

# 23

## Fever of Unknown Origin

Hongming Zhuang and Ghassan El-Haddad

### Definition and Classification

#### General Criteria

The original criteria for fever of unknown origin (FUO) as set forth in 1961 by Petersdorf and Beeson were fever higher than 38.3°C on several occasions of at least 3 weeks' duration and uncertain diagnosis after 1 week of study in the hospital (1). This definition was later revised, and the criterion of 1 week of hospitalization has been replaced by 3 days of hospitalization or three outpatient visits (2,3). In addition to the previously described classic FUO, additional categories have been added: nosocomial, neutropenic, and HIV-associated FUO (3,4).

Nosocomial FUO refers to the hospitalized patient with a temperature of  $\geq 38.3^{\circ}\text{C}$  ( $\geq 101^{\circ}\text{F}$ ) on several occasions, who is receiving acute care, and in whom infection was not manifest or incubating on admission. The diagnosis of nosocomial FUO is made after 3 days of illness under investigation, including at least 2 days' incubation of cultures. Examples of diseases causing nosocomial FUO are septic thrombophlebitis, sinusitis, *Clostridium difficile* colitis, and drug fever.

Neutropenic FUO includes patients with fever of  $\geq 38.3^{\circ}\text{C}$  ( $\geq 101^{\circ}\text{F}$ ) on several occasions, a neutrophil count either  $< 500$  cells/ $\mu\text{L}$  or expected to reach that level in 1 to 2 days, in whom initial cultures are negative and the diagnosis remains unknown after 3 days of investigation. Frequent causes of neutropenic FUO are perianal infection, aspergillosis, and candidemia.

The HIV-associated FUO refers to HIV-positive patients with fever of  $\geq 38.3^{\circ}\text{C}$  ( $\geq 101^{\circ}\text{F}$ ) on several occasions for 4 weeks as an outpatient or 3 days of illness as an inpatient under investigation, including at least 2 days for cultures to incubate. *Mycobacterium avium intracellulare* (MAI) infection, tuberculosis, non-Hodgkin's lymphoma, and drug fever are common causes of HIV-associated FUO.

#### Pediatric FUO

Fever is a common presenting problem in children. Approximately 30% of pediatric outpatient visits in the United States are because of

fever, which is brief and self-limited in the majority of cases (5). Fever of unknown origin in children is a great diagnostic challenge for pediatricians. Due to the paucity of data in children, the definition of FUO is slightly different from adults, and there is no one agreed-upon definition. Several studies defined fever in children as FUO when it lasted 1 to 3 weeks without diagnosis (6–10). The definition of FUO in children that is currently used by most authorities is fever of at least 8 days' duration, in which no diagnosis is apparent after initial workup either in the hospital or as an outpatient. Fever of unknown origin has to be differentiated from fever without localizing signs, which does not meet the criteria for FUO, and where the development of additional clinical manifestations over a shorter period of time leads to less extensive diagnostic testing before confirming the nature of the disease.

## Epidemiology and Etiology

Several studies on FUO carried out since 1961 found that infections, malignancies, and noninfectious inflammatory diseases cause the majority of classic FUO (1,11–13). In the current series on adults with FUO, infections were the most frequent causes of FUO, followed by malignancies, and then noninfectious inflammatory diseases (13,14). However, in children, infection is a more common cause of FUO than in adults, accounting for 30% to 50% of the cases, followed by connective tissue diseases (CTDs) and then neoplasm (7% to 13%) (8,9). Most cases of FUO in children as well as in adults represent unusual manifestations of common diseases, rather than a common manifestation of a rare disease. The common etiologies that should be considered in children with FUO are presented in Table 23.1.

The most common systemic infections in the United States that are implicated in children with FUO are salmonellosis, tuberculosis, rickettsial infections, spirochetal infections, cat-scratch disease, infectious mononucleosis, cytomegalovirus (CMV) infection, and viral hepatitis.

Autoimmune diseases occur with equal frequency in adults and children (10% to 20% of cases), but certain diseases such as systemic lupus erythematosus (SLE), Wegener's granulomatosis, and polyarteritis nodosa are more common in adults, whereas juvenile rheumatoid arthritis (JRA, now called juvenile idiopathic arthritis, JIA) is particularly common in children (8,15,16). Juvenile rheumatoid arthritis accounts for >90% of connective tissue diseases that cause FUO, followed by SLE and other types of vasculitis (6,8,9,17). Some autoimmune diseases that occur exclusively in adults are adult Still's disease, giant cell arteritis, and polymyalgia rheumatica. Temporal arteritis, polymyalgia rheumatica, sarcoidosis, rheumatoid arthritis, and Wegener's granulomatosis account for 25% to 30% of all FUOs in patients over 65 years of age (15).

