IDSA — Infectious Diseases Society of America    hivma — hiv medicine association    OXFORD

# Using Nuclear Medicine Imaging Wisely in Diagnosing Infectious Diseases

Andrea Censullo[1] and Tara Vijayan,[2]

[1]Division of Infectious Diseases, Cedars-Sinai Medical Center, University of California, Los Angeles; [2]Division of Infectious Diseases, David Geffen School of Medicine, University of California, Los Angeles

In recent years, there has been an increasing emphasis on efficient and accurate diagnostic testing, exemplified by the American Board of Internal Medicine's "Choosing Wisely" campaign. Nuclear imaging studies can provide early and accurate diagnoses of many infectious disease syndromes, particularly in complex cases where the differential remains broad.

This review paper offers clinicians a rational, evidence-based guide to approaching nuclear medicine tests, using an example case of methicillin-sensitive *Staphylococcus aureus* (MSSA) bacteremia in a patient with multiple potential sources. Fluorodeoxyglucose-positron emission tomography (FDG-PET) with computed tomography (CT) and sulfur colloid imaging with tagged white blood cell (WBC) scanning offer the most promise in facilitating rapid and accurate diagnoses of endovascular graft infections, vertebral osteomyelitis (V-OM), diabetic foot infections, and prosthetic joint infections (PJIs). However, radiologists at different institutions may have varying degrees of expertise with these modalities.

*Regardless, infectious disease consultants would benefit from knowing what nuclear medicine tests to order when considering patients with complex infectious disease syndromes.*

**Keywords.** fever of unknown origin; nuclear medicine imaging; osteomyelitis; prosthetic joint infection; vascular graft infection.

A 66-year-old man was admitted to the hospital with fever. He had a past medical history significant for diabetes (complicated by peripheral neuropathy, Charcot foot, and nephropathy), an aortic aneurysm surgically repaired with an endovascular graft, a right total knee arthroplasty, and chronic low back pain attributed to degenerative disc disease of the lumbar spine. His exam was notable for a slightly swollen right knee without erythema or warmth and a deep nonpurulent ulcer on the plantar surface of his left foot, which did not probe to bone. He had slight paraspinal tenderness without vertebral tenderness on palpation of the lumbar spine. He was found to have methicillin-sensitive *Staphylococcus aureus* (MSSA) on multiple blood cultures. Transthoracic echocardiography and transesophageal echocardiography were negative for vegetations or valvular abnormalities. A plain radiograph of his left foot did not demonstrate bony erosions to suggest osteomyelitis. A magnetic resonance image (MRI) of the same foot showed

some mild soft tissue swelling and marrow edema, but the differential included osteomyelitis versus Charcot foot.

He was started on an oxacillin infusion. His blood cultures became negative after 3 days of therapy. Determining the source of this infection is necessary to guide decisions regarding further management. Diagnostic delays for some infections (such as endovascular graft infections) may have serious consequences. However, choosing diagnostic tests that will yield the most fruitful and timely results remain challenging.

Nuclear medicine imaging can be an excellent resource in trying to diagnose complicated infections such as the case presented here. In this review, we discuss the utility of different nuclear medicine imaging modalities for each of 5 common infectious disease syndromes.

## DIABETIC FOOT OSTEOMYELITIS

Although his clinical exam and imaging findings are equivocal given his underlying Charcot arthropathy, our patient is at significant risk of having diabetic foot osteomyelitis (DFO). Historically, a triple-phase bone scan with technetium-99m-labeled bisphosphonates ($^{99m}$Tc) was used to diagnose DFO, but this has been replaced by MRI as the preferred first imaging test. Bone scanning still may have a role in DFO, particularly when MRI is contraindicated (ie, metal implants, significant renal failure) or inconclusive [1]. The degree of radiopharmaceutical uptake in bone scans depends on blood flow and rate of new bone formation. Osteomyelitis will show focal hyperperfusion in phase 1 (arterial phase), soft tissue inflammation

in phase 2 (caused by increased vascular permeability or what is known as the blood pool phase), and focal bone localization in phase 3 (osteoblastic activity). A triple-phase bone scan can demonstrate the presence of OM within 2–3 days of the onset of infection, compared with a plain radiograph which can take 2–3 weeks [2].

Reported sensitivity of a bone scan ranges from 80% to 90%, but specificity is less than 50% because it cannot distinguish from other conditions such as Charcot arthropathy, bony metastasis, fracture, trauma, or recent surgery [3]. Given the poor specificity of the bone scan, labeled leukocytes (often referred to as a tagged WBC scan) can be paired with the bone scan, resulting in an improved specificity of 80%–90% [3].

