recruited from our university hospital (n=38) and five community hospitals (n=32) in the same region. The final clinical diagnosis was used for comparison with the FDG-PET results. Of all scans, 33% were clinically helpful. Positive predictive value of FDG-PET was 70% and negative predictive value was 92%. Contribution of FDG-

PET to the final diagnosis did not differ significantly between patients diagnosed in the university hospital and patients in the community hospitals. FDG-PET contributed significantly more often to the final diagnosis in patients with continuous fever than in patients with periodic fever. FDG-PET was not helpful in any of the patients with normal erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). It is concluded that FDG-PET is a valuable imaging technique as part of a diagnostic protocol in the general patient population with FUO and a raised ESR or CRP. Despite the low contribution of FDG-PET in periodic fever, FDG-PET should nevertheless be added to the diagnostic protocol in these patients, because it has a very high negative predictive value.

Results from the same FUO study described in chapter 8 regarding the final diagnoses and the number and sort of additional diagnostic tests are presented in **chapter 9**. Patients from our university hospital were characterized by more secondary referrals and a higher percentage of periodic fever than those referred to the community hospitals. Infection was the cause of the fever in 16%, a neoplasm in 7%, non-infectious inflammatory diseases in 22%, miscellaneous causes in 4%, and in 51%, the cause of fever was not found. There were no differences in the number and sort of final diagnoses or regarding the number and type of investigations between the university and community hospitals. Significant predictors for reaching a diagnosis included: continuous fever, fever present for <180 days, elevated ESR, CRP, or LDH, leucopenia, thrombocytosis, abnormal chest CT and abnormal FDG-PET. For future FUO studies, we recommend to abandon the requirement of hospital admission and to use a quality-related criterion of a set of obligated investigations. Except for tests from the obligatory part of our protocol and cryoglobulins in an early stage, followed by FDG-PET, and in a later stage by abdominal and chest CT, temporal artery biopsy in patients of 55 years or older and possibly bone marrow biopsy, other tests should not be used as screening investigations. Since significant differences between patients investigated in the university hospital and the community hospitals were absent, it is concluded that our structured diagnostic protocol is applicable to FUO in general.

Chapter 10 contains a general discussion of the results presented in this thesis and their possible future implications.

Samenvatting

Samenvatting

Bij patiënten met koorts zonder bekende oorzaak ofwel febris e causa ignota (febris e.c.i.) en bij patiënten met een mogelijke infectie of ontsteking is het van belang dat zo snel mogelijk de juiste diagnose wordt gesteld zodat op korte termijn begonnen kan worden met een gerichte behandeling. Vaak wordt de behandelend arts door klachten en lichamelijke verschijnselen gewezen in de richting van de aard en lokalisatie van de infectie of ontsteking. Toch is bij veel van deze patiënten aanvullend beeldvormend onderzoek nodig. Voor het lokaliseren van ontstekings- of infectiehaarden kan gebruik gemaakt worden van radiologische technieken, zoals röntgenfoto's, echografie, CT-scans of MRI, maar ook van scintigrafische technieken. Bij scintigrafisch onderzoek krijgt de patiënt een radiofarmacon toegediend. Dit is een middel dat radioactief gelabeld is, waardoor gammastraling wordt uitgezonden. Deze straling kan met behulp van een gammacamera zichtbaar gemaakt worden. Door nu een radiofarmacon te kiezen dat zich ophoopt in infectie- en ontstekingshaarden, kunnen deze haarden afgebeeld worden. In de laatste dertig jaar zijn verschillende van deze radiofarmaca ontwikkeld. Voor het opsporen van infecties en ontstekingen wordt tegenwoordig routinematig gebruik gemaakt van ^{67}gallium-citraat, radioactief gelabelde witte bloedcellen (leukocyten), radioactief gelabeld immuunglobuline (IgG) en radioactief gelabelde antistoffen tegen witte bloedcellen. Elk van deze stoffen heeft echter nadelen, zoals een hoge stralenbelasting, hoge opname van de stof in weefsels of organen zonder ontsteking, gecompliceerde bereiding of de noodzaak tot het werken met mogelijk besmet bloed. Er is daarom behoefte aan een radiofarmacon dat deze nadelen niet of in mindere mate heeft.

