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Molecular Imaging of Infection

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Abstract: Molecular imaging of infection has been part of diagnostic imaging since the early days of radiopharmaceuticals. This chapter discusses the properties of diagnostic radiopharmaceuticals ^{67}Ga-citrate, ^{111}In- and ^{99m}Tc-labeled leukocytes and ^{18}F-FDG, along with when they are best deployed. Imaging of infection is best performed with ^{18}F-FDG for the majority of indications. This chapter explores the currently available means of diagnosis and best practices.

Keywords: ^{111}In-oxine labeled leukocytes; ^{67}Ga-citrate; ^{99m}Tc-methylenediphosphonate; ^{99m}Tc-sulfur colloid; molecular imaging of infection

INTRODUCTION

Nuclear medicine plays a crucial role in the diagnosis of infections (1, 2). Initially, Gallium-67 citrate served as one of the pioneering radioactive materials for detecting and pinpointing infections within the body. The innovation of techniques for labeling white blood cells (leukocytes) and tracking their movement to infection sites marked a significant leap forward in this field. While Fluorodeoxyglucose (18F-FDG) has proven highly effective in identifying infections, its lack of specificity is a limitation; it also accumulates in tumors and areas of non-infectious inflammation. In response,

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extensive research has been undertaken to create Positron Emission Tomography (PET) radiopharmaceuticals that are more selective than 18F-FDG for diagnosing infections. This chapter offers an overview of various radiotracers and their evolving role in infection diagnosis (Table 1).

^{67}Ga-CITRATE

The mechanism of localization of ^{67}Ga-citrate is not well understood but has been postulated to reflect iron metabolism. ^{67}Ga-citrate has a half-life of 78 hours, is cyclotron produced, and decays by electron capture, with the critical organ being the colon. Its photopeaks are 93, 185, 300 and 394 keV. Given the long half-life, this agent is not recommended for pediatric patients. Historically, ^{67}Ga-citrate has been used for the imaging of lymphoma, which occasionally helps in the incidental detection of other tumors. In the past, ^{67}Ga-citrate was the preferred agent for the study of sarcoidosis, which is now better evaluated with ^{18}F-fluorodexyglucose (^{18}F-FDG) positron emission tomography (PET). In addition, ^{67}Ga-citrate could be used in the setting of vertebral osteomyelitis since it has better overall performance, however, ^{67}Ga-citrate is falling out of favor due to its long half-life, relatively high radiation dose, and unfavorable imaging characteristics (1, 2). Figure 1 shows normal biodistribution of ^{67}Ga-citrate.

^{111}In-OXINE LABELED LEUKOCYTES

This radiopharmaceutical requires the patient's own blood for labeling of autologous leukocytes. Following labeling, care must be taken to ensure that the same patient receives its own labeled leukocytes. This can be a challenge, especially if more than one patient is being evaluated with labeled leukocytes on the same day. The mechanism of localization is direct visualization of the infectious process due to accumulation of radiolabeled leukocytes. ^{111}In has a 67-hour half-life, is cyclotron produced, and decays via electron capture. The photopeaks are 173 keV and 247 keV. Patients need to have adequate blood counts for appropriate labeling, with a minimum of 4,000 white blood cells. To label the leukocytes, about 20 mL of blood is withdrawn and is usually sent to a central radiopharmacy for radiolabeling, then returned the same day for injection. The normal biodistribution of ^{111}In-oxine -labeled leukocytes is shown in Figure 2. Importantly, ^{111}In-oxine labeled leukocytes do not have normal activity in the urinary tract or gastrointestinal tract, so if infection is suspected in the abdomen, this would be the labeled leukocyte of choice (2). Labeled leukocytes can also be used in applications such as the diabetic foot and Charcot joint to evaluate infection, along with additional or potentially concomitant dual isotope imaging (if performed with ^{111}In-oxine labeled leukocytes) with ^{99m}Tc-sulfur colloid bone marrow imaging. This has a sensitivity and specificity rivaling that of magnetic resonance imaging (MRI). MRI often is difficult to interpret in the setting of diabetic foot and Charcot joint infections. Labeled leukocytes are poor at detecting vertebral osteomyelitis (3) and somewhat less poor at detecting etiologies of fever of unknown origin (4–6). FDG PET/CT outperforms in this setting.

