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Role of PET/CT in Workup of Fever without a Source[1]

Elizabeth H. Dibble, MD
Don C. Yoo, MD
Richard B. Noto, MD

Abbreviation: FDG = fluorine 18 fluorodeoxyglucose

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[1]From the Department of Diagnostic Imaging, Alpert Medical School of Brown University and Rhode Island Hospital, 593 Eddy St, Providence, RI 02903. Presented as an education exhibit at the 2014 RSNA Annual Meeting. Received March 8, 2015; revision requested July 22 and received September 4; accepted October 16. For this journal-based SA-CME activity, the authors D.C.Y. and R.B.N. have provided disclosures (see end of article); the other author, the editor, and the reviewers have disclosed no relevant relationships. **Address correspondence to** E.H.D. (e-mail: *edibble@lifespan.org*).

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SA-CME LEARNING OBJECTIVES

After completing this journal-based SA-CME activity, participants will be able to:

- Describe the epidemiology, causes, and workup of fever without a source.
- Determine the appropriate imaging modalities to evaluate fever without a source with a focus on nuclear medicine studies.
- Describe the relative imaging costs to radiology departments in the workup of fever without a source with a focus on radiopharmaceutical costs.

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Fever without source is a febrile illness without localizing signs or initial obvious cause. Early workup will often include chest radiography and computed tomography (CT) of the abdomen and pelvis, with or without CT of the chest. To evaluate localizing signs or symptoms or to further evaluate findings from initial studies, targeted imaging according to body part can be performed by using radiography, ultrasonography, CT, or magnetic resonance (MR) imaging. Nuclear medicine studies can provide imaging of the whole body and may be helpful when the clinical and conventional imaging workup findings are negative or equivocal in identifying a source of fever. Nuclear medicine studies can be used to detect pathologic changes early in a disease course, even in the absence of an anatomic abnormality. Gallium 67 scintigraphy, indium 111– and technetium 99m–labeled leukocyte scintigraphy, and fluorine 18 fluorodeoxyglucose positron emission tomography (PET)/CT studies are all useful in the evaluation of fever, but the radiopharmaceutical cost for PET/CT is much lower than that for radiolabeled leukocyte studies. The increased use of bundled payments for inpatient admissions requires updated cost evaluations for the preferred nuclear medicine study. For inpatients in whom the findings from the initial clinical workup and imaging studies are nondiagnostic, PET/CT examination may be preferable to radiolabeled leukocyte studies because of its high sensitivity and lower cost. Negative findings at PET/CT can be helpful in excluding a suspected site of infection, and positive findings at PET/CT can be helpful in confirming a suspected site of infection or in identifying an unexpected cause of fever.

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Introduction

Fever is a common problem among people of all ages worldwide. Fever without a source is a febrile illness without localizing signs or initial obvious cause. Fever without a source is well described in the pediatric literature (1,2), but adult patients also frequently present with fever with no readily apparent source. Fever of unknown origin, a subtype of fever without a source, is defined as fever on several occasions and illness lasting longer than 3 weeks after appropriate workup (3). This 3-week period allows time for diagnostic evaluation and for resolution of many self-limiting viral syndromes; however, life-threatening fevers may have no apparent source after a standard workup has been completed but before 3 weeks have elapsed.

Fever may be due to infection, inflammation, or malignancy. The initial workup for fever without a source typically involves obtaining a patient history; conducting a physical examination; performing

TEACHING POINTS

- Positive PET/CT findings can yield an unexpected cause of fever or can help confirm a suspected site of infection. Negative PET/CT findings can help exclude a suspected site of infection.
- In the evaluation of suspected osteomyelitis, we prefer PET/CT to radiolabeled leukocyte studies.
- Current changes in reimbursement structures require different cost evaluations; bundled payments limit the need for itemized reimbursement analyses and increase the need for cost-effectiveness analyses.
- The radiopharmaceutical cost for PET/CT is much lower than the radiopharmaceutical cost for radiolabeled leukocyte studies.
- With appropriate clinical correlation and communication with referring clinicians, PET/CT can be useful for evaluating fever, even in inpatients with complicated multiple findings.

laboratory tests including a complete blood cell count, blood chemistry analysis, liver function tests, and urinalysis; and acquiring chest radiographs (4). Further testing, imaging, or biopsy of suspected sites of infection should be performed as appropriate on the basis of clinical signs and symptoms. Further imaging often includes dedicated imaging of specific body parts on the basis of the results of clinical assessment. Whole-body imaging can be performed by using nuclear medicine studies.

In this article, the role of imaging in the diagnosis and management of fever without a source is discussed with a focus on positron emission tomography (PET)/computed tomography (CT). The imaging appearance of many causes of fever and the imaging costs to a radiology department are reviewed with a focus on radiopharmaceutical costs.

Imaging Studies for Fever without a Source

Chest radiography is fast and inexpensive and is part of a typical initial workup of fever without a source (4). Chest CT is more sensitive than chest radiography for the detection of airspace disease, nodules, and lymphadenopathy (5–8). It may be performed in conjunction with abdominal and pelvic CT when no localizing signs or symptoms are present. Abdominal and pelvic CT examinations have essentially replaced exploratory laparotomies in the search for occult abscesses. Abdominal ultrasonography (US) and magnetic resonance (MR) imaging are particularly useful in pediatric or pregnant patients because of the lack of ionizing radiation. CT, US, and radiography performed with or without MR imaging are useful in the evaluation of the musculoskeletal system particularly when assessing for the presence of gas in the soft tissues, fluid collections, or osteomyelitis (9), respectively. Targeted imaging evaluation of fever without a source is performed according to body part (Table 1).

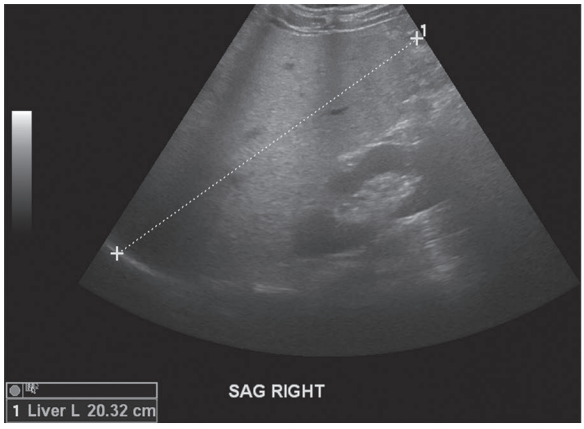
Nuclear medicine studies can provide imaging of the whole body and are often used as a last resort when the findings from radiography, US, CT, or MR imaging of the chest, abdomen, pelvis, or extremities are negative or equivocal in identifying a source of fever. Nuclear medicine studies can be used to detect pathophysiologic changes early in the course of a disease even in the absence of anatomic abnormalities (Fig 1).