^{18}F-fluorodeoxyglucose (FDG) positron emissie tomografie (PET) is een nieuwe techniek die routinematig gebruikt wordt bij patiënten met kanker, maar die de laatste jaren ook een rol begint te spelen bij het afbeelden van infecties en ontstekingen. Het FDG is een suikermolecuul, dat gelabeld wordt met de positron-emitter ^{18}F. Positronemissie houdt in dat positief geladen deeltjes (positronen) worden uitgezonden. Een positron versmelt met het dichtstbijzijnde negatief geladen elektron, waarbij de deeltjes worden omgezet in twee gammastralen, die onder een hoek van 180° worden uitgezonden en kunnen worden gedetecteerd door een PET-camera. Door het gelijktijdig detecteren van twee fotonen is de resolutie van een PET-camera beter dan van een gammacamera. FDG hoopt zich fysiologisch op in hart, hersenen, nieren en blaas en in wisselende mate in de darm, maar ook in kwaadaardige cellen en in geactiveerde ontstekingscellen, zodat het gebruikt kan worden voor de afbeelding van tumoren en infectie- en ontstekingshaarden. De resultaten van eerdere studies naar de waarde van FDG-PET in de diagnostiek van febris e.c.i., orthopedische infecties en niet-infectieuze vaatontsteking (vasculitis) waren veelbelovend. Het doel van de studies in dit proefschrift was om de klinische waarde van FDG-PET bij patiënten met febris e.c.i. en verschillende infecties en ontstekingen verder te onderzoeken.

In **hoofdstuk 1** wordt een overzicht gegeven van de verschillende scintigrafische technieken, die in de praktijk gebruikt worden bij de detectie van infecties en ontstekingen en van technieken die op dit moment nog verder onderzocht worden. Een grote verscheidenheid aan radiofarmaca is ontwikkeld die verschillende stadia van het ontstekingsproces afbeelden. Verschillende niet-

specifieke radiofarmaca zijn in gebruik, zoals ^{67}gallium-citraat en radioactief gelabeld IgG, die zich ophopen in ontstekingshaarden vanwege de verhoogde doorlaatbaarheid van de vaatwand, die ontstaat ten gevolge van deze ontsteking. Andere radiofarmaca hopen zich specifiek op in ontstekingshaarden door binding aan geactiveerde cellen aan de binnenzijde van de bloedvatwand (endotheel), door verhoogde instroom van witte bloedcellen (bijv. radioactief gelabelde leukocyten of anti-granulocytenantistoffen), door toegenomen glucoseopname in geactiveerde witte bloedcellen (FDG) of door directe binding aan micro-organismen. De leukocytenscan, het gebruik van witte bloedcellen van de patiënt zelf, die buiten het lichaam gelabeld worden met ^{111}indium of ^{99m}technetium, wordt beschouwd als de gouden standaard voor wat betreft de scintigrafische afbeelding van infectie en ontsteking. Langzamerhand vindt er echter een verschuiving plaats van niet-specifieke, tijdrovende of zelfs risicovolle methoden naar meer verfijnde, specifieke methoden. In de afgelopen paar jaar is gebleken dat ook FDG-PET in staat is om infecties en ontstekingen af te beelden met een hoge sensitiviteit. Er wordt een kort overzicht gegeven over de resultaten van eerdere studies naar de waarde van FDG-PET bij febris e.c.i., infecties van het skelet, geïnfecteerde gewrichtsprotheses, vasculitis, ontstekingsziekten van de darm, sarcoidose en reumatoïde artritis.

Vasculitis is een ontsteking van de vaatwand, die kan leiden tot ernstige aantasting van allerlei organen. Er bestaan verschillende vormen van vasculitis en klachten zijn bij dit ziektebeeld vaak aspecifiek. Er zijn geen klinisch-chemische testen die specifiek zijn voor vasculitis. Ook is het afbeelden van vasculitis met echografie, CT en MRI vaak moeilijk, zodat een diagnose in veel gevallen pas laat gesteld kan worden. In **hoofdstuk 2.1** worden drie patiënten beschreven bij wie een FDG-PET-scan heeft geleid tot de diagnose van verschillende vormen van vasculitis, namelijk respectievelijk polyarteritis nodosa, de ziekte van Wegener en reuscelarteritis. Deze drie casus illustreren de veelbelovende rol van FDG-PET bij de afbeelding van vaatwandontsteking. Daarnaast wordt een overzicht gegeven van alle eerdere studies waarbij gekeken werd naar het gebruik van FDG-PET bij patiënten met vasculitis.

In **hoofdstuk 2.2** worden de resultaten beschreven van 7 FDG-PET scans bij 3 patiënten met de autosomaal dominante vorm van congenitale cystennieren. Dit is een aangeboren aandoening waarbij in de loop van het leven vele grote cysten in beide nieren en vaak ook in de lever ontstaan. Hierbij neemt de nierfunctie af en is er een grote kans op infectie van de cysten, waarbij het zeer moeilijk is om met conventionele technieken, zoals echografie of een CT-scan, een geïnfecteerde cyste te onderscheiden van een niet-geïnfecteerde cyste. Bij deze 3 patiënten die verdacht werden van een geïnfecteerde nier- of levercyste, identificeerde FDG-PET de geïnfecteerde cysten betrouwbaar in 2 episoden met geïnfecteerde niercysten, 2 episoden met geïnfecteerde levercysten en één episode met zowel een geïnfecteerde niercyste als een geïnfecteerde levercyste. In één geval normaliseerde de FDG-opname na antibiotische behandeling van een geïnfecteerde levercyste. Tevens was de FDG-PET-scan normaal op een moment dat gedacht werd aan een geïnfecteerde levercyste, maar de klachten later verklaard bleken te worden door een andere oorzaak. Er wordt geconcludeerd dat FDG-PET een veelbelovende nieuwe beeldvormende techniek is die een vroege en betrouwbare diagnose van geïnfecteerde nier- en/of levercysten bij patiënten met congenitale cystennieren mogelijk maakt.