To perform a WBC scan, a total WBC count of at least 2000 cells/μL is required [2]. Leukocytes are removed from the patient and tagged with a radioactive tracer, usually either $^{99m}$Tc or 111-indium. Next, the radiolabeled cells are re-infused into the patient where they then accumulate at a focus of inflammation or infection. Given its poor resolution, a tagged WBC scan alone cannot distinguish bone from soft tissue, so it must be combined with another study such as a bone scan to evaluate for OM. Other limitations of the tagged WBC scan include the time-consuming nature of the study, as well as the cost of tagging the WBCs, which can amount to over $1000 [3].

Over the years, studies have shown promising results for the diagnosis of musculoskeletal infections by combining $^{99m}$Tc-sulfur colloid imaging (referred to as marrow imaging) plus a tagged WBC scan [4, 5]. Although both the radiotracer $^{99m}$Tc-sulfur colloid and leukocytes travel to the bone marrow, $^{99m}$Tc-sulfur colloid does not accumulate in areas where the normal marrow has been replaced by infection. Therefore, in OM, one would expect to see accumulation of tagged WBC but no activity on the sulfur colloid marrow imaging [6]. This would be helpful in our patient with Charcot arthropathy and surrounding soft tissue infection, where both the bone scan and tagged WBC scan may yield an incorrectly positive result. A study in patients with Charcot arthropathy found that this combination was indeed superior to a triple-phase bone scan either alone or in combination with a tagged WBC scan for the diagnosis of DFO [4]. In a patient without Charcot foot, colloid imaging may not be required, and a triple-phase bone scan combined with a tagged WBC scan would be a good adjunct when MRI is contraindicated or inconclusive.

Single-photon emission CT (SPECT) is a nuclear medicine technique that can generate three-dimensional information and can be used with various radioisotopes. It is still being evaluated for its application in DFO. One recent study found similar sensitivity and specificity of $^{99m}$Tc-labeled WBC scan plus SPECT imaging compared with traditional MRI for the diagnosis of DFO [7].

A final modality that can be used for the diagnosis of DFO is PET, in which radioactive fluorine is attached to fluorodeoxyglucose ($^{18}$F-FDG). This radiotracer will accumulate in locations of increased glucose metabolism in infectious (ie, macrophages), inflammatory, and malignant processes [1, 3]. Clinical studies on F-FDG-PET comparing diabetic with nondiabetic patients have suggested no difference in accuracy, although one study demonstrated a decreased uptake of FDG in ovarian cancer cells grown in media containing 300 mg/dL glucose, suggesting an effect of acute hyperglycemia [8, 9].

A recent meta-analysis of 9 studies evaluating $^{18}$F-FDG-PET, either alone or combined with CT scanning, demonstrated a pooled sensitivity and specificity for diagnosing DFO of 74% and 91%, respectively [10]. However, there was a wide range of sensitivities, including 1 small study reporting low sensitivity (29%) in patients with diabetic foot ulcer without clinical signs of osteomyelitis (OM) who ultimately had biopsy-proven OM [10–12]. A major limitation of this meta-analysis was the wide variation in the gold standard used. Most studies used only clinical monitoring as the gold standard, and only a minority used bone biopsy [10]. A large multicenter study using bone biopsy as the gold standard would help clarify the accuracy of $^{18}$F-FDG-PET imaging in diabetic foot infections.

## VERTEBRAL OSTEOMYELITIS

A spinal or paraspinal infection is also a concern in this patient with back pain and high-grade bacteremia. Although MRIs are quite reliable for the diagnosis of epidural abscesses, there may be clinical situations in which an MRI can give misleading results for the diagnosis of vertebral osteomyelitis (V-OM) (Figure 1). Degenerative disc disease can sometimes be mistaken for infectious endplate abnormalities on MRI (resulting in a false positive). Similarly, MRIs may on occasion miss the diagnosis of V-OM [13]. Clinical features such as the presence or absence of fever or leukocytosis combined with MRI results often will lead to the correct diagnosis, but if the clinical suspicion is high and MRI features are not definitive, or if MRI is contraindicated in situations such as in the presence of some pacemakers or severe renal insufficiency, nuclear medicine studies may be considered as an alternative diagnostic modality.

