Continuing Education on Radionuclide Imaging of Musculoskeletal Infection: A Review

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ABSTRACT

There are numerous imaging tests for diagnosing musculoskeletal infection. Radiographs are routinely performed, because even when not diagnostic, they provide an anatomic overview of the region of interest that could influence subsequent procedure selection and interpretation. Magnetic resonance imaging is sensitive and provides superb anatomic detail. Bone scintigraphy accurately diagnoses osteomyelitis in bones not affected by underlying conditions. Gallium-67 is used primarily for spondylodiscitis. Although in-vitro labeled leukocyte imaging is the radionuclide test of choice for complicating osteomyelitis such as diabetic pedal osteomyelitis and prosthetic joint infection, it is not useful for spondylodiscitis. Antigranulocyte antibodies and antibody fragments have limitations and are not widely available. $^{111}$In-Biotin is useful for spondylodiscitis. Radiolabeled synthetic fragments of the antimicrobial peptide ubiquicidin are promising infection specific agents. Fluorine-18 FDG is the radionuclide test of choice for spondylodiscitis. Its role in diabetic pedal osteomyelitis and prosthetic joint infection is not established. Preliminary data suggest gallium-68 may be useful in musculoskeletal infection. Iodine-124 fialuridine initially showed promise as an infection specific radiopharmaceutical but subsequent investigations were disappointing. The development of positron emission computed tomography/computed tomography (PET/CT) and single photon emission computed tomography/computed tomography (SPECT/CT) imaging systems, which combine anatomic and functional imaging, has revolutionized diagnostic imaging. These hybrid systems are redefining the diagnostic workup of patients with suspected or known infection and inflammation by improving diagnostic accuracy and influencing patient management.
Key words: FDG, gallium, labeled leukocytes, osteomyelitis, PET/CT, SPECT/CT.

Acute osteomyelitis arises hematogenously or via direct inoculation. Local risk factors include open fractures, recent surgery, and orthopedic hardware. Systemic risk factors include diabetes, immunosuppression, and substance abuse (1). The diagnosis is not always obvious and imaging procedures are part of the diagnostic work-up. There are numerous tests from which to choose, none of which is optimal for every situation.

MORPHOLOGIC IMAGING

Radiography

Radiographs are the initial imaging study performed for suspected osteomyelitis. Early findings include soft tissue swelling and blurring of adjacent fat planes. Medullary trabecular lysis, cortical destruction, and periosteal reaction may not appear for more than a week (Supplemental Fig. 1). Although sensitivity and specificity only range from about 50% to 75% and from 75% to 83%, respectively, radiographs provide an anatomic overview of the area(s) of interest potentially guiding selection and interpretation of subsequent procedures (2).

Magnetic Resonance Imaging

The earliest findings, which can appear within two days after onset of infection, are a decrease in signal intensity on T1-weighted sequences and an increase in signal intensity on fat suppressed T2-weighted sequences caused by inflammatory marrow edema (Supplemental Fig. 2). Periosteal reaction and adjacent soft tissue edema appear later. Intravenous contrast is useful for evaluating abscesses and differentiating synovial
fluid from synovial thickening. The test has a very high negative predictive value for excluding osteomyelitis. Its positive predictive value, the ability to differentiate osteomyelitis from noninfectious causes of abnormal marrow signal intensity, is lower (2).

**Computed Tomography and Ultrasonography**

Computed tomography (CT) and ultrasonography are not primary imaging modalities for osteomyelitis. On CT, acute osteomyelitis appears as an area of increased density in the medullary cavity, accompanied by blurring of fat planes, periosteal reaction, and cortical loss (2).

Ultrasoundography is useful in regions complicated by orthopedic instrumentation and in patients for whom magnetic resonance imaging is contraindicated. The diagnosis of acute osteomyelitis is made by identification of a subperiosteal abscess. Prior to the formation of a subperiosteal abscess, the diagnosis may be missed. Soft tissue abscesses adjacent to bone may be misinterpreted as subperiosteal abscesses (2).