In **hoofdstuk 2.3** wordt een patiënt met febris e.c.i. beschreven bij wie de oorzaak van de koorts niet bekend was ondanks zeer uitgebreide diagnostiek inclusief een leukocytenscan. Met behulp van FDG-PET werd vervolgens een infectie van de poortader van de lever, ook wel septische tromboflebitis van de vena portae ofwel pyleflebitis, gediagnosticeerd. Verder wordt een overzicht gegeven van de beschikbare literatuur over deze zeldzame en moeilijk te diagnosticeren aandoening.

In **hoofdstuk 2.4** worden drie patiënten beschreven met positieve bloedkweken voor de gist *Candida* gerelateerd aan een infectie van een centrale lijn voor parenterale voeding of medicatie. Het is bekend dat een bloedbaaninfectie met *Candida* (candidemie) evenals andere bloedbaaninfecties kan leiden tot infectiehaarden elders in het lichaam (strooihaarden). Bij deze drie patiënten leidde een FDG-PET-scan onverwacht tot het vinden van strooihaarden in de longen. Deze diagnose werd bevestigd door een CT-scan en de goede reactie op medicamenteuze therapie. Deze drie casus laten zien dat met FDG-PET een vroege diagnose van strooihaarden bij candidemie mogelijk is en dat deze techniek gebruikt kan worden bij het vervolgen van het effect van de behandeling.

In **hoofdstuk 3** worden de resultaten weergegeven van alle FDG-PET-scans die verricht werden in de periode van januari 1999 tot en met april 2003 vanwege de verdenking op vasculitis (n=20), het vervolg van een eerder gediagnosticeerde vasculitis (n=5) of vanwege febris e.c.i. met een uitslag passend bij vasculitis (n=2). Het resultaat van de FDG-PET-scan werd vergeleken met de uiteindelijke diagnose, die gebaseerd was op de criteria van het "American College of Rheumatology" uit 1990. Op grond van deze criteria worden verschillende vormen van vasculitis onderscheiden en ingedeeld. FDG-PET was goed-positief bij 10 patiënten, goed-negatief bij 14 patiënten en fout-negatief bij 3 patiënten. Met een positief voorspellende waarde van 100% en een negatief voorspellende waarde van 82% lijkt FDG-PET een veelbelovende nieuwe diagnostische techniek voor de diagnose en de bepaling van de uitgebreidheid van verschillende vormen van vasculitis, inclusief reuscelarteritis, polyarteritis nodosa, Takayasu arteritis, Churge-Strauss-syndroom en de ziekte van Wegener. Verder wijzen deze resultaten erop dat FDG-PET een bruikbare methode kan worden voor het vervolgen van het effect van behandeling van vasculitis.

In **hoofdstuk 4** wordt een prospectieve pilotstudie beschreven waarin de bruikbaarheid van FDG-PET bij het afbeelden van lipodystrofie bij patiënten met een HIV-infectie wordt onderzocht. Lipodystrofie is een bijwerking van de medicamenteuze HIV-therapie (antiretrovirale therapie) en wordt gekenmerkt door onder andere vetophoping in de buik(wand) en afname van de hoeveelheid vet in het gezicht en onderhuids in de ledematen in combinatie met veranderingen in de suiker- en vetstofwisseling. De oorzaak van dit syndroom is niet geheel duidelijk. Het gaat in elk geval gepaard met een verhoogde (ontstekings)activiteit van het vetweefsel. Samen met bijwerkingen op celniveau (mitochondriële toxiciteit) van bepaalde medicijnen die gebruikt worden bij de behandeling van HIV (nucleoside reverse transcriptase remmers) veroorzaakt dit metabole stress met als gevolg verhoogde opname van glucose. Stavudine is één van de bovengenoemde nucleoside reverse transcriptaseremmers. Duidelijk verhoogde onderhuidse FDG-opname werd gezien bij 3 van de 4 HIV-patiënten met lipodystrofie die behandeld werden met een stavudinebevattend

medicatieregime. Verhoogde FDG-opname was afwezig bij HIV-geïnfecteerde controlepatiënten zonder lipodystrofie. Aldus bleek het mogelijk te zijn om lipodystrofie af te beelden met behulp van FDG-PET. Daarnaast ondersteunen deze resultaten de hypothese dat stavudine-gerelateerde lipodystrofie is geassocieerd met verhoogde glucoseopname ten gevolge van metabole stress van vetweefsel in reactie op antiretrovirale therapie.