In contrast to the good sensitivity in diagnosing DFO, a triple-phase bone scan is neither sensitive nor specific for V-OM (Figure 1). False negatives have been reported in the elderly, and although the exact mechanism is unknown, it has been postulated to be from atherosclerosis-induced ischemia. Another major limitation is that bony remodeling may persist for months after an inflammatory or infectious event, leading to false positive results on bone scan. Therefore, bone scanning should not be the only radionuclide modality used in V-OM. A bone scan can be combined with a Gallium – 67 scan to improve the specificity for the diagnosis of V-OM [6] (Figure 1).

Tagged WBC scans are not helpful for diagnosing V-OM. For unknown reasons, V-OM may demonstrate "decreased" uptake (photopenia) on tagged WBC scans compared with
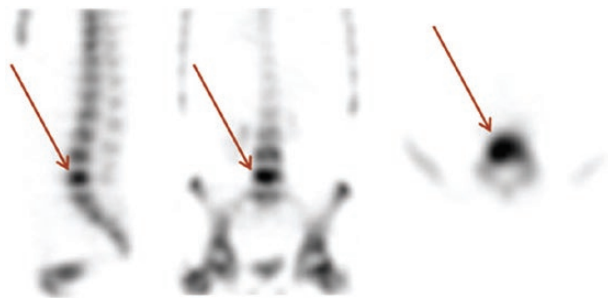
**Figure 1.** 99mTc-hydroxymethylene diphosphonate bone SPECT scan of patient with osteomyslitis of fifth lumbar vertebra (arrows). This research was original published in JNMT. Martin Gotthardt et al. J. Nucl. Med. Technol. 2013; 41:157–69. ©by the Society of Nuclear Medicine and Molecular Imaging, Inc.

healthy bone, but this finding is not specific for infection and can occur with tumor, infarction, Paget's disease, or even previously treated OM. On the other hand, if uptake is increased, it is virtually diagnostic of V-OM, but this occurs in less than 50% of proven V-OM [14].

Gallium ($^{67}$Ga) scintigraphy used with planar or SPECT with CT imaging can be used adjunctively for the diagnosis of V-OM (Figure 1). Gallium does not need to be attached to leukocytes, as is the case with technetium, because gallium has a unique mechanism of uptake at sites of inflammation. Gallium binds transferrin and is extravasated at sites of inflammation due to increased vascular permeability. It then binds lactoferrin, which is secreted by leukocytes at sites of inflammation [15]. There can be increased uptake in trauma and tumors, limiting the specificity. In addition, there is a delay between injection of the radiotracer and the imaging test (up to 3 days) [6, 16].

Indium-111 biotin scintigraphy ($^{111}$indium-biotin) is a newer method that may become a useful diagnostic test for V-OM in the future. However, $^{111}$indium-biotin currently is not commercially available. Unlike gallium tracers, it does not accumulate in the normal bone or bone marrow, and it is postulated to be more specific for bacterial infection because biotin seems to be passively transported into bacteria [17]. Single-photon emission CT/CT can be combined with the $^{111}$indium-biotin scintigraphy to improve anatomic localization as well as to help differentiate soft tissue infection from bone infection. By using SPECT/CT with $^{111}$indium-biotin, one study demonstrated a sensitivity and specificity of 92% in diagnosing V-OM [17].

The $^{18}$F-FDG-PET is the nuclear medicine technique most strongly supported by the literature for the diagnosis of V-OM. It can be especially helpful if the MRI is indeterminate due to degenerative disc disease. One study evaluated $^{18}$F-FDG-PET in 30 patients with vertebral endplate abnormalities on MRI and found that $^{18}$F-FDG-PET was 100% sensitive and specific for V-OM, and it was excellent at differentiating infection from degenerative changes [13]. Another prospective study evaluated the use of $^{18}$F-FDG-PET with the addition of CT scanning and demonstrated a sensitivity of 89%, specificity of 88%, and overall accuracy of 88% for diagnosing V-OM [18].

One advantage of $^{18}$F-FDG-PET scans is that they normalize within 3–4 months after trauma or surgery. Foreign implants (within 1 year of implantation) and malignancy can demonstrate increased uptake, limiting the specificity in those cases [6].

## PROSTHETIC JOINT INFECTIONS

The definitive diagnostic test for PJIs are a cell count and culture obtained from synovial fluid via a joint aspiration. The decision to perform a joint aspiration in the setting of known hardware is complicated by the small risk of introducing bacteria to the joint space. In theory, a good clinical exam and history, as well as nonspecific laboratory findings such as an elevated C-reactive protein, will guide this decision, but certain imaging studies may provide additional evidence. Plain radiographs are of course the simplest and easiest study and may demonstrate joint space widening, radiolucency, migration, and osteolysis, but such findings can indicate an aseptic process as well. Moreover, x-rays are less sensitive in early-onset infections [19].