Radiolabeled autologous leukocytes are used to detect abnormal granulocyte localization and are particularly useful in the setting of suspected infection (Fig 2). Autologous leukocytes are harvested by using venipuncture, are labeled ex vivo with radiopharmaceutical agents, and are readministered intravenously. When used in combination with technetium 99m (^{99m}Tc) bone marrow scintigraphy, indium 111 (^{111}In)–labeled leukocyte imaging can be used to differentiate marrow activity from osteomyelitis (10) (Fig 3). Radiolabeled leukocyte studies are limited in patients with neutropenia, and low leukocyte counts can make ^{111}In labeling for single photon emission computed tomography (SPECT) or SPECT/CT difficult to perform. In addition, radiopharmaceutical agents for labeling leukocytes are expensive and time consuming to use, and radiolabeled leukocytes are complicated to prepare. Unlike ^{111}In scintigraphy, a ^{99m}Tc-labeled leukocyte study is a same-day study that has higher leukocyte counts, allowing SPECT and SPECT/CT to be performed more easily. Technetium 99m–labeled leukocytes, however, are excreted through the gastrointestinal and genitourinary tracts, which limits the evaluation for pathologic conditions in the abdomen. An exception to this is the evaluation of inflammatory bowel disease; ^{99m}Tc-labeled leukocytes may be more sensitive than ^{111}In-labeled leukocytes for this indication, but images must be acquired before physiologic bowel activity begins to appear at approximately 4 hours after injection in adults (11,12).

PET/CT is useful in the detection of infection, inflammation, and malignancy. Increased expression of the facultative glucose transporters (GLUT transporters) by tumor cells, increased production of glycolytic enzymes by tumor cells, and increased uptake of FDG by tumoral stroma (perhaps caused by an inflammatory response) allow depiction of malignant cells with PET/CT imaging (13–15). Like tumor cells, inflammatory and granulation tissues have increased expression of facultative GLUT transporters and increased production of glycolytic enzymes (16). PET and PET/CT have been helpful in diagnosing various infectious causes of fever, including tuberculosis, Q fever, babesiosis, *Bartonella*,

Table 1: Imaging Modalities for Fever without a Source according to Body Part

Body Part and Imaging Modality	Characteristics of Modality
Chest	
Radiography	Fast, inexpensive, evaluate for pneumonia and adenopathy
CT	Further evaluate respiratory symptoms or abnormal chest radiograph, identify small nodules and adenopathy
Abdomen and pelvis	
CT	Has replaced exploratory laparotomy in search for occult abscess; can be used to identify lymphadenopathy; limitation: ionizing radiation
US	No ionizing radiation; useful to assess for fluid collections, especially in children; limitations: operator dependence, unable to image many areas
MR imaging	No ionizing radiation; useful for detecting abdominal abscesses; limitations: cost, lengthy imaging times
Extremities	
CT	Useful to evaluate for gas in soft tissues, bone erosion, or fluid collections
US	No ionizing radiation; useful to assess for fluid collections, especially in children; limitations: operator dependence, unable to image many areas
MR imaging	No ionizing radiation; useful to evaluate for osteomyelitis, myositis, and abscesses; limitations: cost, lengthy imaging times



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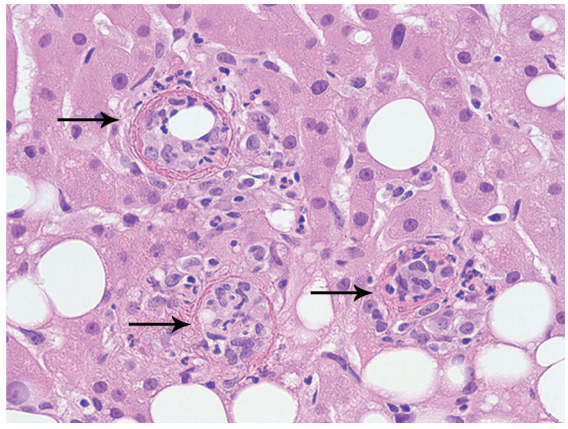

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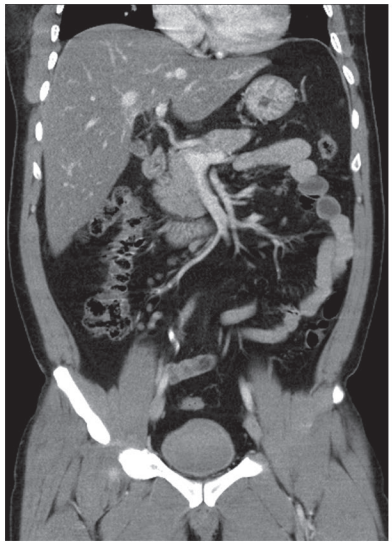

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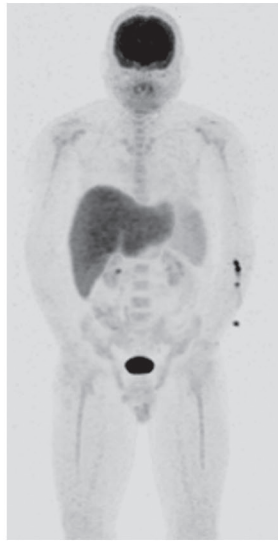


c.

Figure 1. Q fever in a 40-year-old man who presented with fever. **(a)** Sagittal gray-scale US image of the right upper quadrant shows hepatomegaly and diffusely hyperechoic hepatic tissue compatible with hepatic steatosis. **(b)** Coronal contrast material–enhanced CT image of the abdomen and pelvis shows hepatomegaly and diffuse hypoattenuation of the liver parenchyma, findings compatible with hepatic steatosis, but findings were otherwise normal. The patient was sent home. He returned to the emergency room 4 days later with persistent fever. **(c)** Coronal maximum intensity projection image from fluorine 18 fluorodeoxyglucose (FDG) PET/CT performed to evaluate fever without a source shows diffuse increased hepatic uptake of FDG and an otherwise normal distribution of activity, findings that prompted a liver biopsy. **(d)** Photomicrograph of tissue obtained at liver biopsy shows fibrin ring granulomas (arrows) with a central lipid vacuole, findings that are classically associated with Q fever; Q fever was confirmed serologically. (Hematoxylin-eosin stain; original magnification, ×400.) (Fig 1d courtesy of Chad J. Ellermeier, MD, Warren Alpert Medical School of Brown University, Providence, RI.)