Lymphoma and leukemia are the two most common malignancies presenting as FUO in children. The frequency of neoplasms decreased

Table 23.1. Etiologies to be considered in children with fever of unknown origin (FUO)

Infections	Noninfectious inflammatory diseases	Miscellaneous causes
Generalized	JRA	Central nervous system dysfunction
Hepatitis viruses	SLE	Diabetes Insipidus
Cytomegalovirus	Crohn's disease	Drug fever
HIV	Ulcerative colitis	Familial dysautonomia
EBV	Sarcoidosis	(Riley-Day syndrome)
Cat-scratch disease	Kawasaki's disease	Factitious fever
Tuberculosis (TB)		Thyroiditis
Brucellosis	Neoplasms	Periodic fevers (e.g. familial Mediterranean fever)
Leptospirosis		Infantile cortical hyperostosis
Malaria	Non-Hodgkin's lymphoma	Pancreatitis
Salmomellosis	Hodgkin's disease	Hypothalamic-central fever
Toxoplasmosis	Leukemia	Thrombophlebitis
Tularemia	Renal cell carcinoma	Pulmonary embolism
Localized	Hepatoma,	Serum sickness
Arthritis	Neuroblastoma	Factitious fever-
Osteomyelitis	Wilms' tumor	Ectodermal dysplasia
Intraabdominal abscesses		
Upper respiratory tract infections (URI)		
Urinary tract infection (UTI)		

in two series (12,18), which was attributed to improved diagnostic imaging techniques.

Despite extensive investigations, 10% to 20% of FUO cases in children remain undiagnosed.

## Diagnosis

Despite the fact that most children with FUO have a self-limited disease, it is still a very serious clinical problem, with mortality reaching 6% to 9% in two series of children with FUO (8,9). The diagnostic approach in children with FUO starts with a thorough history and physical examination, supplemented by laboratory and radiographic tests. Repeated histories and physical examination are important to better elucidate the etiology of FUO. The age of the patient, history of exposure to wild or domestic animals, history of unusual dietary habits or travel, medication history, and ethnic background are very helpful in evaluating FUO. After the screening laboratory and radiographic tests, additional tests should be guided by the history and physical examination.

## Radiographic Evaluation of Children with FUO

After obtaining a regular chest radiograph, further radiographic examination of specific areas such as the nasal sinuses, mastoids, and gastrointestinal (GI) tract should be performed following special indications. Inflammatory bowel disease should be excluded in children with abdominal complaints, persistent fever, elevated erythrocyte sedimentation rate (ESR), anorexia, and weight loss. Finding a cost-effective diagnostic imaging procedure is challenging for the clinicians.

Echocardiograms are useful to evaluate the heart when suspecting infective endocarditis (19). Ultrasonography (US) is often used to investigate fluid collections, abscesses (20,21), and thrombophlebitis (22). Computed tomography (CT) or magnetic resonance imaging (MRI) is helpful in the detection of neoplasms and abscesses in the abdomen and in the investigation of lesions in the head, neck, and chest (23–28), as well as for osteomyelitis (29). Magnetic resonance imaging is rarely used in the initial evaluation of FUO except in certain cases such as spinal epidural abscesses (30). Laparotomy has been nearly replaced by noninvasive imaging techniques, especially in the search for occult abscesses or hematomas in patients with FUO. However, laparotomy is very helpful when noninvasive imaging measures are nondiagnostic and CT- or ultrasound-guided aspiration or biopsy fails to make the diagnosis (31).

## Radionuclide Scans

Gallium-67- and indium-111-labeled leukocytes have a higher overall yield than CT or US in diagnosing FUO because the images cover the whole body (32,33). In patients with FUO, gallium 67 is useful for the detection of malignancies and of granulomatous and inflammatory disorders (34), whereas indium-111-labeled leukocytes are more useful for detecting localized infectious and inflammatory processes (35). Different technetium-99m ( $^{99m}\text{Tc}$ )-labeled compounds are being studied for potential clinical use in patients with FUO, such as  $^{99m}\text{Tc}$ -hexamethylpropylene-amine-oxime (HMPAO)-labeled leukocytes (36),  $^{99m}\text{Tc}$ -ciprofloxacin (37), and  $^{99m}\text{Tc}$ -labeled monoclonal antibodies (38,39).

## FDG-PET Scan

### *Mechanisms of FDG Uptake by the Cells*

Currently, 18-fluoro-2-deoxyglucose (FDG) is the most clinically used radiotracer in positron emission tomography (PET). It competes with glucose for transport into the cell and for enzymatic phosphorylation by hexokinase, which enables us to image glucose metabolism in the body. Once FDG enters the cell, it is phosphorylated by hexokinase and trapped inside, which leads to an increase in its concentration with time (40). The uptake of FDG by the malignant cells is directly proportional to glucose metabolism (41). There is enhanced glycolysis in malignant

cells, which is related to high intracellular enzyme levels of hexokinase (42) and increased expression of surface glucose transporter proteins (GLUT) (43).

Infectious, inflammatory, and granulomatous diseases have increased glycolysis, which makes them readily visualized by FDG-PET scanning (44). Glycolysis is enhanced in inflammatory cells when the latter are stimulated, and this includes neutrophils, monocytemacrophages, and lymphocytes (45–48). This has been mainly attributed to a high concentration of GLUT and a high affinity of these transporters for FDG. Especially, many investigations have demonstrated that there are increased levels of GLUT on the inflammatory cells when they are activated by inflammatory signals (46,47,49). Intratumoral inflammatory reactions also have a high rate of glycolysis (50,51).

### *Rationale for the Use of FDG-PET in FUO*

The fact that FDG is not a tumor-specific substance can be exploited in a positive matter in the setting of FUO because infections, inflammations, and malignancies account for the great majority of FUO cases.