Magnetic resonance images are the preferred technique for most bone and joint infections, but the presence of hardware may result in artifact abnormalities. Recent metal suppression techniques such as multiacquisition with variable-resonance image combination or slice encoding for metal artifact correction have been used by specific producers of MRI machines and have greatly reduced the artifact abnormalities seen with older MRI machines, allowing for greater resolution and improved diagnosis of hardware failure with or without infection [20, 21]. However, not all imaging centers and hospitals have adopted such techniques, and nuclear medicine modalities may provide an option that is equally or more accurate.

The preferred nuclear medicine study for PJIs is the tagged WBC bone marrow scintigraphy with sulfur colloid, which has a reported accuracy of 86%–98% [19]. The most common radiotracer used in these studies is indium-111. As mentioned above, a positive result occurs when the signals conferred by the tagged WBCs and the sulfur colloid are discordant, because infections will suppress the uptake of sulfur colloid [22]. The data on $^{18}$F-FDG-PET/CT have been mixed and are not useful within the first year of implantation, because postoperative inflammation will result in false-positive results [19].

## ENDOVASCULAR GRAFT INFECTIONS

Perhaps one of the more pressing diagnoses to exclude in our patient is the possibility of an endovascular graft infection. Endovascular graft infections are difficult to manage medically and almost always necessitate surgical intervention. If surgical intervention is not a possibility, chronic suppression with antimicrobials is a second-line option. Given the morbidity of the

**Table 1. Overview of Nuclear Medicine Studies and Clinical Applications**

| Modality | Mechanism | Attributes | Applications |
|---|---|---|---|
| Tagged WBC | WBCs are separated from blood and tagged with indium or technetium | Cost of tagging WBCs is high (>$1000) but typically covered by insurance companies if infection is an indication. Requires at least 2 days (harvest of WBC then infusion). May be best used when paired with other modalities | DFO VGI PJI (with sulfur colloid scintigraphy or bone marrow scintigraphy |
| Positron emission tomography (PET) | Gamma cameras detect positron emitting radioisotope ($^{18}$F) and create 3D images. Metabolic and functional information F-FDG (glucose) | Cost of FDG is low (>$100) but currently not covered by insurance companies for infection Fair spatial resolution (3–5 mm). Good contrast resolution. Moderate radiation, depending on radiotracer, but high radiation when combined with CT | DFO- limited V-OM VGI FUO Can be combined with CT for better spatial resolution |
| Single-photon emission tomography (SPECT) | Gamma cameras detect gamma emitting radioisotope and create 3D images. Metabolic and functional information | Less expensive than PET Limited spatial resolution compared with PET (8-10mm) Good contrast resolution Low radiation exposure, depending on radio-tracer, but high radiation when combined with CT | Coronary artery disease V-OM Possible utility in DFO (over PET due to cost and no need for FDG). Needs to be combined with CT for spatial resolution |
| Scintigraphy (planar) • Gallium • Technetium-99m • Indium-biotin | Gamma cameras detect radioisotope and create 2D images. Bone scintigraphy is also known as bone scan | Often paired with other imaging modalities to improve test characteristics, ie, triple phase bone scan. High radiation exposure with Gallium. Indium-biotin maybe more specific for infection | DFO V-OM (Ga) FUO (if PET/CT unavailable) |

Abbreviations: CT, computed tomography; DFO, diabetic foot osteomyelitis; FDG, fluorodeoxyglucose; FUO, fever of unknown origin; Ga, gallium; OM, osteomyelitis; PJI, prosthetic joint infections; VGI, vascular graft infections; V-OM, vertebral osteomyelitis; WBC, white blood cells; 3D, 3 dimensional.

disease as well as the morbidity of the intervention, establishing an accurate diagnosis is imperative.

The gold standard in diagnosing mycotic aneurysms has been CT angiography (CTA). However, the test characteristics of CTAs in diagnosing endovascular graft infections, particularly soon after surgery, are poor. Although air bubbles around the site of the graft may suggest infection, 50% of CTAs will have this finding for weeks to months after surgery. Hematomas and lymphoceles may also reduce the specificity of CT scans, and the sensitivity is particularly poor in low-grade infections [1]. Tagged white blood scans have been evaluated as a diagnostic method with sensitivities ranging from 50% to 100% [23, 24]. However, the limited spatial resolution of tagged WBCs may decrease its sensitivity for low-grade infections considerably.