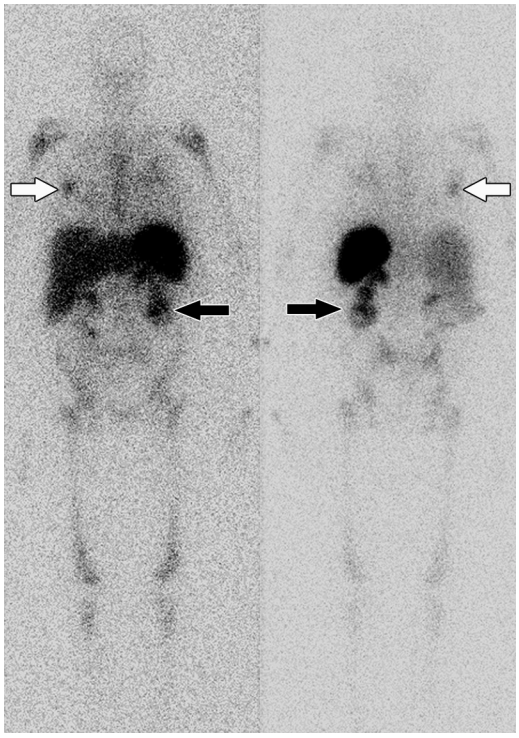


Figure 2. Pyelonephritis and pneumonia in a 50-year-old woman with fever and a history of B-cell lymphoma. Anterior (left) and posterior (right) planar scintigraphic images from a ^{111}In-labeled leukocyte scan show a focus of moderately intense activity (white arrows) in the peripheral right midportion of the hemithorax that is suspicious for early pneumonia. Increased activity is also depicted in the bilateral renal collecting systems and, to a lesser extent, the renal cortices, which is seen asymmetrically more on the left (black arrows), a finding suggestive of bilateral pyelonephritis. The patient's condition improved with broad-spectrum antibiotic therapy for pyelonephritis and pneumonia.

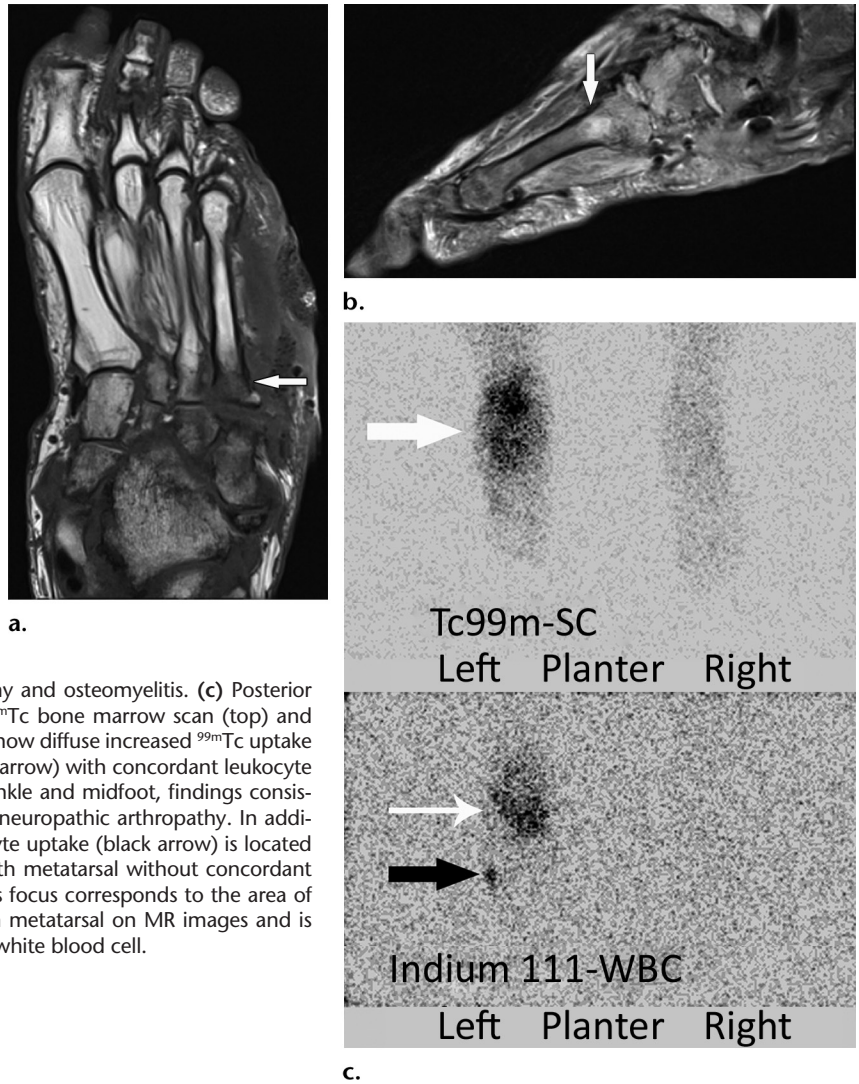
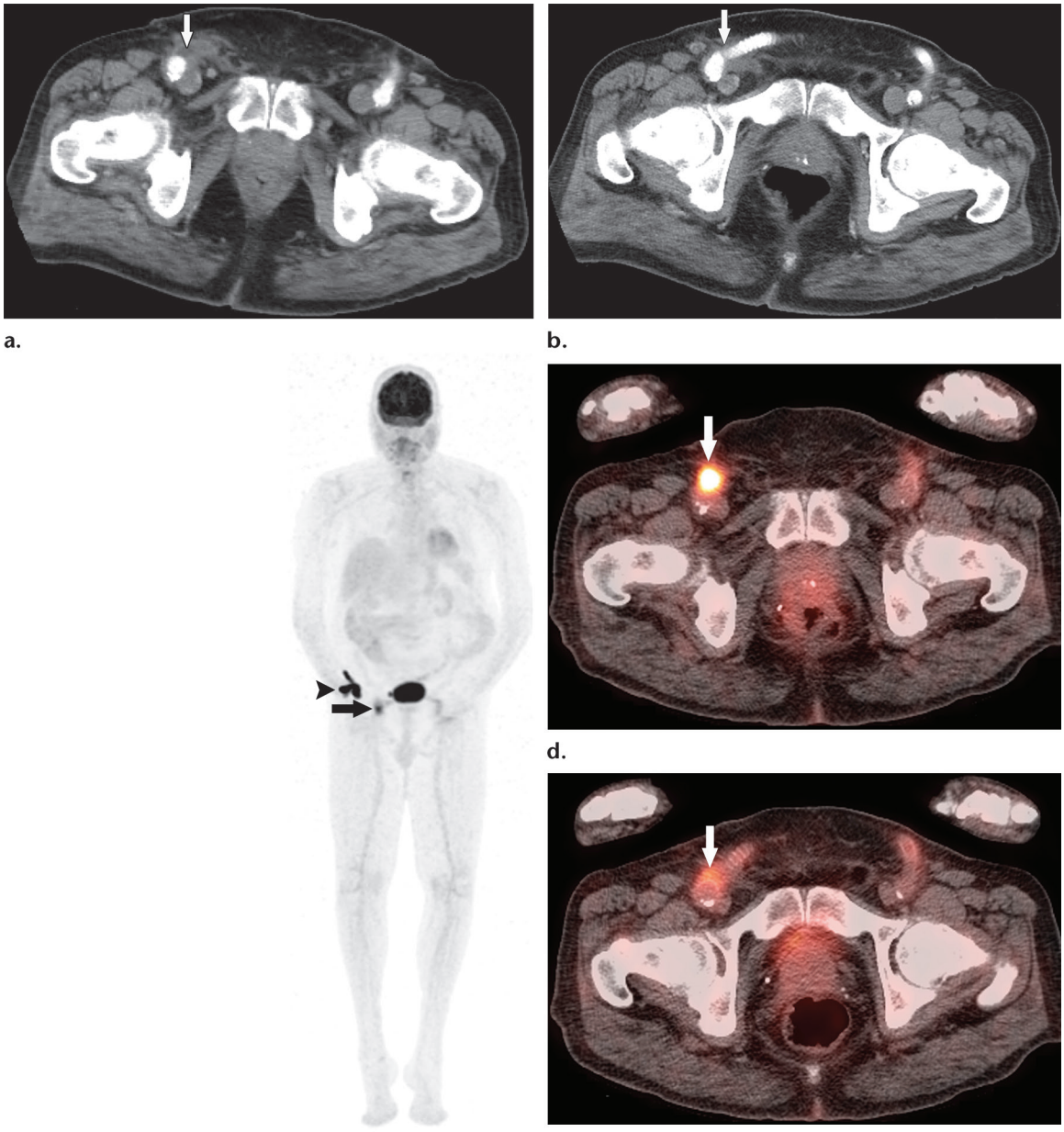