Fluorodeoxyglucose-PET has proven to be a very accurate modality for the detection of a large number of malignancies (52). Conventional anatomic imaging modalities rely on size as a criterion to distinguish between malignant and benign diseases; FDG-PET reflects the biochemical alterations within tumors, facilitating a functional assessment of malignancies. This has proven to provide a very accurate assessment of solitary pulmonary nodules, lymphoma, non-small cell lung cancer, colorectal cancer, malignant melanoma, head and neck cancers, and breast cancers (52). The success of PET is not limited to the staging of malignancies but goes beyond that to the accurate assessment of restaging and evaluation of response to therapy. This has been particularly proven in lymphoma in the adult (53,54) and pediatric (55) populations, and it has a direct impact on the management of patients with FUO because lymphoma accounts for the majority of cancers causing FUO. Fluorodeoxyglucose-PET is able to differentiate necrotic tissue from viable tumor and has proven its superiority to other imaging techniques in the initial staging of lymphoma, in monitoring response to therapy, and in detecting residual tumor (53,54).

Many metabolically active infectious and inflammatory disorders can be readily visualized by FDG-PET scanning (56,57) (Table 23.2). Fluorodeoxyglucose-PET has a high accuracy in detecting chronic osteomyelitis (58), especially in the central skeleton, which was found to be superior to antigranulocyte antibody scintigraphy (59,60) and to indium-111-labeled leukocytes (61). Although CT and MRI provide excellent anatomic details, they have limited capacity to differentiate postsurgical changes from infection, and, in contrast to FDG-PET, they are hindered by metal implants (62,63). Fluorodeoxyglucose-PET can differentiate between normal bone

**Table 23.2. Common causes of FUO reportedly detected by FDG-PET**

<b>Infections</b>	<b>Inflammatory/granulomatous</b>	<b>Neoplasms</b>
Subphrenic abscess	Takayasu's arteritis	Hodgkin's disease
Pneumonia	Rheumatoid arthritis	Non-Hodgkin's lymphoma
Osteomyelitis	Wegener's granulomatosis	Colon carcinoma
Vascular graft infection	Sarcoidosis	Renal cell carcinoma
Tuberculosis	Thyroiditis	Sarcoma
Sinusitis	Enterocolitis	Pheochromocytoma
Mastoiditis	Myositis	
	Gastritis	
	Giant cell arteritis	

healing following a fracture or surgical intervention and osteomyelitis or malignancy (64,65). In patients with prostheses, FDG-PET can assess the presence of a superimposed infection, especially in hip prostheses and, to a lesser extent, in knee prostheses (66). Fluorodeoxyglucose-PET can be used to diagnose infections related to diabetes, especially in the evaluation of the diabetic foot (67). Human immunodeficiency virus (HIV)-positive patients constitute a special group of patients because they are prone to opportunistic infections and malignancies, especially lymphoma. In a report on HIV-positive patients with FUO, FDG-PET had a sensitivity of 92% and a specificity of 94% for localizing a focal pathology that needed treatment (68). Fluorodeoxyglucose-PET was able to differentiate lymphoma from nonmalignant lesions in the central nervous system in HIV-positive patients (69). Although FDG-PET cannot clearly distinguish between granulomatous diseases such as sarcoidosis and lymphoma, it can localize the active lesions (70,71), which can be biopsied for a timely and minimally invasive diagnosis. The early diagnosis of vasculitis, especially large-vessel vasculitis, prevents progression to the occlusive phase of the disease. In this regard, FDG-PET has demonstrated high specificity and high sensitivity to detect and assess the activity of large-vessel vasculitis (72,73). It can noninvasively detect and quantitatively assess the disease activity in inflammatory bowel disease (74,75). Fluorodeoxyglucose uptake in the synovium measured using the standard uptake values (SUVs) facilitates the quantitative assessment of synovial activity (76), which has been particularly helpful in assessing the disease activity in patients with rheumatoid arthritis (77). The increase in SUV and the number of PET-positive joints correlated with swelling and tenderness of the joints, ultrasonography, synovial thickness, and inflammatory serum markers (ESR and C-reactive protein). This facilitates the measurement of disease activity in the joints of patients with rheumatologic diseases. Other infectious or inflammatory process that can be visualized with FDG-PET are thrombophlebitis (78,79), infected implantable devices (80), and pleural diseases (81).

*Advantages of FDG-PET over Other Nuclear Medicine Techniques*

Currently, gallium-67 scanning is the most commonly used radiotracer for the evaluation of FUO (32). However, FDG-PET has many advantages over conventional nuclear medicine techniques. Fluorodeoxyglucose offers a better tracer kinetic, a favorable 110-minute half-life, better spatial resolution ( $\pm 5$  to 8 mm resolution for PET vs. 10 to 15 mm for single photon emission computed tomography, SPECT), better lesion-to-background ratio (82), low dose to the patient, and the possibility for quantification decreasing the variability between readers. To date there have been no reported side effects from the injection of FDG. Whole-body FDG-PET scanning is completed approximately 2 hours from the injection, which results in earlier reporting than with other radiotracers (83). An important safety factor is that, in contrast to labeled leukocytes, in FDG-PET there is no handling of blood products. Fluorodeoxyglucose-PET is more sensitive in chronic, low-grade infections, has high accuracy in the central skeleton, and a high interobserver agreement (59,84,85). Another major advantage of FDG-PET over gallium in the evaluation of FUO patients is the ability to visualize and assess the degree of activity in a variety of inflammatory vessel diseases (83). It has been reported that FDG-PET can clearly visualize sarcoid lesions in the lungs and brain when concurrent gallium scans are negative (86).