The $^{18}$F-FDG-PET/CT demonstrates excellent test characteristics, with both a sensitivity and specificity of over 90%,
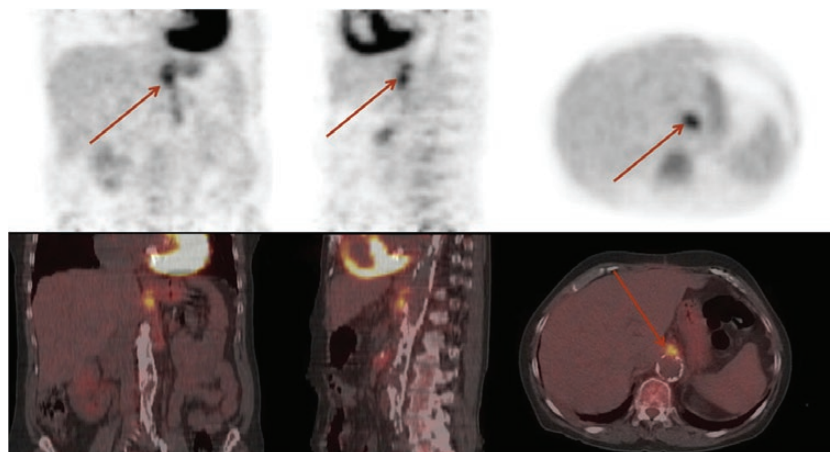


**Figure 2.** $^{18}$F-FDG PET/CT scan of patient with provend *Escherichia coli* infection of vascular graft. This research was original published in JNMT. Martin Gotthardt et al. J. Nucl. Med. Technol. 2013; 41:157–69. ©by the Society of Nuclear Medicine and Molecular Imaging, Inc.

provided that strict interpretation criteria are used (Figure 2) [25]. There may be chronic aseptic inflammation around the synthetic graft material that results in mild to moderate uptake, but a focal area of abnormal uptake will improve the specificity and positive predictive value. In one study, focally intense lesions on PET combined with an irregular boundary noted on CT predicted 97% of prosthetic graft infections [26].

The degree of FDG avidity may predict infection to some extent. For example, mycotic aneurysms alone are in general more FDG avid (greater than 4.5 standardized uptake values) than uninfected aneurysms [27]. Specific cutoff criteria have not been evaluated for endovascular graft infections, and this is an area that merits further research.

## FEVER OF UNKNOWN ORIGIN

Our patient does not meet criteria for fever of unknown origin (FUO) because he has positive blood cultures, but there may be some parallels with the workup of FUO given the unclear source of the bacteremia. This section will review the utility of various nuclear medicine studies for the evaluation of an FUO.

There are many published diagnostic algorithms for FUO, many of which include nuclear medicine tests [28]. Nuclear medicine imaging tests may be particularly well suited for imaging in FUO because they can image the entire body at once. Most modalities can identify infections, malignancies, and inflammatory states such as large vessel vasculitides, which together comprise the majority of FUO etiologies. Furthermore, because nuclear medicine tests often detect functional and metabolic changes, they may become positive early in the course of a disease before morphologic changes take place and can be detected on conventional imaging such as plain radiography or CT [29].

Two-dimensional gallium scintigraphy was previously considered the nuclear medicine test of choice for FUO.

However, it is time consuming and exposes the patient to a large amount of radiation. It has largely been replaced by $^{18}$F-FDG-PET scanning because of the higher sensitivity and specificity compared with a gallium scan, in addition to the better spatial resolution [30].

A major limitation is that $^{18}$F-FDG has physiologic uptake in the brain, heart, bowel, urinary tract, and even occasionally in the bone marrow, limiting its usefulness in these areas [1]. The $^{18}$F-FDG-PET may be even more useful if combined with CT to allow better anatomic localization. One study retrospectively evaluated 112 patients with FUO who underwent $^{18}$F-FDG PET/CT and found that $^{18}$F-FDG-PET/CT contributed to the diagnosis 66% of the time, and a final diagnosis was made in 74% of the patients [29]. Other studies have shown that FDG-PET/CT contributed to the diagnosis of FUO 46%–90% of the time, more often than other modalities [29, 31, 32].

The $^{18}$F-FDG-PET/CT scanning has also been shown to be very helpful in finding sites of metastatic infections during Gram-positive bacteremia, as in our patient, and has been suggested as a diagnostic tool in all patients with high-risk Gram-positive bacteremia as well as those at risk for disseminated infection [1].