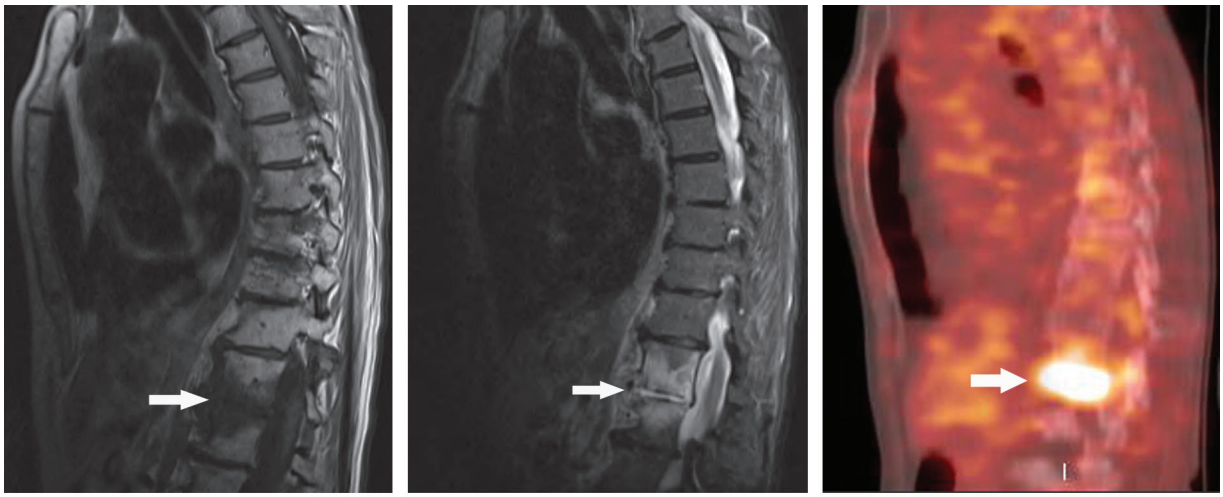
Figure 3. Osteomyelitis and neuropathic arthropathy in a 43-year-old woman with diabetes, fever, and a history of fifth ray amputation 2 weeks earlier. **(a)** Axial T1-weighted MR image of the left foot shows postsurgical changes related to the fifth ray amputation, as well as an area of T1 hypointensity (arrow) at the base of the fourth metatarsal, a finding that could represent acute neuropathic arthropathy or osteomyelitis. In addition, midfoot and hindfoot neuropathic arthropathy is unchanged from the appearance on previous images. **(b)** Sagittal short tau inversion-recovery MR image of the left foot shows edema at the base of the fourth metatarsal (arrow) and throughout the surrounding muscles, findings that could be compatible with acute neuropathic arthropathy or osteomyelitis. A combined ^{99m}Tc–sulfur colloid *(SC)* and ^{111}In-labeled leukocyte study was subsequently performed to distinguish between neuropathic arthropathy and osteomyelitis. **(c)** Posterior plantar scintigraphic images from a ^{99m}Tc bone marrow scan (top) and ^{111}In-labeled leukocyte scan (bottom) show diffuse increased ^{99m}Tc uptake on the bone marrow scan (thick white arrow) with concordant leukocyte uptake (thin white arrow) in the left ankle and midfoot, findings consistent with inflammatory changes from neuropathic arthropathy. In addition, a small focus of increased leukocyte uptake (black arrow) is located in the region of the left proximal fourth metatarsal without concordant uptake on the bone marrow scan. This focus corresponds to the area of abnormal signal intensity in the fourth metatarsal on MR images and is compatible with osteomyelitis. *WBC* = white blood cell.

Figure 4. Right groin phlegmon in an 82-year-old man with a history of peripheral vascular disease who was admitted with group B streptococcal bacteremia and suprapubic pain. The patient had undergone femorofemoral bypass graft placement 1 month previously. **(a, b)** Axial contrast-enhanced CT images (**a** obtained lower than **b**) show inflammatory stranding (arrow on **a**) adjacent to the right origin of the femoral artery bypass graft as well as a patent graft (arrow on **b**). There was no drainable fluid collection. **(c)** Coronal maximum intensity projection image from FDG PET/CT performed to evaluate possible graft infection and exclude other sources of bacteremia shows increased activity in the right groin (arrow), as well as injection site activity in the right hand (arrowhead). **(d, e)** Axial fused PET/CT images (**d** obtained lower than **e**) show increased FDG activity corresponding to the right origin of the femorofemoral bypass graft (arrow on **d**) and a small phlegmon (arrow on **e**) that does not appear to extend into the bypass graft. The patient recovered with long-term antibiotic suppression therapy for a presumed infection involving the origin of the femorofemoral bypass graft.