**RADIONUCLIDE IMAGING**

**Bone scintigraphy**

Bone scintigraphy is performed with technetium-99m ($^{99m}$Tc) labeled diphosphonates. Uptake depends on blood flow and rate of new bone formation. Three-phase bone scintigraphy usually is performed for osteomyelitis and consists of the perfusion phase, followed immediately by the soft tissue phase. The skeletal phase is performed two to four hours later. Focal hyperperfusion, focal hyperemia, and focally
increased bony uptake is the classic appearance of osteomyelitis. The test is sensitive and specific in otherwise normal bone. Preexisting conditions such as fracture, orthopedic hardware, and adjacent soft tissue infection decrease specificity (3).

**Gallium-67 scintigraphy**

Gallium-67 (\(^{67}\text{Ga}\)) uptake in infection is multifactorial. Approximately 90\% of the injected \(^{67}\text{Ga}\) is in plasma, nearly all of which initially is transferrin bound. Increased blood flow and vascular membrane permeability result in increased delivery and accumulation of \(^{67}\text{Ga}\) at foci of infection. \(^{67}\text{Ga}\) binds to lactoferrin, which is present in most infections. Direct bacterial \(^{67}\text{Ga}\) uptake has been reported. Siderophores, chelates produced by bacteria, are \(^{67}\text{Ga}\) avid. The siderophore-gallium complex presumably is transported into the bacterium and phagocytized by macrophages. Some \(^{67}\text{Ga}\) may be transported by circulating leukocytes. Imaging usually is performed 18-72 hours after injection. Currently \(^{67}\text{Ga}\) imaging is used primarily for spondylodiscitis (Fig. 1) (3).

**Labeled leukocyte scintigraphy**

*In vitro labeled leukocytes.* \(^{111}\text{In}\) oxyquinolone (In) and \(^{99m}\text{Tc-exametazime}\) (Tc) are most often used to label leukocytes in-vitro. Leukocyte uptake depends on intact chemotaxis, number and types of cells labeled and cellular response to a particular stimulus. The circulating leukocyte count should be 2000/\(\mu\)L or more for diagnostically acceptable images. Because the majority of leukocytes labeled usually are neutrophils, labeled leukocyte imaging is most sensitive for neutrophil-mediated infections. There is intense pulmonary activity on images obtained soon after labeled leukocyte infusion,
caused by cellular activation during labeling, which impedes passage of labeled leukocytes through the pulmonary vasculature (4).

Advantages of the $^{111}$In radiolabel include stability, a normal distribution at 24 hours post infusion limited to liver, spleen and bone marrow and ability to perform delayed imaging. Complementary bone marrow imaging can be performed before, simultaneously with, or after In-labeled leukocyte imaging. Disadvantages include limited resolution, and the 18-30 hour delay between injection and imaging (4).

Tc-labeled leukocyte distribution is more variable because some of the technetium elutes from the leukocytes and is excreted via the kidneys and hepatobiliary system. Therefore, in addition to reticuloendothelial system visualization, the urinary tract, bowel, and gallbladder often are seen. Higher resolution images and ability to detect abnormalities shortly after injection are advantages of Tc-labeled leukocytes. Disadvantages include label instability and short half-life of $^{99m}$Tc, which limits delayed imaging. There should be two to three days between Tc-labeled leukocyte and marrow imaging (4).

Leukocytes accumulate in infection and marrow and it is not always possible to differentiate between them on labeled leukocyte images. $^{99m}$Tc-sulfur colloid bone marrow (marrow) imaging facilitates this differentiation. Both radiopharmaceuticals accumulate in marrow; only labeled leukocytes accumulate in infection. Labeled leukocyte/marrow imaging is positive for osteomyelitis when activity is present on the labeled leukocyte image without corresponding activity on the marrow image (Figs. 2 and 3). Labeled leukocyte/marrow imaging accuracy is approximately 90% (5). Dual
time point imaging at 3-4 and 20-24 hours after labeled leukocyte infusion has been suggested as an alternative to labeled leukocyte/marrow imaging (6).

**In-vivo labeled leukocytes.** Besilesomab, a murine monoclonal IgG1 antibody, binds to cross-reacting antigen-95 on granulocyte and granulocyte precursor cell membranes. About 10% of $^{99m}$Tc-besilesomab is neutrophil bound. Twenty percent circulates freely, localizing in infection through nonspecific mechanisms. The incidence of human antimurine antibody, or HAMA, response, which occurs in more than 30% of patients receiving repeated injections, is a disadvantage (7).