In **hoofdstuk 5** worden de resultaten beschreven van alle FDG-PET-scans (n=40) die verricht werden bij patiënten die verdacht werden van strooihaarden bij een bacteriële bloedbaaninfectie (bacteriëmie) of candidemie in de periode van oktober 1998 tot en met september 2004. De uitslag van de FDG-PET-scans werden vergeleken met die van veel routinematig gebruikte beeldvormende technieken en de uiteindelijke klinische diagnose. Uiteindelijk werd bij 75% van deze patiënten één of meerdere strooihaarden gediagnosticeerd. Hoewel er gemiddeld al 4 beeldvormende onderzoeken verricht waren voordat FDG-PET werd aangevraagd, werd met behulp van FDG-PET bij 45% een nieuwe klinisch relevante infectiehaard gediagnosticeerd hetgeen resulteerde in aanpassing van de behandeling. In deze groep patiënten met een hoog risico op strooihaarden was de positief voorspellende waarde van FDG-PET 91% en de negatief voorspellende waarde 100%. Deze resultaten suggereren dat FDG-PET een waardevolle beeldvormende techniek zou kunnen zijn bij patiënten met een hoog risico op strooihaarden zelfs als andere beeldvormende onderzoeken geen afwijkingen laten zien.

In **hoofdstuk 6** wordt een overzicht gegeven van de nieuwe aangepaste definitie van febris e.c.i. en van mogelijke oorzaken van continue koorts en periodieke koorts. Er wordt een diagnostisch algoritme voorgesteld waarin het zorgvuldig afnemen van de anamnese, het lichamelijk onderzoek en de verplichte onderzoeken in een zoektocht naar potentieel diagnostische “clues” (PDC’s) de belangrijkste stap zijn. PDC’s zijn alle symptomen en afwijkende uitslagen van onderzoeken die de behandelend arts op het spoor kunnen zetten van een bepaalde ziekte. Na het uitsluiten van zelfveroorzaakte koorts en geneesmiddelenkoorts moet verdere diagnostiek gebaseerd worden op een beperkte lijst met de meest waarschijnlijke diagnoses. Bij patiënten zonder bruikbare PDC’s, wordt geadviseerd bepaalde onderzoeken te verrichten onderverdeeld in een eerste en tweede stap. Als dan nog steeds geen diagnose gesteld kan worden en de klinische conditie van de patiënt stabiel is, lijkt het raadzaam om af te wachten en alert te zijn op het ontstaan van nieuwe PDC’s. In patiënten met periodieke of aanvalsgewijs optredende koorts wordt geadviseerd om alleen diagnostiek te doen naar aanleiding van PDC’s passend bij specifieke oorzaken van periodieke koorts. Ondersteunende behandeling met NSAID’s (bepaalde ontstekingsremmers, zoals diclofenac of naprosyne) kan geprobeerd worden bij patiënten bij wie geen diagnose gesteld wordt. Bij de meeste patiënten bij wie het aanbevolen aanvullend onderzoek in deze fase geen diagnose oplevert, is febris e.c.i. een goedaardig en vaak zelflimiterend ziektebeeld. Daarom worden andere therapeutische proefbehandelingen bijv. met antibiotica, corticosteroïden (bijv. prednison) of middelen tegen tuberculose alleen aangeraden bij patiënten met een snelle klinische verslechtering.

Hoofdstuk 7 beschrijft een retrospectieve studie naar de waarde van FDG-PET bij 35 patiënten met febris e.c.i. en 55 patiënten die verdacht werden van een focale infectie of een focaal ontstekingsproces. De resultaten van de FDG-PET-scans, verricht in de periode van januari 1999 tot en met december 2002, werden vergeleken met de uiteindelijke klinische diagnose. Bij 19 van de 35 patiënten met febris e.c.i. (54%) kon uiteindelijk een diagnose gesteld worden. Van alle FDG-PET-scans droeg 37% bij aan het stellen van de diagnose. Bij de patiënten met febris e.c.i. was de positief voorspellende waarde 87% en de negatief voorspellende waarde 95%. Bij de patiënten die verdacht werden van een focale infectie of ontstekingsproces was de positief voorspellende waarde 95% en de negatief voorspellende waarde 100%. Geconcludeerd wordt dan ook dat FDG-PET een waardevolle beeldvormende techniek lijkt te zijn bij patiënten met febris e.c.i. en bij deze patiëntenpopulatie met de verdenking op verschillende infecties en ontstekingen. Verder zou FDG-PET een waardevolle techniek kunnen worden bij het evalueren van het effect van behandeling van infectieuze en inflammatoire aandoeningen in die gevallen waarbij de afwijkingen niet goed afgebeeld kunnen worden met conventionele technieken.