TABLE 1 **Radiopharmaceuticals and properties (modified from Sethi, et al. Am J Roentgenol. 2019; 213:300-308.) (2)**

Agent	Physical half-life	Administered Activity	Photon Energy (% abundance)	Mechanism of localization	Important consideration(s)
^{67}Ga-citrate	78 hours		93 keV (41%)		
^{99m}Tc-MDP	6 hours	13-30 mCi (481-1110 MBq)	140 keV (99%) 185 keV (23%) 300 keV (18%) 394 keV (4%)	Localized to hydroxyapatite matrix in areas of increased bony turnover, including infection	Non-specific
^{111}In-WBC	67 hours	0.3-0.5 mCi (11.1-18.5 MBq)	174 keV (90%) 247 keV (94%)	Direct imaging of WBC/ infectious area	Higher radiation dose, generally avoided in pediatric patients; poor photon characteristics; need to wait longer to image; need at least 4k WBCs; limited administered activity makes images noisy; expensive radionuclide
^{99m}Tc-Sulfur Colloid	6 hours		140 keV (99%)	Bone marrow imaging	Used to augment imaging in the setting of orthopedic hardware or diabetic foot infection
^{99m}Tc-WBC	6 hours	5-10 mCi (185-370 MBq)	140 keV (99%)	Direct imaging of WBC/infectious area	Better radiation dose; early imaging possible; better imaging characteristics; need at least 4k WBCs
^{18}F-FDG	110 min	10-20 mCi (370-740 MBq)	511 keV	Metabolic trapping	Fastest of the nuclear methods for infection. Non-specific: can image infection, inflammation and malignant processes

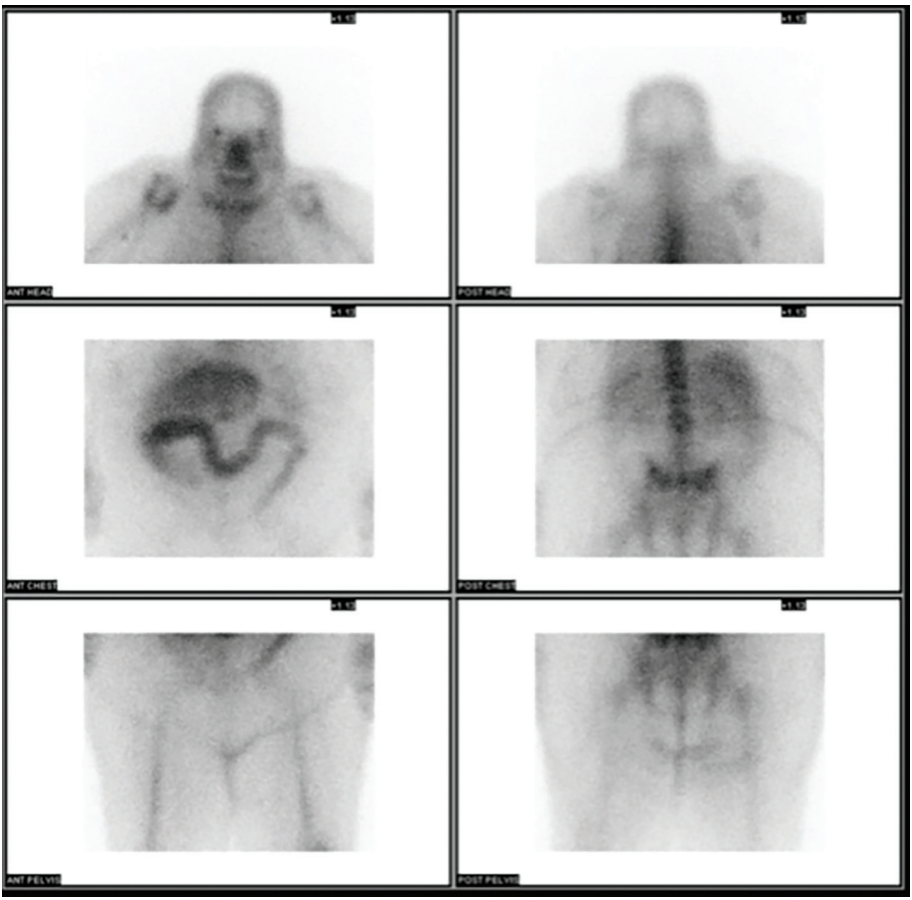

Figure 1 Normal distribution of ^{67}Ga-citrate. Anterior and posterior planar images of the head, neck, chest, abdomen, pelvis and proximal lower extremities demonstrate normal biodistribution of ^{67}Ga-citrate.

^{99m}Tc-HMPAO-LABELED LEUKOCYTES

This radiopharmaceutical also requires the patient's own blood for labeling of autologous leukocytes with similar requirements for number of leukocytes and labeling process as ^{111}In-Oxine labeled leukocytes. Similar care with delivery of the labeled leukocytes to the correct patient should be employed. ^{99m}Tc has a half-life of 6 hours and a photopeak of 140 keV, decaying by isomeric transition (7). ^{99m}Tc-HMPAO-labeled leukocytes will have normal activity in the bowel and urinary tract. Normal biodistribution is shown in Figure 2.