Sulesomab is a 50 kDa fragment antigen binding (Fab’) portion of an IgG1 class murine monoclonal antibody that binds to normal cross-reactive antigen-90 on leukocytes. Approximately 3-6% of the $^{99m}$Tc-sulesomab injected is associated with circulating neutrophils; by 24 hours about 35% is in the marrow. Initial investigations suggested that uptake in infection includes binding to circulating neutrophils and to leukocytes present at the site of infection. Subsequent data suggest accumulation in infection is nonspecific (7).

Interleukin 8, a chemotactic cytokine that binds to α chemokine, or CXC, receptors types 1 and 2 on leukocytes, rapidly accumulates in infection. Limited investigations suggest that this agent accurately diagnoses musculoskeletal infection (7).

**$^{111}$In-Biotin**

Biotin, or vitamin B7, which is important in glucose metabolism, is a bacterial growth factor (8). $^{111}$In-Biotin, alone and combined with streptavidin has been used for imaging infection. Advantages include same day imaging, and little or no bone marrow uptake. Antibiotic therapy does not affect sensitivity (7).
Radiolabeled antibiotics

Radiolabeled antibiotics were an attempt at developing infection specific agents. The most extensively investigated radiolabeled antibiotic is $^{99m}$Tc-ciprofloxacin. Initial investigations reported high sensitivity and specificity. Subsequent investigations raised serious questions about specificity, and enthusiasm for radiolabeled antibiotics has faded (7).

Radiolabeled antimicrobial peptides

Antimicrobial peptides (AMPs), part of the natural defenses of most living organisms, are small, cationic and amphipathic (hydrophilic and hydrophobic). Their expression may be constant or induced on contact with microbes. They may be transported by circulating leukocytes. AMPs kill microbes but are not harmful to mammalian cells and their therapeutic and diagnostic potential is being investigated (7,9,10). Radiolabeled synthetic fragments of ubiquicidin (UBI), which is present in murine macrophages, have been the most extensively studied AMPS (7,10,11). $^{99m}$Tc-UBI-29-41 appears to be sensitive and specific for musculoskeletal infection, and has shown promise for monitoring treatment response (7). Gallium-68 labeled UBI 29-41 successfully detects bacterial infection (11).

$^{18}$F-fluorodeoxyglucose (FDG)

FDG is transported into cells via glucose transporters and phosphorylated by hexokinase to $^{18}$F-2$^\ast$.$^{18}$F-FDG-6 phosphate but not metabolized further. Uptake by leukocytes depends on cellular metabolic rate and number of glucose transporters. There
is an increased number and expression of glucose transporters by activated inflammatory cells, and an increased affinity of these transporters for FDG (3).

FDG-positron emission tomography (PET) is a relatively high resolution imaging test that provides precise radiopharmaceutical localization. The small FDG molecule enters poorly perfused areas rapidly. Imaging typically is performed about one hour after injection. Uptake usually normalizes within three to four months after trauma or surgery and degenerative bone changes ordinarily show only mildly increased uptake (3).

**18F-FDG labeled leukocytes**

In an effort to develop a more specific PET radiopharmaceutical, leukocytes have been labeled in-vitro with FDG. Disadvantages include the 110 minute half life of fluorine-18 which precludes off-site labeling and delayed imaging, a lower and more variable labeling efficiency than that of 111In-oxine and rapid FDG elution from leukocytes (3).

**Gallium-68**

Although the imaging characteristics of gallium 68-citrate (68Ga) are superior to those of 67Ga, uptake mechanisms are the same. Disadvantages of 67Ga, including uptake in inflammation, trauma, and tumor also apply to 68Ga-citrate. Another potential disadvantage is its short half-life (68 minutes). Complexing 68Ga with peptides may overcome these problems (12).
**Iodine-124 Fialuridine**

Fialuridine is a specific substrate of bacterial thymidine kinase. In a pilot study all eight patients with musculoskeletal infection demonstrated $^{124}$I-fialuridine accumulation in the infection. There was no abnormal uptake in the control (13). Results of subsequent investigations, however, have been disappointing (14,15).