*Advantages of FDG-PET Over Anatomic Imaging*

Timely identification and localization of the source of FUO is critical for the management of patients. Therefore, FDG-PET scanning is very helpful in this regard because it can detect early changes at the molecular level before they become apparent on anatomic imaging. Fluorodeoxyglucose-PET images the whole body in one study. Post-therapy tissue changes such as scarring, edema, and necrosis may alter the identification of recurrent tumor with anatomic imaging. Regardless of anatomic changes after chemotherapy and radiation therapy, FDG-PET can detect residual disease and has a high negative predictive value for viable disease in a residual anatomic abnormality, reaching 97% in some cases (87). Therefore, equivocal radiographic findings can be accurately characterized with FDG-PET. There is also increasing concern about the risk of radiation (88), radiocontrast-induced nephropathy (89), and allergic reactions (90) to patients imaged with CT. Furthermore, FDG-PET is able to detect early inflammatory and infectious lesions when anatomic imaging modalities reveal no abnormalities (91).

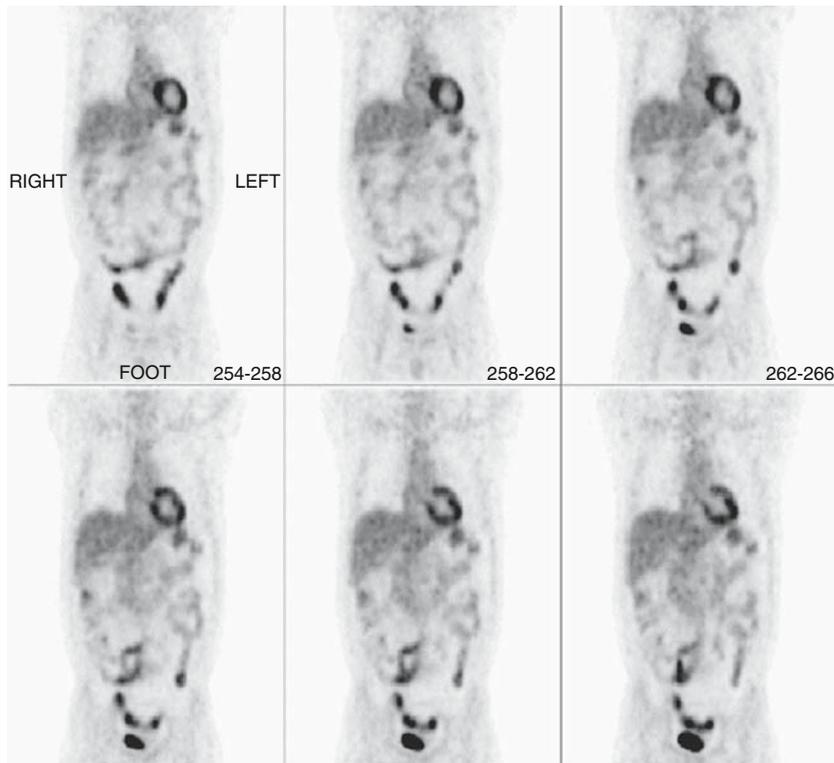
*FDG-PET and Biopsy*

As opposed to the other noninvasive diagnostic approaches in FUO, biopsy is a directed invasive intervention, which is often required to make a diagnosis. The most common biopsies performed in an FUO scenario are bone marrow, liver, lymph node, temporal artery, pleura, and pericardium. However, biopsy has spatial limitations, and a negative biopsy result may well be a false-negative finding due to sampling

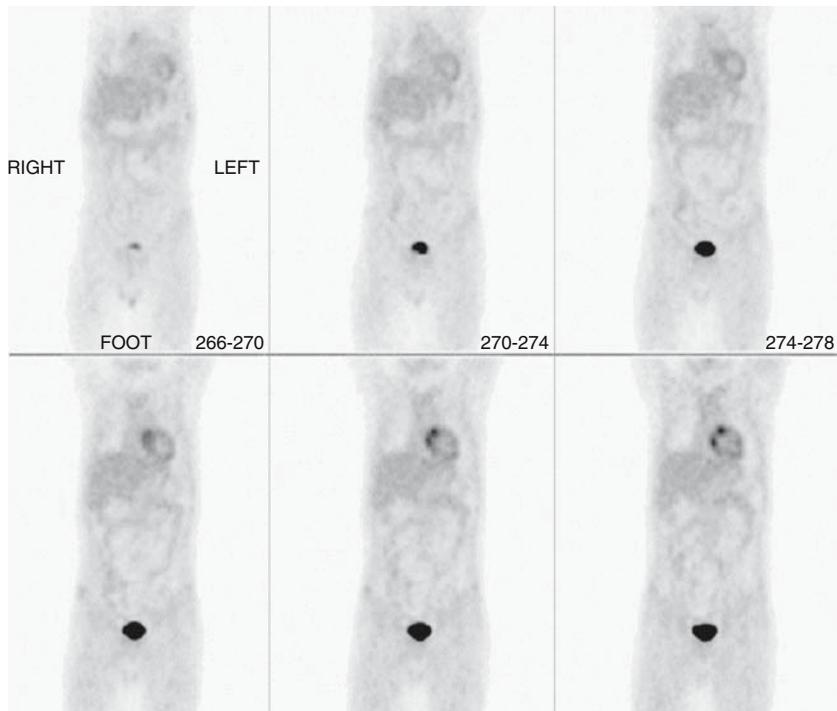
errors. The combination of anatomic imaging and FDG-PET either through a software fusion or a combined PET-CT scanner leads to better localization of functional abnormalities. The registration of anatomic and functional images can be used to guide biopsies to the metabolically active area (92), which can increase the yield of this approach and decrease the need for unnecessary procedures.