Tagged WBC scanning may not be helpful in cases of FUO because the leukocytes that are labeled are neutrophils, which mainly accumulate in foci of bacterial infections; typical bacterial infections make up a minority of causes of FUO (15%–40%) [1]. The sensitivity and specificity of tagged WBC reported in the literature varies widely from 60% to 100% and 33% to 92%, respectively [33].

If there is strong suspicion for a bacterial infection, a tagged WBC scan may be helpful. A tagged WBC scan can be done with various radiotracers including indium or technetium, and each has different properties; often the decision of which radiotracer
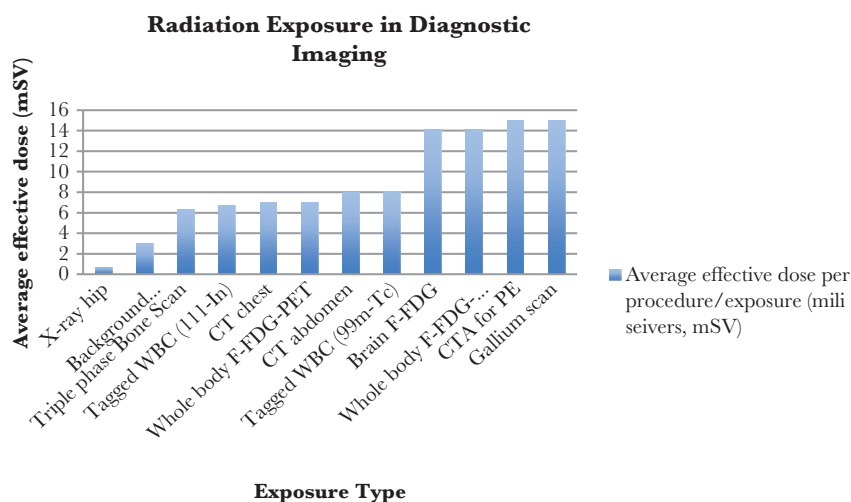


**Figure 3.** Radiation exposure of various imaging modalitites (computed tomography [CT] vs nuclear medicine). CTA, CT angiography; F-FDG-PET, fluorodeoxyglucose-positron emission tomography; PE, pulmonary embolism; WBC, white blood cells.

to use will be made in conjunction with a radiologist. The physiologic distribution of indium-111 is limited to the liver, spleen, and bone marrow, whereas $^{99m}$Tc has physiologic uptake in the urinary tract, large bowel, and occasionally gallbladder. The presence of physiologic uptake may make the utility for diagnosing infection in these areas less ideal. A scan using $^{99m}$Tc is faster, requiring only several hours after the reinfusion of WBC into the patient compared with up to 30 hours using indium-111.

## CONCLUSIONS

There are a variety of nuclear medicine techniques available to complement traditional imaging and assist with the diagnostic workup of complicated infectious disease syndromes such as the case presented in this review (Table 1). For this gentleman with multiple potential infectious etiologies of his fever and sources of his MSSA bacteremia, a tagged WBC scan would be a good first diagnostic test, but the limited resolution may make it difficult to diagnose endovascular infections, which arguably is the more pressing diagnosis to make. A tagged WBC scan combined with a sulfur colloid bone marrow imaging may help distinguish his DFO from Charcot, as well as determining his likelihood of a PJI, because both may have implications for treatment duration or the need for further surgical management. However, if the tagged scan is negative, we would recommend trying to obtain an $^{18}$F-FDG-PET/CT quickly to assess for the presence of an endovascular infection.

Like any other diagnostic test, false positives can occur in many conditions such as trauma, autoimmune diseases, or malignancy, and nuclear medicine imaging should always be interpreted in the appropriate clinical context. Other infection-specific nuclear medicine modalities, such as radiopharmaceutical-labeled antibacterials, antimycobacterial drugs, antifungal drugs, and even antimicrobial peptides, are currently under investigation and may at some point offer even greater accuracy [34]. Early studies are promising, but more research is needed, including cost-benefit analyses, before they will be routinely available.

A discussion about radiographic imaging techniques is incomplete without a brief mention of the relative radiation exposure of different modalities (Figure 3). In general, the level of radiation exposure conferred by nuclear medicine techniques is similar to that of CT scans, with a range of 2–15 milliSieverts (mSv). The International Commission on Radiologic Protection recommends limiting artificial radiation to no more than 50 mSv a year. All of the modalities discussed in this paper have radiation doses ranging from 6 to 15 mSv, $^{18}$F-FDG-PET and gallium scintigraphy have the highest levels of radiation with 14 and 15mSv, respectively, comparable to a CT done to rule out pulmonary embolism (15 mSv) or a coronary angiography (16 mSv) [35].