In geen van de eerdere studies waarin de waarde van FDG-PET is onderzocht bij patiënten met febris e.c.i. is een gestructureerd diagnostisch protocol gebruikt. Ook werden in geen van deze studies patiënten uit algemene ziekenhuizen geïncludeerd. In **hoofdstuk 8** worden de resultaten beschreven van een prospectieve studie, die opgezet werd om het gebruik van FDG-PET als onderdeel van een gestructureerd diagnostisch protocol te valideren in de algemene populatie patiënten met febris e.c.i.. Tussen december 2003 en juli 2005 werden 70 patiënten met febris e.c.i. geïncludeerd. Van deze 70 patiënten waren er 38 afkomstig uit het UMC St Radboud en 32 uit 5 algemene ziekenhuizen in dezelfde regio. De resultaten van de FDG-PET-scans werden vergeleken met de uiteindelijke klinische diagnose. Van alle FDG-PET-scans droeg 33% bij aan de uiteindelijke diagnose. De positief voorspellende waarde van FDG-PET was 70% met een negatief voorspellende waarde van 92%. De bijdrage van FDG-PET aan de uiteindelijke diagnose verschilde niet significant tussen patiënten die gediagnosticeerd werden in het UMC St Radboud en patiënten die afkomstig waren uit de algemene ziekenhuizen. FDG-PET droeg significant vaker bij aan de uiteindelijke diagnose bij patiënten met continue koorts dan bij patiënten met periodieke koorts. Bij geen van de patiënten met zowel een normaal C-reactief proteïne als een normale bezinking (CRP en BSE, bepaalde ontstekingsparameters in het bloed) droeg FDG-PET bij aan de diagnose. Er wordt geconcludeerd dat FDG-PET, als onderdeel van een diagnostisch protocol, een waardevolle afbeeldingstechniek is bij alle patiënten met febris e.c.i. die een verhoogde BSE en/of een verhoogd CRP hebben. Ondanks de lage bijdrage van FDG-PET aan de uiteindelijke diagnose bij patiënten met periodieke koorts, zou FDG-PET bij deze moeilijk te diagnosticeren patiëntenpopulatie vanwege de zeer hoge negatief voorspellende waarde toch toegevoegd moeten worden aan het diagnostisch protocol.

In **hoofdstuk 9** worden de resultaten met betrekking tot de uiteindelijke klinische diagnose en het aantal en de soort aanvullende diagnostische onderzoeken, verkregen uit dezelfde febris e.c.i.-studie, die beschreven werd in hoofdstuk 8, gepresenteerd. De patiëntengroep die gediagnosticeerd werd in het UMC St Radboud werd gekenmerkt door meer verwijzingen vanwege

een “second opinion” en een hoger percentage patiënten met periodieke koorts in vergelijking met patiënten verwezen naar de algemene ziekenhuizen. De koorts werd veroorzaakt door een infectie bij 16% van alle patiënten, door kanker in 7%, een niet-infectieuze inflammatoire aandoening in 22%, overige verklaringen werden gevonden in 4% en bij 51% kon geen diagnose gesteld worden. Er was geen verschil in het aantal en de soort diagnostische onderzoeken tussen het UMC St Radboud en de algemene ziekenhuizen. Een uiteindelijke diagnose werd significant vaker gesteld bij patiënten met continue koorts, een duur van de koorts korter dan 180 dagen, verhoogde BSE, CRP of lactaatdehydrogenase (LDH, een bepaald enzym o.a. afkomstig uit de lever), een tekort aan witte bloedcellen (leukopenie), een overmaat aan bloedplaatjes (thrombocytose), een afwijkende CT-scan van de borstorganen (CT-thorax) en/of een abnormale FDG-PET-scan. Voor toekomstige febris e.c.i.-studies adviseren wij om de eis van een ziekenhuisopname te laten vallen en om een kwalitatief criterium bestaande uit een aantal verplichte onderzoeken te gebruiken in plaats van een tijdsgerelateerd criterium. Behalve de verplichte onderzoeken uit ons diagnostisch protocol, gevolgd door FDG-PET en in een latere fase door een CT-scan van thorax en abdomen, een biopt van de arteria temporalis bij patiënten ouder dan 55 jaar en mogelijk een beenmergbiopsie, moeten andere diagnostische testen niet gebruikt worden als screenende onderzoeken bij patiënten met febris e.c.i.. Omdat er geen significante verschillen waren tussen het UMC St Radboud en de algemene ziekenhuizen, concluderen wij dat het voorgestelde diagnostisch protocol van toepassing is op alle patiënten met febris e.c.i..