### *Considerations for Accurate Reading of FDG-PET*

When searching for the source of F.U.O., certain areas of the body can sometimes be difficult to evaluate because of normally high FDG uptake. The kidneys excrete FDG; therefore, there is intense FDG activity in the renal collecting systems, ureters, and bladder. There is also high FDG uptake in the brain and myocardium. Fluorodeoxyglucose activity in the bowel can be variably intense in the adult population (Fig. 23.1), which can decrease the accuracy of FDG-PET in the evaluation of the abdomen. However, FDG-PET can play a major role in the pediatric population because there is usually low FDG activity in the bowel (Fig. 23.2) (57). There is also physiologic activity in the thymus of children and young adults, which usually looks like an inverted V



**Figure 23.1.** Normally increased FDG uptake is noted in the bowel of a 45-year-old patient with a history of tonsillar cancer.



**Figure 23.2.** Normal FDG-PET scan of an 11-year-old boy with a history of Hodgkin's disease. There is a faint activity in the bowel.

(Fig. 23.3) (93). Therefore, accurate interpretation of FDG-PET images requires optimal knowledge of the normal distribution of FDG throughout the anatomic structures of the body and the variations that might occur with age (93).

Certain tumors cannot be easily detected with FDG-PET because of low FDG uptake, such as in hepatocellular carcinoma (94) or certain types of pancreatic tumors.(95) Because of the limited spatial resolution of PET (96), it is also difficult to detect low-grade tumors (e.g., cartilaginous tumors) (97), small lung nodules, and brain metastases (98). Although there has been a report of intra-vascular lymphomatosis presenting as fever of unknown origin (99), FDG-PET remains less effective in the detection of small-vessel disease.

Because FDG follows a similar pathway as glucose, a normalization of blood sugar level is a must in order not to miss any active malignant lesions because of suboptimal image quality (100). However, it is reported that the serum glucose levels do not necessarily affect the accuracy of FDG-PET when inflammatory and infectious lesion is evaluated (101).

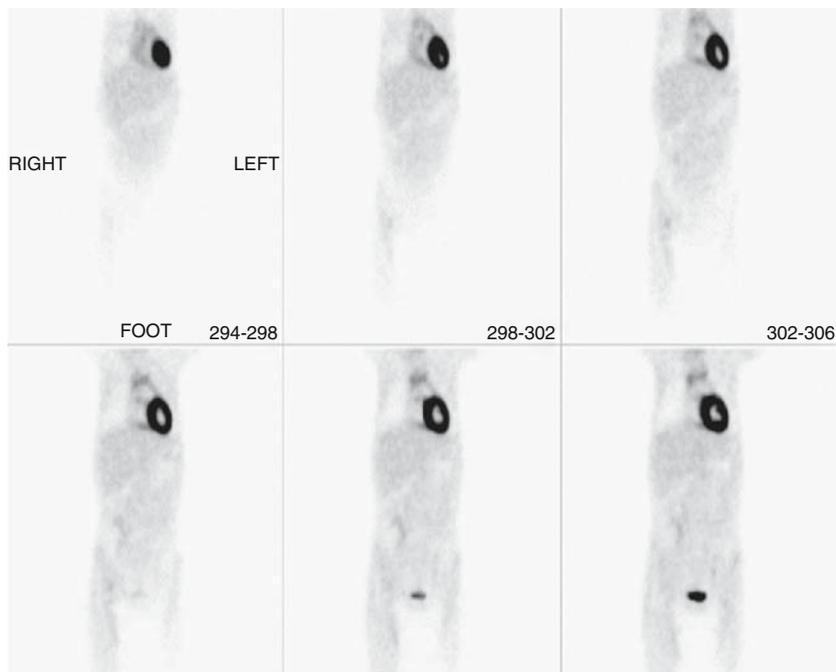
#### *Studies Regarding FDG-PET and FUO*

There have been a limited number of prospective studies regarding FDG-PET scan and FUO. The percentage of FDG-PET scans helpful in