**INDICATIONS**

No one agent is equally efficacious throughout the skeleton. Selecting the most appropriate study depends on the clinical situation. In adults, it is useful to divide musculoskeletal infections into three categories: spine, diabetic foot, and prosthetic joint.

**Spondylodiscitis**

Spondylodiscitis arises hematogenously, via direct external inoculation, and spread from contiguous tissues, and can extend into adjacent soft tissues. Hematogenous pyogenic spondylodiscitis most often involves the lumbar spine. Tuberculous infection more commonly affects the thoracic spine and is more likely to involve more than two vertebrae (16).

Radionuclide imaging is a valuable adjunct to magnetic resonance imaging (MRI) for spondylodiscitis. Although bone scintigraphy is used for screening, false negative results occur. It is not sensitive for detecting soft tissue infections that accompany, or mimic, spinal infections. Scans may remain abnormal for some time after infection has resolved. $^{67}$Ga imaging improves the specificity of, and may detect infection sooner than, bone scintigraphy, and identifies accompanying soft tissue infections (3,17,18). $^{67}$Ga
single photon emission computed tomography/computed tomography (SPECT/CT) reduces false positive and false negative results and identifies soft tissue infection (3).

$^{67}$Ga has disadvantages. Its physical characteristics and normal distribution can confound image interpretation. Although the test may become positive shortly after injection, imaging typically is performed 18-72 hours after injection. $^{67}$Ga accumulates in inflammation, tumor and trauma, which can coexist with, or mimic, infection.

Labeled leukocyte imaging is not useful for diagnosing spondylodiscitis. Approximately 50% of cases present as areas of nonspecific decreased activity (4).

$^{111}$In-biotin accurately diagnoses spondylodiscitis. Performing SPECT/CT accurately differentiates bone from soft tissue infection and helps guide therapy (19,20).

FDG consistently outperforms bone, $^{67}$Ga, and antigranulocyte antibody imaging and compares favorably with MRI (21-30). Gratz et al. (22) reported FDG-PET was superior to MRI for low-grade spondylitis/discitis. Stumpe et al. (25) reported that, in patients with lumbar spine vertebral end-plate abnormalities, FDG-PET was 100% sensitive and specific. MRI was 50% sensitive and 96% specific. In an investigation of patients with inconclusive conventional imaging sensitivity, specificity and accuracy of FDG-positron emission computed tomography/computed tomography (PET/CT) were 81.8%, 100%, 89.5%, respectively, versus 75%, 71.4%, and 74.1% respectively, for MRI (26). Fuster et al. (27) compared FDG-PET/CT and MRI. Sensitivity and specificity for FDG-PET/CT were 83% and 88%, respectively, versus 94% and 38%, respectively for MRI. In patients with brucellar spondylodiscitis, FDG PET/CT identified all foci of infection seen on MRI, revealed additional spinal lesions in 3 patients as well as new paravertebral soft tissue involvement and epidural masses. This additional information
influenced patient management (29). Nakahara et al. (30) reported that FDG-PET/CT was superior to MRI for localizing sites of infection and guiding minimally invasive surgery. 

FDG appears useful for monitoring treatment response in spondylodiscitis. Riccio et al. (31) reported that patients with poor treatment response had persistent bone and soft tissue FDG uptake. FDG uptake confined to the margins of a destroyed disc after treatment did not indicate infection. Successful treatment of brucellar spondylodiscitis was associated with a significant decrease in FDG uptake (29). Skanjeti et al. (28) reported that FDG-PET/CT was more accurate than MRI (90% versus 61.5%) for assessing treatment response.

There are some circumstances in which FDG may be less useful. Differentiating infection from tumor and infection superimposed on tumor may be problematic. Significant focal FDG uptake in degenerative spine disease occasionally occurs (3). Foreign body reaction around uninfected spinal implants may also cause increased uptake (Fig. 4) (32). Regardless, published data support FDG as the nuclear medicine test of choice for diagnosing spondylodiscitis, although more data are needed before concluding it should be the initial imaging test for this entity.

Data about $^{68}$Ga in spondylodiscitis are limited. Nanni et al. (33) reported that the test was 100% sensitive and 76% specific. False positive results were associated with tumor.