In **hoofdstuk 10** wordt aan de hand van de resultaten van dit proefschrift besproken wat de mogelijke rol van FDG-PET zou kunnen zijn bij de diagnostiek van patiënten met febris e.c.i. en infecties en ontstekingen. Tevens wordt het mogelijke vervolg van de onderzoeken in dit proefschrift toegelicht.

Dankwoord

Dankwoord

Mijn dank gaat uit naar iedereen die aan de totstandkoming van dit proefschrift heeft bijgedragen. Een aantal mensen wil ik in het bijzonder bedanken:

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Publications

Publications

De behandeling van hyperthyreoïdie bij kinderen.

C.P. Rovers, B.J. Otten

Tijdschrift voor Kindergeneeskunde 1995;63(6):233-236

LPS-induced cytokine production by mononuclear cells of patients with familial hypercholesterolemia.

N. De Bont, M.G. Netea, C. Rovers, T. Smilde, P.N. Demacker, J.W.M. van der Meer, A.F.H. Stalenhoef

Atherosclerosis 1998;139(1):147-152

LPS-induced cytokine production and expression of beta2-integrins and CD14 by peripheral blood mononuclear cells of patients with homozygous familial hypercholesterolemia.

C. Rovers, M.G. Netea, N. De Bont, P.N. Demacker, C. Jacobs, B.J. Kullberg, J.W.M. van der Meer, A.F.H. Stalenhoef

Atherosclerosis 1998;141(1):99-105

Hepatic steatosis and lactic acidosis caused by stavudine in a HIV-infected patient.

C.P. Bleeker-Rovers, S.W. Kadir, R. van Leusen, C. Richter

The Netherlands Journal of Medicine 2000;57(5):190-193

Tension pneumopericardium caused by positive pressure ventilation complicating anaerobic pneumonia.

C.P.Bleeker-Rovers, F.J.J. van den Elshout, T.I.F.M. Bloemen, H.A.H. Kaasjager

The Netherlands Journal of Medicine 2003;61(2):54-56

Diagnosis of renal and hepatic cyst infections by ^{18}F-fluorodeoxyglucose positron emission tomography in autosomal polycystic kidney disease.

C.P. Bleeker-Rovers, R.G.L. de Sévaux, H.W. van Hamersvelt, F.H.M. Corstens, W.J.G. Oyen

American Journal of Kidney Diseases 2003;41(6):E18-21

^{18}F-fluorodeoxyglucose positron emission tomography in diagnosis and follow-up of patients with different types of vasculitis.

C.P. Bleeker-Rovers, S.J.H. Bredie, J.W.M. van der Meer, F.H.M. Corstens, W.J.G. Oyen

The Netherlands Journal of Medicine 2003;61(10): 323-329

^{18}F-fluorodeoxyglucose positron emission tomography in diagnosis and follow-up of vasculitis: three cases and a review of the literature.

C.P. Bleeker-Rovers, S.J.H. Bredie, J.W.M. van der Meer, F.H.M. Corstens, W.J.G. Oyen

The American Journal of Medicine 2004;116(1):50-53

Clinical value of FDG-PET in patients with fever of unknown origin and patients suspected of focal infection or inflammation.

C.P. Bleeker-Rovers, E.M.H.A. de Kleijn, F.H.M. Corstens, J.W.M. van der Meer, W.J.G. Oyen

European Journal of Nuclear Medicine and Molecular Imaging 2004;31(1):29-37

^{18}F-fluorodeoxyglucose positron emission tomography leading to a diagnosis of septic thrombophlebitis of the portal vein: description of a case history and review of the literature.

C.P. Bleeker-Rovers, G. Jager, C.J. Tack, J.W.M. van der Meer, W.J.G. Oyen

The Journal of Internal Medicine 2004;255(3):419-423

Comment on: Kjaer A, Lebech AM, Eigtved A, Hojgaard L. Fever of unknown origin: prospective comparison of diagnostic value of ^{18}F-FDG PET and ^{111}In-granulocyte scintigraphy.

C.P. Bleeker-Rovers, F.H.M. Corstens, J.W.M. van der Meer, W.J.G. Oyen.

European Journal of Nuclear Medicine and Molecular Imaging 2004;31(9):1342-1343

Radiolabeled compounds in diagnosis of infectious and inflammatory disease.

C.P. Bleeker-Rovers, O.C. Boerman, H.J.J.M. Rennen, F.H.M. Corstens, W.J.G. Oyen

Current Pharmaceutical Design 2004;10(24):2935-2950

^{99m}Tc-labeled IL-8 for scintigraphic detection of pulmonary infections.

H.J.J.M. Rennen, C.P. Bleeker-Rovers, J.E.M. van Eerd, C. Frielink, W.J.G. Oyen, F.H.M. Corstens, O.C. Boerman

Chest 2004;126(6):1954-1961

FDG-PET for visualisation of lipodystrophy in HIV-infected patients.