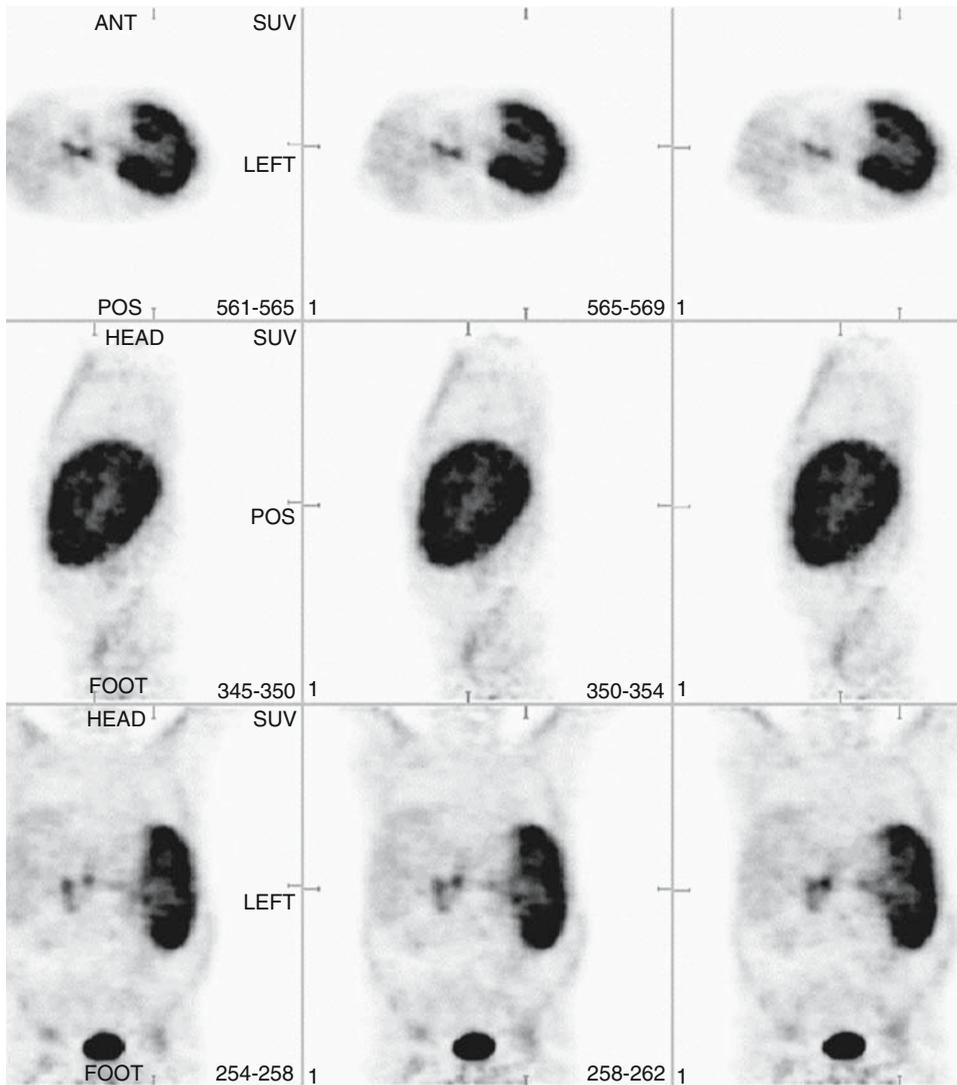
the diagnosis of FOU as reported in the literature ranged from 37% to 69% (83,102–106). This variation is attributed to different factors, including a slightly different definition of FOU, a wide array of heterogeneous disorders, variable FDG-PET techniques, and no structured diagnostic protocol. However, the contributory effect of FDG-PET in the diagnosis of FOU was found to be higher than gallium scintigraphy (25%) (83). Fluorodeoxyglucose-PET was more helpful in the diagnostic process of patients with a suspected focal infection or localized inflammation than in FOU (104). Only one study found that indium-111-labeled granulocyte scintigraphy had a superior diagnostic performance compared to FDG-PET in the evaluation of FOU (106), but in the 19 patients studied, only one patient was diagnosed with malignancy (Hodgkin's disease).

#### *Our Experience with FDG-PET*

We retrospectively reviewed 30 FDG-PET scans of 30 patients (aged 13 to 73 years) who were evaluated at our institution for FOU during the period between 1999 and 2004. Clinical follow-up, which included subsequent conventional imaging studies and/or pathology results, was compared to the FDG-PET scan results. Fluorodeoxyglucose-PET contributed to the diagnosis of 71% of the cases. The causes of fever detected by FDG-PET included pneumonia, non-Hodgkin's lymphoma (Fig. 23.4), Hodgkin's disease (Fig. 23.5), Crohn's disease