Yersinia, toxoplasmosis, cysticercosis, echinococcal cysts, Epstein-Barr virus, cytomegalovirus, thyroiditis, pneumonia, empyema, abdominal and pelvic abscesses, cholangitis and cholangiolitis, dropped gallstones, pyelonephritis, colitis, cecitis (typhlitis), diverticulitis, chronic bacterial prostatitis, chronic epididymitis, infected vascular grafts and lines, septic thrombophlebitis, aneurysm sac infections, joint infections, osteomyelitis, orthopedic infections, and soft tissue and skin infections (16–42). Positive PET/CT findings can yield an unexpected cause of fever or can help confirm a suspected site of infection. Negative PET/CT findings can help exclude a suspected site of infection (Fig 4).

Historically, gallium 67 (^{67}Ga) scintigraphy was the first-line nuclear medicine study used



a. b. c.

Figure 5. Osteomyelitis in an 85-year-old woman with a history of non–small cell lung carcinoma, esophageal carcinoma, and a recent emergency room visit for fever and a urinary tract infection. **(a)** Sagittal T1-weighted MR image acquired for metastatic workup 5 days after the emergency room visit shows abnormal low signal intensity in the T12-L1 disk space and in the T12 and L1 vertebral bodies (arrow). **(b)** Sagittal short tau inversion-recovery MR image shows fluid in the T12-L1 disk space (arrow), edema in the T12 and L1 vertebral bodies, and prevertebral edema and phlegmon, findings that are compatible with discitis and osteomyelitis. FDG PET/CT was performed 4 weeks later for cancer restaging. **(c)** Sagittal fused PET/CT image (bone window) shows increased activity at T12-L1 (arrow) compatible with known discitis and osteomyelitis.

to evaluate fever of unknown origin. Gallium 67 scintigraphy is more useful than radiolabeled leukocyte scintigraphy in the evaluation of spinal osteomyelitis, although ^{67}Ga uptake in areas of bone repair can complicate interpretation (43). FDG PET appears to be more sensitive and specific than ^{67}Ga scintigraphy in the evaluation of fever of unknown origin, including fever caused by spinal infection, and FDG PET also demonstrates improved tracer kinetics, better spatial resolution, and lower radiation exposure and allows for more rapid diagnosis (44–46). PET/CT, by integrating functional with anatomic information, appears to be even more sensitive than PET in diagnosing the source of fever (47).

Investigators have shown that FDG PET is superior to ^{111}In-labeled leukocyte scintigraphy for diagnosing chronic bacterial osteomyelitis and for establishing a source of fever of unknown origin (38,48). The results of only one study demonstrated that ^{111}In-labeled leukocyte scintigraphy was superior to FDG PET for determining the source of infection (49). That study has been criticized for patient selection bias (50) and for the classification of abnormal PET findings as false-positive in patients in whom no cause of fever could be found but no additional tests were performed to explain the abnormal PET findings (51). In the evaluation of suspected osteomyelitis, we prefer PET/CT to radiolabeled leukocyte studies (Fig 5).

PET/CT has also been helpful in diagnosing inflammatory causes of fever including sarcoidosis; lupus; Wegener granulomatosis; subacute thyroiditis; cryptogenic organizing pneumonia; rheumatic fever; pericarditis; autoimmune pancreatitis; inflammatory bowel disease; Henoch-Schönlein purpura; various inflammatory arthritides; various vasculitides; deep venous thrombosis; Castleman disease; Rosai-Dorfman disease; Erdheim-Chester disease; the immune dysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome; the synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome; and familial Mediterranean fever (16,17,21,26,28,34,52–68). PET/CT is also useful and cost-effective in the setting of occult bacteremia (Fig 6); the results from one study demonstrated lower mortality rates and decreased relapse rates in patients who underwent PET/CT for occult bacteremia (69,70). PET/CT images can be acquired less than an hour after FDG injection (71), which is a major benefit from both medical and cost-containment perspectives.

Overall, PET/CT has a high sensitivity ranging from 89% to 100% in the literature and is helpful in 54% of cases (47). The specificity of PET/CT is lower and has a wide range of 23%–87% in the literature (47), likely because PET/CT is nonspecific for infection, inflammation, and tumor. Table 2 summarizes the nuclear medicine studies used to evaluate fever without a source.

The Centers for Medicare and Medicaid Services (CMS) reimburse for these imaging studies differently. A major limitation in the use of FDG PET/CT is that, unlike other imaging studies, it is not yet reimbursable by CMS for the indication of fever (Table 3). Current changes in reimbursement structures require different