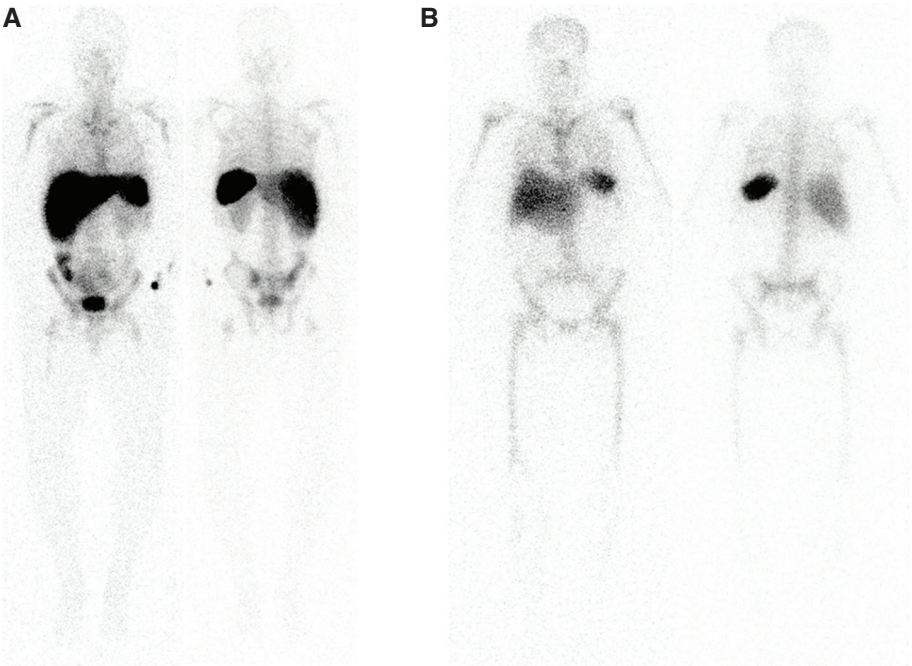

Figure 2 **Normal biodistribution of radiolabeled leukocytes. A.** ^{99m}Tc-HMPAO labeled leukocytes, and **B.** ^{111}In-oxine labeled leukocytes. Note the lack of GI tract and urinary tract activity on the ^{111}In-oxine labeled leukocytes.

^{99}MTC-SULFUR COLLOID

When injected intravenously, the ^{99m}Tc-sulfur colloid goes to the reticuloendothelial system: bone marrow, liver, and spleen. This agent is often used for further evaluation in the context of labeled leukocyte imaging if patients have surgical hardware in the bone or for further evaluation in the setting of diabetic foot infections when osteomyelitis is suspected. If labeled leukocytes are present in an area of uptake seen with bone marrow imaging (so-called matched findings), this does not represent infection, rather it represents reactive bone marrow. On the contrary, if there is an area of labeled leukocyte uptake without bone marrow uptake, this is highly specific for infection. This technique is extremely helpful in the setting of Charcot joint infection, or diabetic foot infection as well as orthopedic hardware infection (8, 9).

^{99}mTc-METHYLENEDIPHOSPHONATE (MDP)

This radiopharmaceutical accumulates at sites of increased bone turnover which could be related to infection as well as non-infectious etiologies associated with increased bone turnover such as trauma or osteoblastic metastatic disease. Patients should be well hydrated prior to imaging. Bone scans with ^{99m}Tc-MDP can be used with a three-phase technique to diagnose osteomyelitis. The three phases are 'blood flow' or angiographic phase imaging which is performed dynamically at the time of injection during short frame acquisition. This focus is on one region of interest. The second phase is the 'blood pool' or soft tissue phase imaging which is taken immediately after the first phase and can be performed focusing on multiple regions or the whole body if needed. If the first two phases are positive, this indicates hyperemia, which can be present in both osseous infectious and non-osseous infections or inflammation (i.e., cellulitis). The third phase is the delayed phase or bone phase which is usually performed 3–4 hours after initial injection. This imaging can also focus on multiple areas or whole-body imaging. If the flow, pool, and bone phases all have increased uptake, this can be seen in multiple settings: osseous infection (osteomyelitis), acute fracture, or even a hypervascular malignancy. Patient history is key to making the right diagnosis (10, 11). Single photon emission computed tomography (SPECT) with computed tomography (SPECT/CT) has become immensely helpful in the setting of infection imaging for the single-photon imaging agents. This can help with anatomic localization and further improve the specificity of the findings based on associated CT abnormalities (12–15).