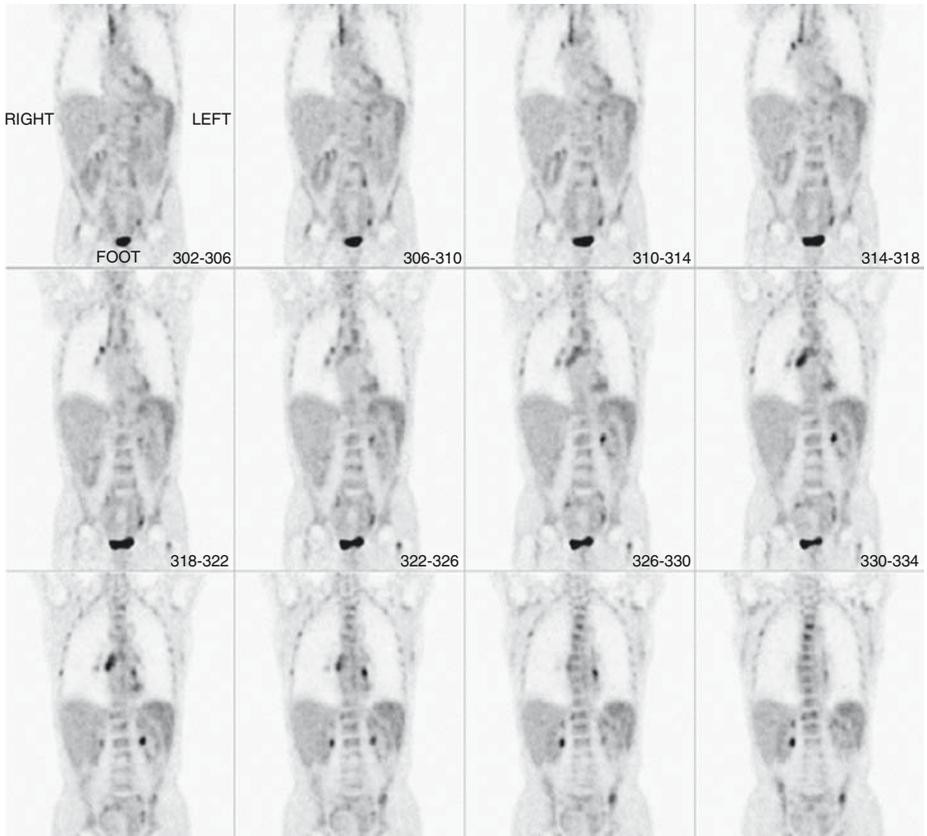


**Figure 23.3.** Normal FDG uptake is seen in the thymus of a 10-year-old patient.

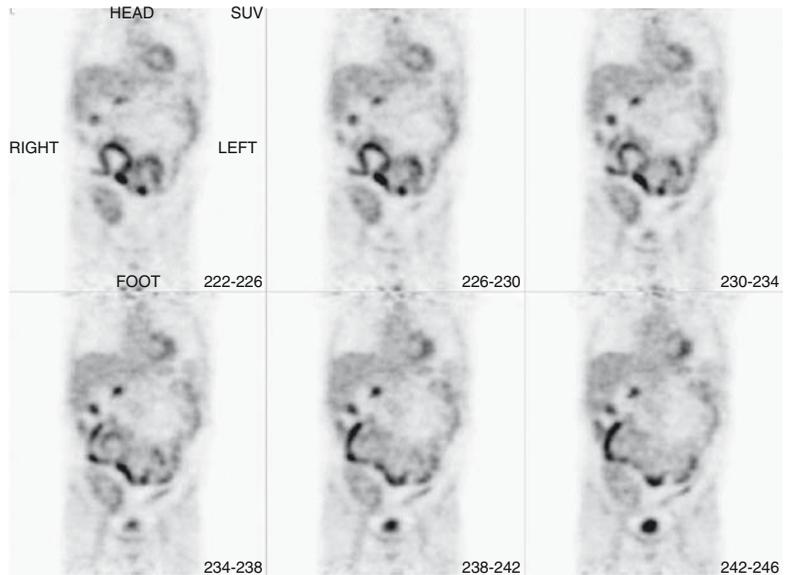


**Figure 23.4.** Intense FDG uptake is seen in the spleen, which is markedly enlarged, and two foci of abnormal uptake are visible in the upper abdomen, representing lymphadenopathy. The patient was diagnosed with non-Hodgkin's lymphoma.