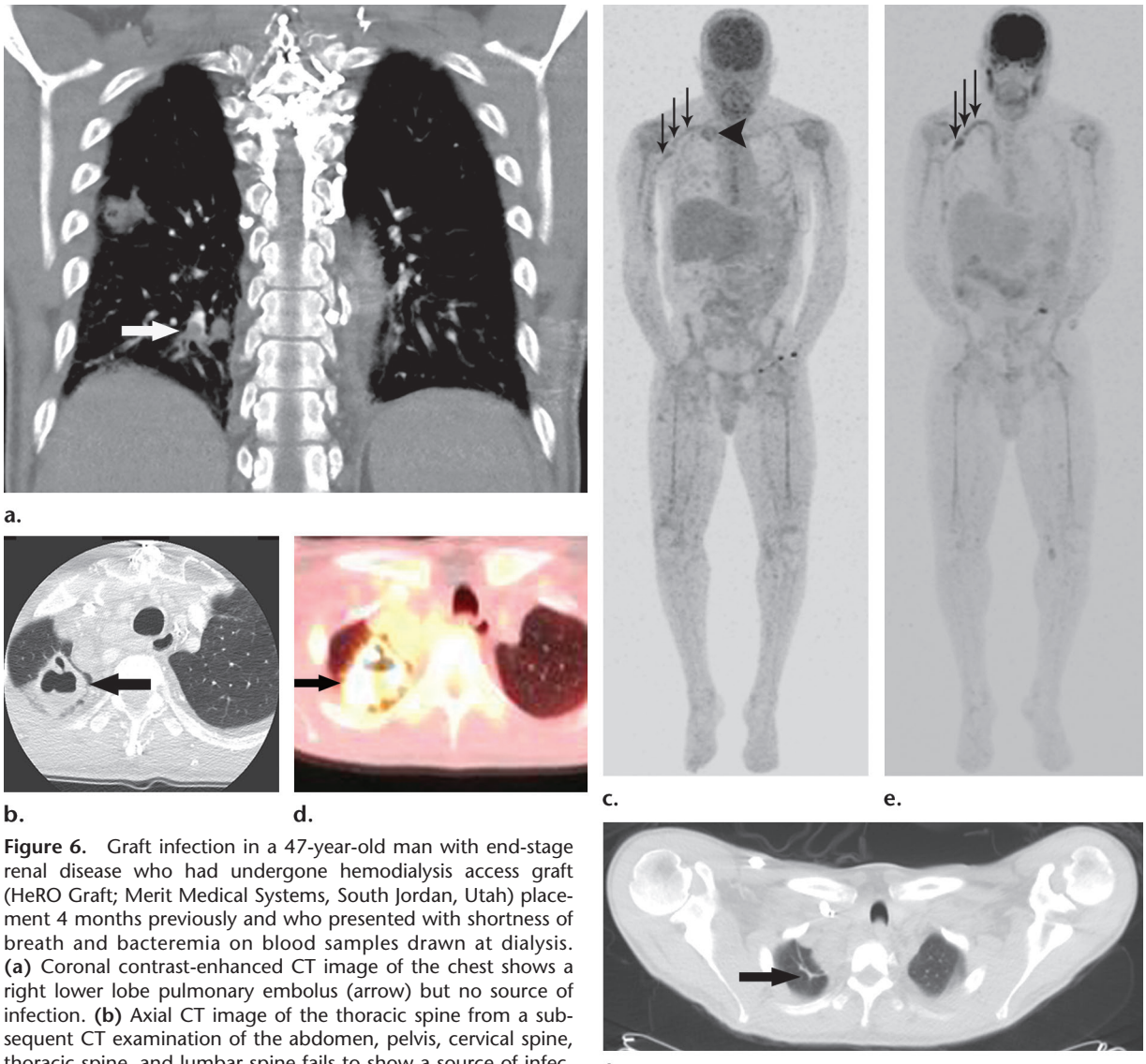


Figure 6. Graft infection in a 47-year-old man with end-stage renal disease who had undergone hemodialysis access graft (HeRO Graft; Merit Medical Systems, South Jordan, Utah) placement 4 months previously and who presented with shortness of breath and bacteremia on blood samples drawn at dialysis. **(a)** Coronal contrast-enhanced CT image of the chest shows a right lower lobe pulmonary embolus (arrow) but no source of infection. **(b)** Axial CT image of the thoracic spine from a subsequent CT examination of the abdomen, pelvis, cervical spine, thoracic spine, and lumbar spine fails to show a source of infection but does show a new cavitary lung lesion (arrow) that was suspicious for septic embolus. A transesophageal echocardiogram was negative for endocarditis. **(c)** Coronal maximum intensity projection image from FDG PET/CT performed to evaluate for the source of bacteremia and septic embolus shows increased activity associated with the cavitary lung lesion (arrowhead) and mild linear increased activity associated with the patient's right upper extremity graft (arrows). **(d)** Axial fused PET/CT image shows increased activity (arrow) that corresponds to the cavitary lung lesion seen on CT images. Because the patient was dependent on the graft for dialysis, he was discharged on antibiotic therapy with a plan to remove the infected portion of the graft once blood cultures were negative for bacteria for 48 hours; however, the patient continued to have positive blood cultures and was readmitted for definitive treatment of bacteremia 2 months later. Repeat PET/CT was performed to reevaluate for the source or sources of bacteremia. **(e)** Coronal maximum intensity projection image shows more intense activity at the graft site (arrows). **(f)** Axial CT image from PET/CT shows resolution of the cavitary lung lesion with only minimal scarring (arrow). The graft was removed, and graft infection was confirmed at histopathologic examination.

cost evaluations; bundled payments limit the need for itemized reimbursement analyses and increase the need for cost-effectiveness analyses. Cost-effectiveness analyses include the imaging study costs to the hospital or radiology department, and the costs to perform imaging studies may differ greatly, although the effectiveness of these studies in establishing diagnoses may be similar. In addition to equipment and labor costs, cost analyses should include radiopharmaceutical costs. Gallium 67–citrate agents are the least expensive radiopharmaceutical agents described, and ^{111}In-labeled leukocyte agents are the most expensive radiopharmaceutical agents described with a cost 8.8 times that of ^{67}Ga-citrate. The radiopharmaceutical cost for FDG PET/CT is much lower than the radiopharmaceutical cost for radiolabeled leukocyte studies (Table 4). Although the per-study technical costs, including equipment, labor, and maintenance costs, are higher for PET/CT than they are for planar, SPECT, or SPECT/CT imaging, these costs represent fixed costs, whereas radiopharmaceutical costs represent variable costs. In the era of

RadioGraphics

Table 2: Nuclear Medicine Studies for Whole-Body Imaging to Evaluate Fever without a Source

Imaging Study	Indications	Contraindications	Advantages	Limitations
^{67}Ga scintigraphy	Inflammatory conditions, infection	None	Least expensive radiopharmaceutical agent, reimbursable for suspected infection, can be used in patients with neutropenia, more useful than radiolabeled leukocytes for spinal infection, useful in outpatients suspected of having spinal infections	GI excretion limits evaluation for abdominal pathologic conditions, less useful than PET/CT for spinal infection
^{111}In-labeled leukocyte scintigraphy	Infection	Absolute: none; relative: neutropenia	Reimbursable for suspected infection, more specific than ^{67}Ga scintigraphy and PET/CT for infection, can be combined with bone scan or bone marrow scan to evaluate for osteomyelitis, useful in outpatients suspected of having infection	Expensive radiopharmaceutical agent, limited evaluation of nongranulocytic processes, limited use in patients with neutropenia, low leukocyte counts make SPECT difficult
^{99m}Tc-labeled leukocyte scintigraphy	Infection	Absolute: none; relative: neutropenia	Reimbursable for suspected infection, more specific than ^{67}Ga scintigraphy and PET/CT for infection, ability to perform same-day study, feasibility of performing SPECT/CT, useful in outpatients suspected of having infection who need same-day study	Expensive radiopharmaceutical agent, limited evaluation of nongranulocytic processes, limited use in patients with neutropenia, GI and GU excretion limits evaluation for abdominal pathologic conditions
FDG PET/CT	Malignancy, inflammatory conditions, infection	Absolute: none; relative: hyperglycemia	Relatively inexpensive radiopharmaceutical agent, may be the most cost-effective study for inpatients suspected of having infection, same-day study, high sensitivity	Not yet reimbursable for suspected infection; nonspecific for infection, inflammation, and tumor

Note.—GI = gastrointestinal, GU = genitourinary.