**Diabetic pedal osteomyelitis**

Diabetics can have a significant foot infection without systemic response, and the diagnosis of osteomyelitis often is overlooked (34). Labeled leukocyte imaging is the
radionuclide “gold standard” for diagnosing diabetic pedal osteomyelitis. Planar In-labeled leukocyte imaging sensitivity and specificity range from 72% -100% and from 67% - 100%, respectively. Planar Tc-labeled leukocyte imaging sensitivity and specificity range from 86% -93% and from 80% to 98%, respectively (3). Results using radiolabeled antigranulocyte antibodies and antibody fragments are similar (35-37).

SPECT/CT is useful in suspected pedal osteomyelitis (38-42). Heiba et al. (39) found simultaneous dual isotope In-labeled leukocyte/99mTc-MDP SPECT/CT and marrow imaging was significantly more accurate than planar imaging and single isotope SPECT/CT, facilitating precise labeled leukocyte localization and improving reader confidence. In another investigation dual isotope SPECT/CT was more accurate than conventional imaging for diagnosing and localizing infection, helped guide patient management and was associated with a shorter hospital stay (40).

Filippi et al. (41) reported that Tc-labeled leukocyte SPECT/CT changed study interpretation in more than half the cases, confirming or excluding osteomyelitis, and precisely defining the extent of infection (Fig. 5). Erdman et al. (42) developed the Composite Severity Index for Tc-labeled leukocyte SPECT/CT. The likelihood of a favorable outcome varied inversely with the Composite Severity Index score, which predicted outcome more accurately than classifying studies as positive or negative for osteomyelitis.

Vouillarmet et al. (43) used Tc-labeled leukocyte SPECT/CT to monitor treatment response in diabetics with pedal osteomyelitis. The test was negative in 22 patients and positive in seven patients, including five who subsequently relapsed. Sensitivity, specificity, positive predictive value and negative predictive value for osteomyelitis...
relapse were 100%, 91.5%, 71.5% and 100%. Lazaga et al. (44) reported that Tc-labeled leukocyte SPECT/CT was 90% sensitive and 56% specific for determining treatment response.

Although most investigations involve labeled leukocyte imaging, Aslangul et al. (45) reported $^{67}$Ga SPECT/CT was 88% sensitive and 93.6% specific for diabetic pedal osteomyelitis.

Several groups have investigated FDG in diabetic foot infections (46-53). Basu et al. (46) reported that FDG-PET was 94% accurate for differentiating osteomyelitis and soft tissue infection from the neuropathic joint. Nawaz et al. (47) reported that FDG-PET was 81% accurate for pedal osteomyelitis. Kagna et al. (49) reported that FDG-PET/CT was 96% accurate for pedal osteomyelitis.

Yang et al. (50) reported that FDG-PET was 93.8% accurate for pedal osteomyelitis. Sensitivity was nearly identical for patients with serum glucose levels above and below 150 mg/dL, 88.9% and 88.3% respectively. The investigators concluded that mildly to moderately elevated serum glucose levels do not adversely affect sensitivity.

Shagos et al. (51) reported that FDG-PET was more specific than bone scintigraphy for osteomyelitis, while bone scintigraphy was more sensitive than FDG-PET for the neuropathic joint. Schwegler at al. (52) reported that FDG-PET detected two of seven cases (29% sensitivity) of osteomyelitis. They speculated that low sensitivity may have been related to decreased inflammatory response in the study population and/or impaired bony uptake of FDG, because of insulin resistance. Motion artifacts and limited spatial resolution also may have contributed to low sensitivity.
Familiari et al. (53) compared FDG-PET/CT to planar Tc-labeled leukocyte imaging. FDG-PET/CT accuracy was 54%, improving to 62% when CT findings were included. Planar Tc-labeled leukocyte imaging accuracy was 92%.

The role of FDG for diagnosing diabetic pedal osteomyelitis is uncertain. Limitations of available data include varying methodology, different patient populations, inconsistent correlation with MRI, absence of a uniform truth standard and few comparative studies with labeled leukocyte imaging (54,55). Treglia et al. (55) in a meta-analysis, reported a sensitivity and specificity of 74% and 91% for FDG. They concluded that large multicenter studies using bone biopsy as the gold standard are warranted.