C.P. Bleeker-Rovers, A.J. van der Ven, B. Zomer, L.-F. de Geus-Oei, P. Smits, P.P. Koopmans, F.H.M. Corstens, W.J.G. Oyen

AIDS 2004;18(18):2430-2432

Pyrexia of unknown origin.

C.P. Bleeker-Rovers, J.W.M. van der Meer

Medicine 2005;33(3):33-36

Diagnosis of *Candida* lung abscesses by ^{18}F-fluorodeoxyglucose positron emission tomography in three patients with catheter-related candidemia.

C.P. Bleeker-Rovers, A. Warris, J.P.H. Drenth, F.H.M. Corstens, W.J.G. Oyen, B.J.Kullberg

Clinical Microbiology and Infection 2005;11(6):493-495

An incidental finding on ^{18}F-fluorodeoxyglucose positron emission tomography in a patient with syphilis and HIV co-infection.

K. Kösters, C.P. Bleeker-Rovers, R. van Crevel, W.J.G. Oyen, A.J.A.M. van der Ven

Infection 2005;33(5-6):387-389

^{18}F-fluorodeoxyglucose positron emission tomography in detecting metastatic infectious disease.

C.P. Bleeker-Rovers, F.J. Vos, G.J.A. Wanten, J.W.M. van der Meer, F.H.M. Corstens, B.J. Kullberg, W.J.G. Oyen

The Journal of Nuclear Medicine 2005;46(12):2014-2019

LPS-induced release of IL-1beta, IL-1Ra, IL-6, and TNF-alpha in whole blood from patients with familial hypercholesterolemia: no effect of cholesterol-lowering treatment.

N. de Bont, M.G. Netea, C. Rovers, T. Smilde, A. Hijmans, P.N. Demacker, J.W.M. van der Meer, A.F.H. Stalenhoef

Journal of Interferon and Cytokine Research 2006;26(2):101-107

FDG-PET reduces unnecessary hemithyroidectomies for thyroid nodules with inconclusive cytology.

L.-F. de Geus-Oei, G.F.F.M. Pieters, J.J. Bonenkamp, A.H. Mudde, C.P. Bleeker-Rovers, F.H.M. Corstens, W.J.G. Oyen

The Journal of Nuclear Medicine 2006;47(5):770-775

FDG-PET for imaging of non-osseous infection and inflammation.

F.J. Vos, C.P. Bleeker-Rovers, F.H.M. Corstens, B.J. Kullberg, W.J.G. Oyen

The Quarterly Journal of Nuclear Medicine and Molecular Imaging 2006;50(2):121-130

Detection of pacemaker and lead infection with FDG-PET.

F.J. Vos, C.P. Bleeker-Rovers, A.P.J. van Dijk ,W.J.G. Oyen

European Journal Of Nuclear Medicine and Molecular Imaging, 2006;33(10):1245

Complicated infection caused by *Staphylococcus aureus* or *Streptococcus* species bacteraemia.

M.L.H. Cuijpers, F.J. Vos, C.P. Bleeker-Rovers, P.F.M. Krabbe, P. Pickkers, A.P.J. van Dijk, G.J.A. Wanten, P.D. Sturm, W.J.G. Oyen, B.J. Kullberg

European Journal of Clinical Microbiology and Infectious Diseases, in press

^{99m}Tc-labeled interleukin-8 for the scintigraphic detection of infection and inflammation: first clinical evaluation.

C.P. Bleeker-Rovers, H.J.J.M. Rennen, O.C. Boerman, A.B. Wymenga, E.P. Visser, J.H. Bakker, J.W.M. van der Meer, F.H.M. Corstens, W.J.G. Oyen

The Journal of Nuclear Medicine, in press

A prospective multi-center study on fever of unknown origin: the yield of a structured diagnostic protocol.

C.P. Bleeker-Rovers, F.J. Vos, E.M.H.A. de Kleijn, A.H. Mudde, A.S.M. Dofferhoff, C. Richter, T.J. Smilde, P.F.M. Krabbe, W.J.G. Oyen, J.W.M. van der Meer

Medicine (Baltimore), in press

A prospective multi-center study of the value of FDG-PET as part of a structured diagnostic protocol in patients with fever of unknown origin.