Table 3: Centers for Medicare and Medicaid Services Imaging Reimbursements in 2014

Imaging Study	Ambulatory Payment Classification Fee ($)	Professional Fee ($)
Chest radiography	62.80	9.57–11.40
Chest CT	138.49–272.66	52.97–65.10
Abdominal and pelvic CT	264.77–427.21	91.21–95.21
US	147.36	42.31
MR imaging	322.80–467.02	76.13–90.46
^{67}Ga scintigraphy	719.41 (AIWB)	43.38 (AIWB)
^{111}In-labeled leukocyte scintigraphy	719.41 (AIWB)	43.38 (AIWB)
^{99m}Tc-labeled leukocyte scintigraphy	719.41 (AIWB)	43.38 (AIWB)
FDG PET/CT	Not reimbursed for fever without a source	Not reimbursed for fever without a source

Note.—AIWB = abscess imaging whole body.

Table 4: Relative Costs for Radiopharmaceutical Agents

Imaging Study	Cost for Radiopharmaceutical Agent
^{67}Ga scintigraphy	Reference cost (least expensive)
^{111}In-labeled leukocyte scintigraphy	8.8 × reference cost (most expensive)
^{99m}Tc-labeled leukocyte scintigraphy	8.1 × reference cost
FDG PET/CT	1.2 × reference cost

Note.—Reference cost is the cost on which the others are based.

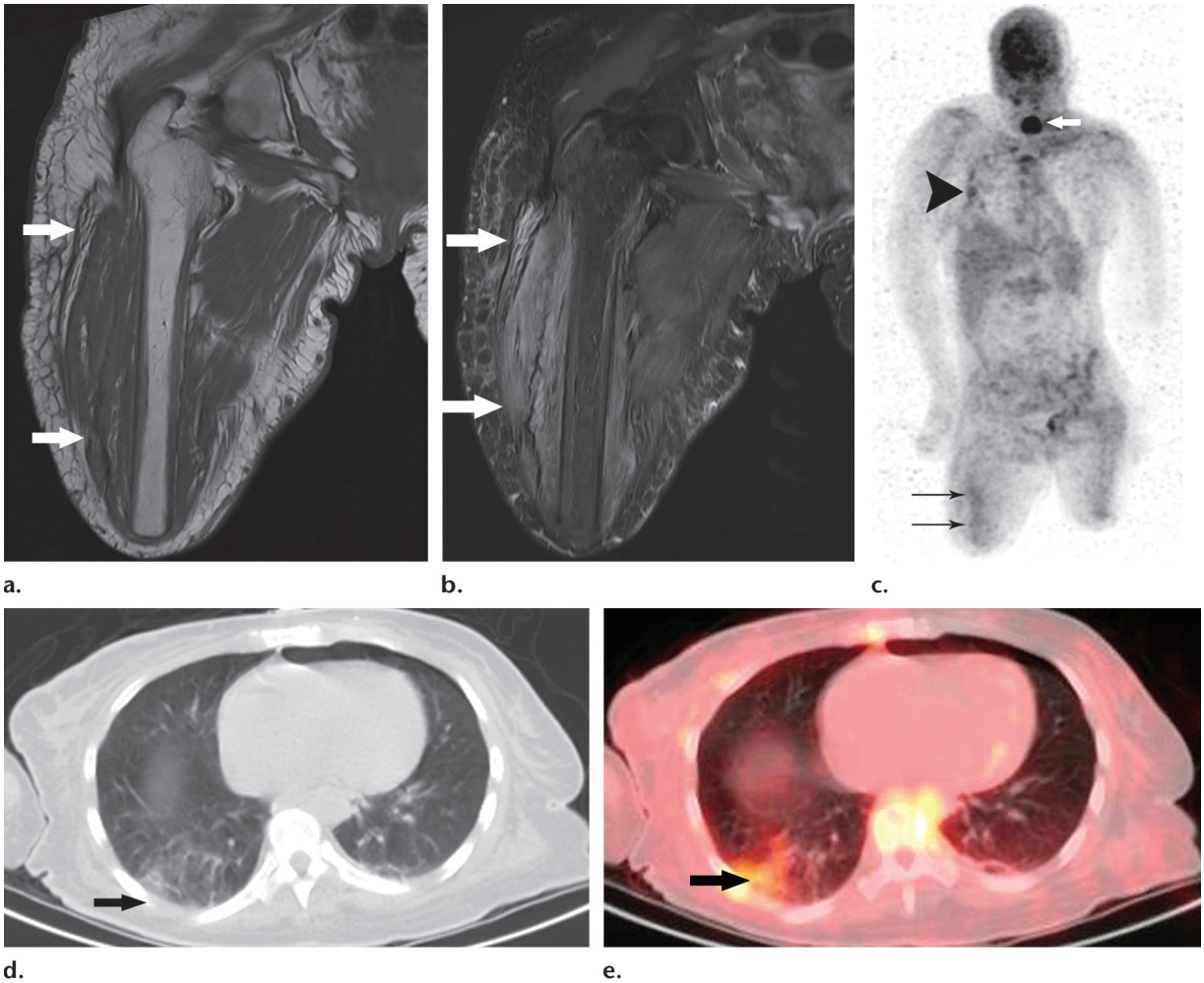


Figure 7. Aspiration and right lower extremity soft tissue infection in a 47-year-old woman with a history of peripheral vascular disease who presented with fever and right lower extremity erythema. The patient had undergone bilateral above-the-knee amputations more than 1 year previously. **(a, b)** Coronal T1-weighted **(a)** and short tau inversion-recovery **(b)** MR images show subcutaneous and intramuscular edema (arrows) in the right lower extremity, but there is no abscess or abnormal osseous signal intensity to suggest osteomyelitis. **(c)** Coronal maximum intensity projection image from FDG PET/CT performed for persistent fevers shows increased activity in the right side of the chest (arrowhead) and in the right lower extremity (black arrows). The intense focus of increased activity in the neck (white arrow) represents physiologic vocal cord activity. **(d)** Axial CT image from PET/CT shows airspace disease (arrow) in the right lung. **(e)** Axial fused PET/CT image shows increased activity (arrow) associated with ill-defined airspace disease in the right lung, a finding compatible with aspiration, which had been clinically suspected. **(f)** Coronal fused PET/CT image shows increased activity (arrows) in the subcutaneous tissues and musculature of the right lower extremity with no evidence of osteomyelitis or abscess and no abnormal activity at the patient's graft sites. The patient underwent surgery to open the skin and wash out the right lower extremity given the persistent fever. No abscess or osteomyelitis was found, and the diagnosis at discharge was calciphylaxis and infection in soft tissues of the right lower extremity.