^{18}F-FDG

This is a PET radiopharmaceutical that has been commonly used in the setting of oncologic imaging but has been found to perform remarkably well in the setting of infection, edging out most of the above agents in terms of performance in multiple studies. Fluorodeoxyglucose (FDG) is localized through metabolic trapping; that is, it diffuses across the cell membrane and is phosphorylated like glucose, but due to its structure cannot proceed further down the glycolytic pathway and be metabolized. In the setting of infection, the sites of FDG accumulation are related to migratory inflammatory cells, microorganisms, and granulation tissue (16). Adequate patient preparation before FDG imaging is required, as this molecular imaging agent can have nonspecific uptake which is affected by patient activities including meals or insulin injection, recent exercise, etc Images obtained with PET have a higher spatial resolution than those obtained with single-photon-emitting tracers. Images are usually taken 1 hour after administration of the radiopharmaceutical. Physiological FDG uptake in most normal organs, except the brain, liver, and genitourinary tract, is relatively low, resulting in relatively high target-to-background ratios (Figure 3). If needed, a contrast-enhanced diagnostic-quality CT can add additional information (17–21). PET/MRI is emerging and may offer

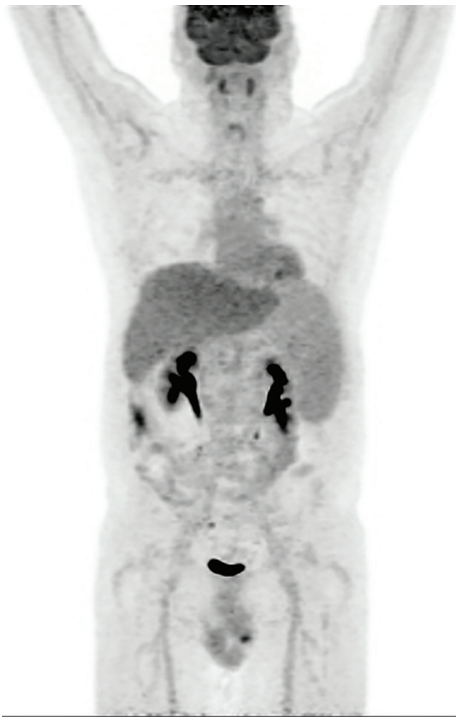

Figure 3 Normal biodistribution of 18F-FDG, but with an enlarged spleen. Note the prominent brain activity, lower-level blood pool activity, more prominent liver activity and physiologic excretion along the urinary tract. Tonsillar, cardiac and bowel activity can be variable.

some advantages over PET/CT. PET/MRI has a lower radiation dose, better co-registration with PET data, and motion correction (22, 23). In addition, MRI has well demonstrated benefits of evaluating soft tissues given its high soft tissue contrast (24). The clinical deployment of these radiopharmaceuticals is summarized in Table 2.

CONCLUSION

Infections are a leading contributor to illness and death globally. Diagnosing infections can be complex, and imaging studies often serve as valuable tools for both confirmation and pinpointing the infection's location. Radiopharmaceuticals, used in conjunction with radiologic imaging, can detect the molecular changes that arise from the interplay between the infection and the body's immune response. Nuclear medicine agents can be directly absorbed by cells, tissues, and

TABLE 2 **Utility of infection imaging by indication (2) (modified from Sethi, et al. Am J Roentgenol. 2019; 213:300-308.)**

Imaging study	OM (not vertebral)	Vertebral OM	Diabetic foot	Orthopedic prosthetic infection	Abd/pelvisinfection	IE	CIDI	FUO
^{67}Ga-citrate	-	+/-	-	-	-	-	-	+/-
3-phase bone scan	+	+	-	+	NA	NA	NA	NA
Labeled leukocytes	+	-	-	+	+ (^{111}In-oxine labeled leukocytes only)	+++	+	+
Labeled leukocytes + SC	NA	NA	+++	++	NA	NA	NA	NA
FDG-PET/CT	++	+++	++	+/-	++	++	+++	+++
MRI	++	+++	++	-	++	+++	+	+
CT	+	+	+	-	++	+	+/-	+

Abbreviations: OM = osteomyelitis, Abd = abdominal, IE = infectious endocarditis, CIDI = cardiac implantable device infection, FUO = fever of unknown origin

Grading system: + = good, ++ = better, +++ = best, +/- = equivocal, - = inadequate study, NA = not applicable

Notes: 1. ^{67}Ga-citrate is falling out of favor due to high radiation dose and suboptimal imaging characteristics. 2. SPECT/CT can be deployed with all single photon molecular imaging for better anatomic localization and enhanced specificity of imaging; it should be added when available.

organs or can be coupled with native substances that are then guided to areas of inflammation. These agents not only illustrate the dynamic physiological changes occurring during an inflammatory response but can also reveal anomalies even before structural alterations become apparent. This chapter has explored various radiopharmaceuticals used in imaging infections. While significant progress has been made, challenges in this field still persist.

Conflict of Interest: The authors declare that they have no potential conflict of interest with respect to research, authorship, and / or publication of this chapter.

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