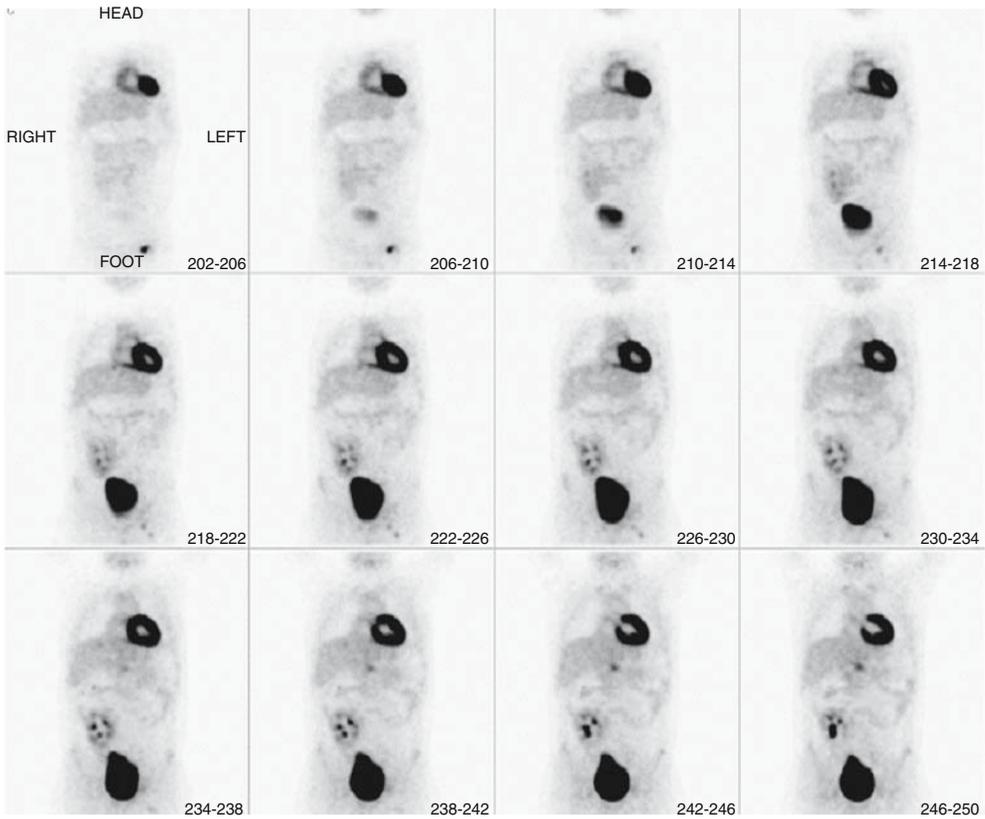
(Fig. 23.6), surgical wound infection, infected liver cysts, leukemia, and metastatic renal cell carcinoma (Fig. 23.7). Fluorodeoxyglucose-PET was falsely negative in three cases of colitis, peritonitis (Fig. 23.8), and rejected renal transplant. Two FDG-PET scans were falsely positive in two patients with suspected abnormal activity in the abdomen; one of them had an eventual diagnosis of endocarditis.



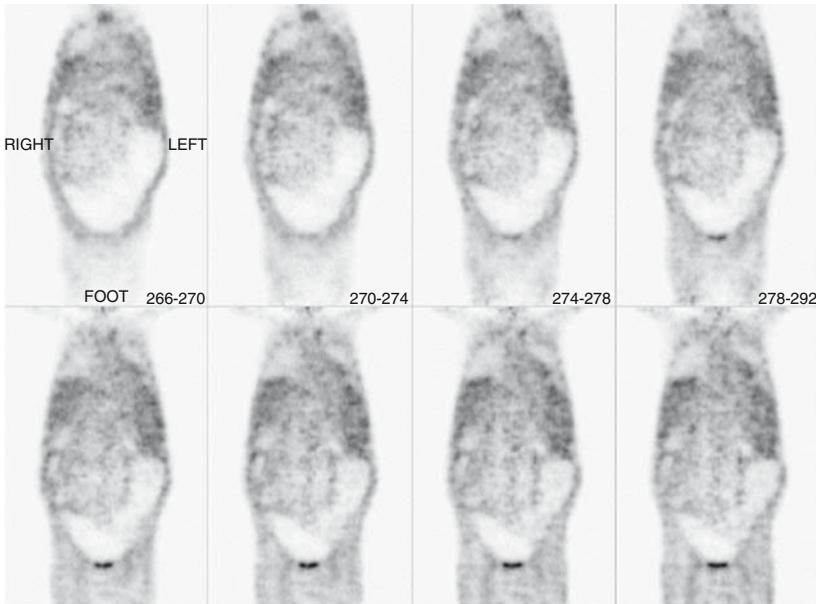
**Figure 23.5.** Abnormal FDG uptake is seen in the bone marrow, as well as in supraclavicular and mediastinal lymph nodes of a patient with FOU. The patient was diagnosed with Hodgkin’s disease.



**Figure 23.6.** Diffuse FDG activity in the bowel. Although this pattern can be seen in normal adult patients, this finding was the only suspicious source of FOU in this patient, with a history of renal transplant. Subsequent colonoscopies and bone marrow biopsies were negative. The patient underwent a laparotomy; after segmental resection of the terminal ileum and cecum, he was diagnosed with Crohn’s disease.



**Figure 23.7.** FDG-PET scan (coronal images) performed on a 13-year-old boy who underwent bilateral nephrectomies and renal transplant for polycystic kidney disease, after the patient developed a fever of unknown origin. Two foci of abnormal FDG uptake were noted in the left inguinal and in the portahepatic regions. There was no evidence of abnormal uptake in the transplanted kidney. Following biopsies, the patient was diagnosed with renal cell carcinoma in the transplanted kidney, which was removed.



**Figure 23.8.** Coronal FDG-PET images of a 44-year-old patient who had a history of liver transplant, presenting with marked abdominal and pelvic ascites. There is a large photopenic area in the abdomen corresponding to the abdominal fluid but no definite evidence of a suspected source of FUO. The patient underwent a paracentesis and was diagnosed with peritonitis.

## Conclusion

Fluorodeoxyglucose-PET is a valuable new imaging technique that has the potential for a major role in patients with FUO. It can detect malignancies as well as infectious and noninfectious inflammatory processes at an early stage of the disease. It has proven its superiority to other currently used conventional nuclear medicine imaging techniques. When ordered early in the diagnostic workup, FDG-PET has the potential to identify the area of abnormal activity where the cause of fever is likely to be found. This adds valuable information that can be used to focus the investigation and to eliminate unnecessary procedures, resulting in better management of the patients.

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