Lastly, addressing the issue of the cost of nuclear medicine imaging is important and complex. Different institutions carry different insurance payment structures that may preclude its use in the inpatient setting, where nuclear medicine studies are more often needed. The Centers for Medicare and Medicaid Services has not approved coverage for PET CTs for the indication of diagnosing infectious diseases [36]. Estimated individual out-of-pocket expenses for PET CT scans are approximately $7000 [37], which make it cost prohibitive for most patients. Further research is needed to address the cost-benefit ratio to make such studies more accessible.

In conclusion, when MRIs or CTs are inconclusive or contraindicated, $^{18}$F-FDG PET/CT, with its excellent test characteristics and anatomic localization, appears to be an excellent imaging modality that can be used to include or exclude many infectious disease syndromes. Early prosthetic joint or diabetic foot infections may be better diagnosed with tagged WBC scan with sulfur colloid imaging. In our experience, different centers have different comfort levels and expertise in using these various imaging modalities for the purpose of diagnosing infections. Additional research is also needed to create more "standardized" algorithms for using nuclear medicine imaging studies in the diagnosis of infectious diseases.

## References

1. Gotthardt M, Bleeker-Rovers CP, Boerman OC, Oyen WJ. Imaging of inflammation by PET, conventional scintigraphy, and other imaging techniques. J Nucl Med Technol **2013**; 41:157–69.
2. Dinh MT, Abad CL, Safdar N. Diagnostic accuracy of the physical examination and imaging tests for osteomyelitis underlying diabetic foot ulcers: meta-analysis. Clin Infect Dis **2008**; 47:519–27.
3. Malhotra R, Chan CS, Nather A. Osteomyelitis in the diabetic foot. Diabet Foot Ankle **2014**; 5.
4. Palestro CJ, Mehta HH, Patel M, et al. Marrow versus infection in the Charcot joint: indium-111 leukocyte and technetium-99m sulfur colloid scintigraphy. J Nucl Med **1998**; 39:346–50.
5. Palestro CJ, Roumanas P, Swyer AJ, et al. Diagnosis of musculoskeletal infection using combined In-111 labeled leukocyte and Tc-99m SC marrow imaging. Clin Nucl Med **1992**; 17:269–73.
6. Palestro CJ. Radionuclide imaging of osteomyelitis. Semin Nucl Med **2015**; 45:32–46.
7. La Fontaine J, Bhavan K, Lam K, et al. Comparison between Tc-99m WBC SPECT/CT and MRI for the diagnosis of biopsy-proven diabetic foot osteomyelitis. Wounds **2016**; 28:271–8.
8. Torizuka T, Clavo AC, Wahl RL. Effect of hyperglycemia on in vitro tumor uptake of tritiated FDG, thymidine, L-methionine and L-leucine. J Nucl Med **1997**; 38:382–6.
9. Yang H, Zhuang H, Rubello D, Alavi A. Mild-to-moderate hyperglycemia will not decrease the sensitivity of 18F-FDG PET imaging in the detection of pedal osteomyelitis in diabetic patients. Nucl Med Commun **2016**; 37:259–62.
10. Treglia G, Sadeghi R, Annunziata S, et al. Diagnostic performance of fluorine-18-fluorodeoxyglucose positron emission tomography for the diagnosis of osteomyelitis related to diabetic foot: a systematic review and a meta-analysis. Foot (Edinb) **2013**; 23:140–8.
11. Haroon A, Zumla A, Bomanji J. Role of fluorine 18 fluorodeoxyglucose positron emission tomography-computed tomography in focal and generalized infectious and inflammatory disorders. Clin Infect Dis **2012**; 54:1333–41.
12. Schwegler B, Stumpe KD, Weishaupt D, et al. Unsuspected osteomyelitis is frequent in persistent diabetic foot ulcer and better diagnosed by MRI than by 18F-FDG PET or 99mTc-MOAB. J Intern Med **2008**; 263:99–106.

13. Stumpe KD, Zanetti M, Weishaupt D, et al. FDG positron emission tomography for differentiation of degenerative and infectious endplate abnormalities in the lumbar spine detected on MR imaging. AJR Am J Roentgenol **2002**; 179:1151–7.

14. Palestro CJ, Love C, Bhargava KK. Labeled leukocyte imaging: current status and future directions. Q J Nucl Med Mol Imaging **2009**; 53:105–23.

15. Becker W, Meller J. The role of nuclear medicine in infection and inflammation. Lancet Infect Dis **2001**; 1:326–33.