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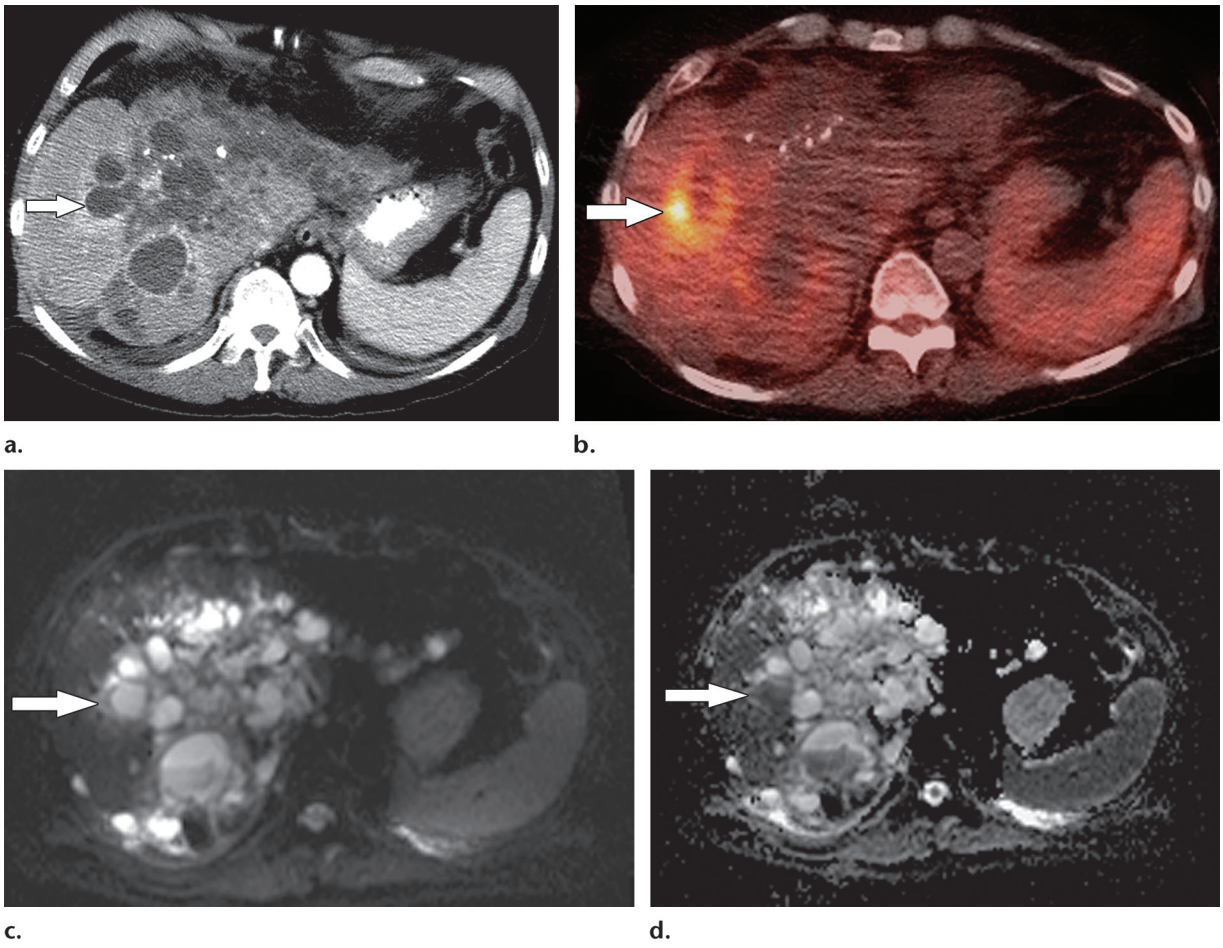

Figure 8. Infected hepatic cyst in a 74-year-old man with polycystic kidney disease who presented with 1 week of low-grade fevers and was found to have bacteremia. **(a)** Axial contrast-enhanced CT image shows enhancement around a liver cyst (arrow), which is new compared with findings on previous images and is suggestive of hyperemia related to infection or inflammation. **(b)** Axial fused FDG PET/CT image from PET/CT performed to evaluate persistent fever, bacteremia, and suspected hepatic cyst infection shows focal increased uptake (arrow) peripherally around the same hepatic cyst. MR imaging was performed to plan for aspiration of the cyst. **(c, d)** Axial diffusion-weighted MR image **(c)** and axial apparent diffusion coefficient map **(d)** show restricted diffusion in the same cyst (arrow), which corresponds to the area of increased activity at PET/CT. Pus was aspirated from the cyst with US guidance by using MR imaging–US fusion technology.

bundled payments, PET/CT may be a more cost-effective study for inpatients with the diagnosis of fever without a source because of the differences in radiopharmaceutical cost, although further studies are warranted.

At our institution, we use PET/CT to evaluate inpatients who are suspected of having infection and who have negative or equivocal findings at initial workup. Inpatients frequently have complicated histories and hospital courses and may have multiple concurrent acute or chronic inflammatory conditions and, not infrequently, more than one source of infection (Fig 7). In our experience, knowledge of detailed surgical histories and clinically suspected sources of infection is critical to optimizing the utility of PET/CT by minimizing false-positive findings. We work closely with the team of physicians who care for the patient, which often includes internal medicine physicians, infectious diseases physicians, and surgeons, to establish a priori what the clinical questions are. Radiologists must have a detailed understanding of physiologic variants, and all PET/CT findings should be correlated clinically and with findings of all available prior imaging studies. Findings from multiple imaging modalities are often complementary (Fig 8). With appropriate clinical correlation and communication with referring clinicians, PET/CT can be useful for evaluating fever, even in complicated inpatients with multiple findings.

Conclusion

Fever without a source may be due to infection, malignancy, or inflammation. In the inpatient setting, fever is often due to infection. For initial studies in febrile patients without localizing signs or symptoms, we recommend chest radiography and CT of the abdomen and pelvis with or without CT of the chest. For inpatients in whom

the findings from the initial workup and imaging studies are nondiagnostic, we typically perform PET/CT instead of radiolabeled leukocyte studies because of the lower radiopharmaceutical cost and high sensitivity. Negative PET/CT findings can be helpful in excluding a suspected site of infection. Positive PET/CT findings can be helpful in confirming a suspected site of infection or in identifying an unexpected cause of fever.

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