**Prosthetic Joint Infection**

Aseptic loosening, the most common cause of prosthetic joint failure, frequently results from an immune response by the patient’s body against one or more of the prosthetic components. The immune response can be accompanied by an intense inflammatory response involving large numbers of leukocytes. Aseptic loosening usually is managed with a single stage exchange arthroplasty requiring one hospital admission and surgical intervention (56).

Infection occurs in 1% to 2% of primary implants, and up to 5% of revision implants. Approximately one third of these infections develop within three months (early), another third within one year (delayed), and the remainder more than one year (late) after surgery (56). The inflammatory reaction accompanying infection can be similar to that in aseptic loosening, except that neutrophils, usually absent in aseptic
loosening, invariably are present in large numbers in infection. Treatment consists of excisional arthroplasty followed by antibiotics and, eventually, revision arthroplasty (56).

Differentiating aseptic loosening from infection, important because their treatments are very different, can be difficult. Signs of infection may be absent. Abnormal laboratory values are suggestive, but not diagnostic, of infection. Joint aspiration with culture is specific; sensitivity, however, is variable (56). Plain radiographs lack specificity. Hardware-induced artifacts limit, to some degree, cross sectional imaging.

Radionuclide imaging has a preeminent position in the evaluation of joint arthroplasty infection. The bone scan has an accuracy of 50%-70%, which does not improve when performed as a three-phase study (56). Combined bone $^{67}$Ga scintigraphy with accuracy of 60%-80%, offers only a modest improvement over bone scintigraphy alone (56). Labeled leukocyte/marrow imaging with an accuracy of about 90% currently is the best imaging test available. All the published studies confirm high specificity; nearly all also indicate high sensitivity (56).

Sensitivity and specificity of $^{99m}$Tc-besilesomab for joint replacement infection range from 67%-91% and 57%-75%, respectively. Complementary bone imaging and semiquantitative analysis improve accuracy (56).

Sensitivity and specificity of $^{99m}$Tc-sulesomab range from 75%-93% and 65% to 86%, respectively. Dual time point imaging, time activity curve analysis, and complementary marrow imaging improve accuracy (56).

Data on SPECT/CT in prosthetic joint infection are encouraging (57-62). Tam et al. (57) reported that the CT component of bone SPECT/CT identifies morphologic
abnormalities that correspond to areas of increased activity on radionuclide images. Joint distension, fluid-filled bursa and intramuscular fluid collections, findings that are sensitive and specific for infection can be identified on the CT component of the examination. Al-Habnani et al. (58) reported that bone SPECT/CT contributed useful information in more than 80% of patients with a painful knee arthroplasty. Filippi et al. (59) reported that Tc-labeled leukocyte imaging accuracy improved from 64% for scintigraphy with SPECT to 100% for SPECT/CT. SPECT/CT precisely localized labeled leukocyte accumulation, facilitating the differentiation of soft-tissue from bone infection. Kim et al. (60) reported sensitivity, specificity and accuracy of 82.0%, 88.0%, and 84.8%, respectively, for planar imaging. Sensitivity, specificity and accuracy increased to 93.3% with SPECT/CT. SPECT/CT precisely localized the site, and accurately delineated the extent, of infection (Fig. 6).

Graute et al. (62) reported sensitivity, specificity, and accuracy of 66%, 60%, and 61%, respectively, for 99mTc-besilesomab planar imaging. By adding SPECT/CT sensitivity, specificity, and accuracy improved to 77%, 89%, and 73%, respectively.

Results of FDG for diagnosing prosthetic joint infection have varied. Good results have been reported by some investigators. Zhuang et al. (63) reported that FDG-PET was 89.5% and 77.8% accurate for hip and knee arthroplasty infection, respectively. Correct diagnosis depended on location, not intensity, of uptake. Reinartz et al. (64) reported that FDG-PET was 95% accurate for hip arthroplasty infection. Basu et al. (65) reported sensitivity and specificity of 81.8% and 93.1% respectively, for hip arthroplasty infection and 94.7% and 88.2%, respectively, for knee arthroplasty infection. Other investigators report similar results (66-68). Some investigators report that FDG uptake around the
femoral head and neck is not specific for infection; others report that this pattern indicates
synovitis plus infection (56,69,70).