16. Love C, Palestro CJ. Nuclear medicine imaging of bone infections. Clin Radiol **2016**; 71:632–46.

17. Lazzeri E, Erba P, Perri M, et al. Scintigraphic imaging of vertebral osteomyelitis with 111in-biotin. Spine (Phila Pa 1976) **2008**; 33:E198–204.

18. Fuster D, Solà O, Soriano A, et al. A prospective study comparing whole-body FDG PET/CT to combined planar bone scan with 67Ga SPECT/CT in the diagnosis of spondylodiskitis. Clin Nucl Med **2012**; 37:827–32.

19. Gemmel F, Van den Wyngaert H, Love C, et al. Prosthetic joint infections: radionuclide state-of-the-art imaging. Eur J Nucl Med Mol Imaging **2012**; 39:892–909.

20. Talbot BS, Weinberg EP. MR imaging with metal-suppression sequences for evaluation of total joint arthroplasty. Radiographics **2016**; 36:209–25.

21. Koff MF, Shah P, Potter HG. Clinical implementation of MRI of joint arthroplasty. AJR Am J Roentgenol **2014**; 203:154–61.

22. Love C, Tomas MB, Marwin SE, et al. Role of nuclear medicine in diagnosis of the infected joint replacement. Radiographics **2001**; 21:1229–38.

23. Fiorani P, Speziale F, Rizzo L, et al. Detection of aortic graft infection with leukocytes labeled with technetium 99m-hexametazime. J Vasc Surg **1993**; 17:87–95.

24. Speziale F, Calisti A, Zaccagnini D, et al. The value of technetium-99m HMPAO leukocyte scintigraphy in infectious abdominal aortic aneurysm stent graft complications. J Vasc Surg **2002**; 35:1306–7.

25. Fukuchi K, Ishida Y, Higashi M, et al. Detection of aortic graft infection by fluorodeoxyglucose positron emission tomography: comparison with computed tomographic findings. J Vasc Surg **2005**; 42:919–25.

26. Spacek M, Belohlavek O, Votrubova J, et al. Diagnostics of "non-acute" vascular prosthesis infection using 18F-FDG PET/CT: our experience with 96 prostheses. Eur J Nucl Med Mol Imaging **2009**; 36:850–8.

27. Deipolyi AR, Rho J, Khademhosseini A, Oklu R. Diagnosis and management of mycotic aneurysms. Clin Imaging **2016**; 40:256–62.

28. Bleeker-Rovers CP, Vos FJ, Mudde AH, et al. A prospective multi-centre study of the value of FDG-PET as part of a structured diagnostic protocol in patients with fever of unknown origin. Eur J Nucl Med Mol Imaging **2007**; 34:694–703.

29. Gafter-Gvili A, Raibman S, Grossman A, et al. [18F]FDG-PET/CT for the diagnosis of patients with fever of unknown origin. QJM **2015**; 108:289–98.

30. Meller J, Altenvoerde G, Munzel U, et al. Fever of unknown origin: prospective comparison of [18F]FDG imaging with a double-head coincidence camera and gallium-67 citrate SPET. Eur J Nucl Med **2000**; 27:1617–25.

31. Kim YJ, Kim SI, Hong KW, Kang MW. Diagnostic value of 18F-FDG PET/CT in patients with fever of unknown origin. Intern Med J **2012**; 42:834–7.

32. Kouijzer IJ, Bleeker-Rovers CP, Oyen WJ. FDG-PET in fever of unknown origin. Semin Nucl Med **2013**; 43:333–9.

33. Lewis SS, Cox GM, Stout JE. Clinical utility of indium 111-labeled white blood cell scintigraphy for evaluation of suspected infection. Open Forum Infect Dis **2014**; 1:ofu089.

34. Akhtar MS, Imran MB, Nadeem MA, Shahid A. Antimicrobial peptides as infection imaging agents: better than radiolabeled antibiotics. Int J Pept **2012**; 2012:965238.

35. Mettler FA Jr, Huda W, Yoshizumi TT, Mahesh M. Effective doses in radiology and diagnostic nuclear medicine: a catalog. Radiology **2008**; 248:254–63.

36. CMS. Center for Medicare and Medicaid Services: Medicare Coverage Database. **2016;** Available at: https://www.cms.gov/medicare-coverage-database. Accessed 22 February 2017.

37. Choosing Wisely. PET scans after cancer treatment.2012; Available at: http://www.choosingwisely.org/patient-resources/pet-scans-after-cancer-treatment/. Accessed 22 February 2017.