C.P. Bleeker-Rovers, F.J. Vos, A.H. Mudde, A.S.M. Dofferhoff, L.-F. de Geus-Oei, A.J. Rijnders, P.F.M. Krabbe, F.H.M. Corstens, J.W.M. van der Meer, W.J.G. Oyen

European Journal of Nuclear Medicine and Molecular Imaging, in press

List of abbreviations

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ACR criteria	American College of Rheumatology 1990 criteria
ACUP	adenocarcinoma with unknown primary
ADPKD	autosomal dominant polycystic kidney disease
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ANCA	antineutrophil cytoplasmic antibody
AST	aspartate aminotransferase
CAPD	continuous ambulatory peritoneal dialysis
CI	confidence interval
CNS	central nervous system
CRP	C-reactive protein
CT	computerized tomography
CVC	central venous catheter
CWH	Canisius Wilhelmina Hospital, Nijmegen, The Netherlands
ERCP	endoscopic retrograde cholangio-pancreaticography
ESR	erythrocyte sedimentation rate
Fab'/F(ab')$_2$	antibody fragments
FAPA syndrome	fever, aphthous stomatitis, pharyngitis, adenitis syndrome
FDG	^{18}F-fluorodeoxyglucose
f-Met-Leu-Phe	formyl-methionyl-leucyl-phenylalanyl
FUO	fever of unknown origin
GH	general hospital
GGT	gamma glutamyltransferase
HAART	highly active antiretroviral therapy
HAMA	human antimouse antibodies
HIG	human polyclonal immunoglobulin
HIV	human immunodeficiency virus
HMPAO	hexamethylpropylene amine oxime
HNP	human neutrophil peptide
HYNIC	hydrazinonicotinamide
ICAM-1	intercellular adhesion molecule-1
ICU	intensive care unit
IgA/IgD/IgG	immunoglobulin A/D/G
IL	interleukin
IL-1ra	interleukin-1 receptor antagonist
JBH	Jeroen Bosch Hospital, 's-Hertogenbosch, The Netherlands
LDH	lactate dehydrogenase
LTB_4	leukotriene B_4
Mab	monoclonal antibody
MCP-1	monocyte chemoattractant protein 1
MIC	minimal inhibitory concentration
MMC	Maxima Medical Center, Veldhoven, The Netherlands
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
NC	not calculated
NCA	non-specific cross-reacting antigen
NHL	non-Hodgkin lymphoma
NIID	non-infectious inflammatory diseases
NL	The Netherlands
NPV	negative predictive value
NRTI	nucleoside reverse transcriptase inhibitor
NSAID	non-steroidal anti-inflammatory drug
OSEM	ordered subsets-expectation maximization
PDCs	potentially diagnostic clues
PEG	polyethylene glycol
PET	positron emission tomography
PF-4	platelet factor 4
PMNs	polymorphonuclear cells
PPV	positive predictive value
RH	Rijnstate Hospital, Arnhem, The Netherlands
RR	relative risk
RUNMC	Radboud University Nijmegen Medical Center
SH	Slingeland Hospital, Doetinchem, The Netherlands
SLE	systemic lupus erythematosis
SSEA-1	stage specific embryonic antigen-1
TPN	total parenteral nutrition
TRAPS	tumor necrosis factor receptor-associated periodic syndrome
UBI	human antimicrobial peptide ubiquicidin
UH	university hospital
US	United States
WBC	white blood cells

Curriculum vitae

Curriculum vitae

Chantal Bleeker-Rovers werd op 26 november 1971 geboren te Veghel. In 1990 behaalde zij het gymnasiumdiploma aan het Zwijsencollege te Veghel (cum laude). Vanaf 1990 studeerde zij geneeskunde aan de Radboud Universiteit Nijmegen, alwaar zij in 1994 het doctoraalexamen behaalde gevolgd door het artsexamen in maart 1997 (beide cum laude). Tijdens haar co-schappen volgde zij gedurende een half jaar een facultatieve stage op de afdeling interne geneeskunde van het UMC St Radboud waar zij onderzoek verrichtte naar de cytokinenproduktie bij familiaire hypercholesterolemie. Na kortdurend AGNIO geweest te zijn op de afdeling interne geneeskunde van het Canisius Wilhelmina Ziekenhuis te Nijmegen, startte zij in augustus 1997 met de opleiding tot internist op de afdeling interne geneeskunde van het Rijnstate Ziekenhuis in Arnhem bij opleider dr. L. Verschoor. Vanaf september 2000 werd de opleiding voortgezet in het UMC St Radboud te Nijmegen bij opleider prof. dr. J.W.M. van der Meer. In het laatste jaar van de opleiding tot internist werd gestart met het in dit proefschrift beschreven onderzoek op de afdeling nucleaire geneeskunde van het UMC St Radboud bij prof. dr. W.J.G. Oyen en prof. dr. F.H.M. Corstens in samenwerking met de afdeling interne geneeskunde. Na haar registratie als internist op 1 augustus 2003 zette zij haar onderzoekswerkzaamheden op deze afdeling voort. Vanaf 1 september 2005 is zij in opleiding voor het aandachtsgebied infectieziekten in het UMC St Radboud bij opleider prof. dr. B.J. Kullberg. Zij is getrouwd met Michiel Bleeker met wie zij twee kinderen heeft, Alex (2001) en Eva (2004).