Results of other investigations have been less satisfactory (71-77). Van Acker et al. reported 100% sensitivity and 73% specificity for prosthetic knee infection (71). Stumpe et al. (73) reported that FDG-PET was 69% accurate for prosthetic hip infection. Stumpe et al. (74) observed that periprosthetic FDG accumulation around a knee arthroplasty is not specific for infection. Delank et al. (75) concluded that FDG-PET was not specific for lower extremity joint arthroplasty infection. Another group of investigators found that the test was neither sensitive (64%) nor specific (67%) for prosthetic hip infection (76). Love et al. (77) reported that FDG was 71% accurate for lower extremity prosthetic joint infection.

Comparative investigations of FDG and bone or labeled leukocyte imaging are contradictory. Some investigations indicate FDG is more accurate than bone scintigraphy; others suggest the opposite (64,71,73). Pill et al. (78) reported that FDG-PET was 95% sensitive and 93% specific for infection. In a subgroup, sensitivity and specificity of labeled leukocyte/marrow imaging were 50% and 95.1%, respectively. Love et al. (77) found labeled leukocyte/marrow imaging was more accurate than FDG (95% vs 71%). Basu et al. (65) compared FDG-PET to labeled leukocyte/marrow imaging in 88 lower extremity arthroplasties (59 hips, 29 knees). Although their specificities were very similar, FDG-PET was significantly more sensitive than labeled leukocyte/marrow imaging (76.9% versus 38.5%) for hip prosthesis infection. All three infected knee arthroplasties were positive on FDG-PET versus only one of three on labeled leukocyte/marrow imaging.
In a recent meta-analysis, the pooled sensitivity and specificity of FDG-PET & PET/CT for lower extremity prosthetic joint infection both were 86% (79).

The development of an infection specific imaging agent would be a substantial improvement over currently available radiopharmaceuticals. Aryana et al. (80) reported that $^{99m}$Tc-UBI 29-was 100% accurate for hip arthroplasty infection. Though encouraging, these results must be confirmed in larger series.
References


Fig. 1. Osteomyelitis cervical spine. On the sagittal CT image (A) there are destructive changes at the C6-C7 level (arrow) corresponding to an area of intense radiopharmaceutical uptake on the sagittal $^{67}$Ga SPECT image (B). (Reproduced with permission, reference #3)
Fig. 2. Infected right upper extremity hardware. Radiograph (A) demonstrates hardware in the distal right humerus. There is spatially incongruent distribution of activity (arrows) on the $^{111}$In-labeled leukocyte (B) and $^{99m}$Tc-sulfur colloid bone marrow (C) images.
Fig. 3. Bone marrow expansion. Irregularly increased activity in the left lower extremity activity on the $^{111}$In-labeled leukocyte image (A) from a patient with sickle cell disease could be interpreted as osteomyelitis. The distribution of activity on the $^{99m}$Tc sulfur colloid bone marrow image (B), however, is the same.
Fig. 4. Uninfected spinal hardware. FDG PET/CT “scout” x-ray (A) demonstrates lumbar spine hardware. Coronal FDG image (B) reveals normal lumbar spine activity. A normal FDG study effectively excludes infection.
Fig. 5. Soft tissue infection left foot. There is increased activity (arrow) underlying the left first metatarsal on the planar Tc-labeled leukocyte image. There is no way to determine if this focus extends into the bone. Coronal SPECT/CT localizes the infection to soft tissue. By precisely localizing areas of radiopharmaceutical uptake, SPECT/CT can guide patient management.
Fig. 6. Infected left hip arthroplasty. There is intense activity along the lateral aspect of the femoral component of the prosthesis (arrow) on the anterior $^{111}$In-labeled leukocyte image (A), with no corresponding activity on the $^{99m}$Tc sulfur colloid bone marrow image (B). The study confirms infection, but provides little information about the extent. On the sagittal (C) SPECT/CT image the infection extends anteriorly and posteriorly into the soft tissues surrounding the prosthesis (arrows). This information is useful for surgical planning.