

ACR–ACNM–SNMMI–SPR PRACTICE PARAMETER FOR THE PERFORMANCE OF NUCLEAR MEDICINE IMAGING OF INFECTION AND INFLAMMATION

The American College of Radiology, with more than 40,000 members, is the principal organization of radiologists, radiation oncologists, and clinical medical physicists in the United States. The College is a nonprofit professional society whose primary purposes are to advance the science of radiology, improve radiologic services to the patient, study the socioeconomic aspects of the practice of radiology, and encourage continuing education for radiologists, radiation oncologists, medical physicists, and persons practicing in allied professional fields.

The American College of Radiology will periodically define new practice parameters and technical standards for radiologic practice to help advance the science of radiology and to improve the quality of service to patients throughout the United States. Existing practice parameters and technical standards will be reviewed for revision or renewal, as appropriate, on their fifth anniversary or sooner, if indicated.

Each practice parameter and technical standard, representing a policy statement by the College, has undergone a thorough consensus process in which it has been subjected to extensive review and approval. The practice parameters and technical standards recognize that the safe and effective use of diagnostic and therapeutic radiology requires specific training, skills, and techniques, as described in each document. Reproduction or modification of the published practice parameter and technical standard by those entities not providing these services is not authorized.

PREAMBLE

This document is an educational tool designed to assist practitioners in providing appropriate radiologic care for patients. Practice Parameters and Technical Standards are not inflexible rules or requirements of practice and are not intended, nor should they be used, to establish a legal standard of care¹. For these reasons and those set forth below, the American College of Radiology and our collaborating medical specialty societies caution against the use of these documents in litigation in which the clinical decisions of a practitioner are called into question.

The ultimate judgment regarding the propriety of any specific procedure or course of action must be made by the practitioner considering all the circumstances presented. Thus, an approach that differs from the guidance in this document, standing alone, does not necessarily imply that the approach was below the standard of care. To the contrary, a conscientious practitioner may responsibly adopt a course of action different from that set forth in this document when, in the reasonable judgment of the practitioner, such course of action is indicated by variables such as the condition of the patient, limitations of available resources, or advances in knowledge or technology after publication of this document. However, a practitioner who employs an approach substantially different from the guidance in this document may consider documenting in the patient record information sufficient to explain the approach taken.

The practice of medicine involves the science, and the art of dealing with the prevention, diagnosis, alleviation, and treatment of disease. The variety and complexity of human conditions make it impossible to always reach the most appropriate diagnosis or to predict with certainty a particular response to treatment. Therefore, it should be recognized that adherence to the guidance in this document will not assure an accurate diagnosis or a successful outcome. All that should be expected is that the practitioner will follow a reasonable course of action based on current knowledge, available resources, and the needs of the patient to deliver effective and safe medical care. The purpose of this document is to assist practitioners in achieving this objective.

¹ *Iowa Medical Society and Iowa Society of Anesthesiologists v. Iowa Board of Nursing*, 831 N.W.2d 826 (Iowa 2013) Iowa Supreme Court refuses to find that the "ACR Technical Standard for Management of the Use of Radiation in Fluoroscopic Procedures (Revised 2008)" sets a national standard for who may perform fluoroscopic procedures in light of the standard's stated purpose that ACR standards are educational tools and not intended to establish a legal standard of care. See also, *Stanley v. McCarver*, 63 P.3d 1076 (Ariz. App. 2003) where in a concurring opinion the Court stated that "published standards or guidelines of specialty medical organizations are useful in determining the duty owed or the standard of care applicable in a given situation" even though ACR standards themselves do not establish the standard of care.

I. INTRODUCTION

This practice parameter was revised collaboratively by the ACR, the American College of Nuclear Medicine (ACNM), the Society of Nuclear Medicine and Molecular Imaging (SNMMI), and the Society for Pediatric Radiology (SPR).

It is intended to guide interpreting physicians in performing nuclear medicine imaging for infection and inflammation. Properly performed imaging with radiopharmaceuticals that localize in inflamed or infected tissue is an effective means of detecting and evaluating many occult or overt inflammatory and infectious conditions. Correlation with clinical findings and/or other imaging modalities is imperative for maximum diagnostic yield.

The reader is referred to these separate practice parameters covering more details on bone and hepatobiliary scintigraphy and neuroinflammation and cardiac sarcoid PET/CT imaging: [ACR–ACNM–SNMMI–SPR Practice Parameter for the Performance of Skeletal Scintigraphy \(Bone Scan\)](#) for osteomyelitis, [ACR–ACNM–SNMMI–SPR Practice Parameter for the Performance of Hepatobiliary Scintigraphy](#) for acute cholecystitis, [ACR–ACNM–ASNR–SNMMI Practice Parameter for Brain PET-CT Imaging in Dementia](#), and [ACR–ACNM–SNMMI–SPR–STR Practice Parameter for the Performance of Cardiac Positron Emission Tomography – Computed Tomography \(PET/CT\) Imaging](#) [1-4].

The application of this practice parameter should be in accordance with the [ACR–ACNM–SNMMI–SPR Practice Parameter for the Use of Radiopharmaceuticals in Diagnostic Procedures](#) [5].

The goal of nuclear medicine imaging for infection and inflammation is to enable the interpreting physician to detect, evaluate, and manage sites of inflamed or infected tissue.

II. INDICATIONS AND CONTRAINDICATIONS

Clinical indications for nuclear medicine imaging of infection and inflammation include, but are not limited to, the following:

1. Fever of unknown origin (FUO)
2. Detection and localization of an unknown source of bacteremia or sepsis
3. Postoperative infections
4. Differentiation of an infection from a tumor
5. Mycobacterial infection (eg, tuberculosis)
6. Opportunistic infection
7. Fungal infection
8. Granulomatous diseases (eg, sarcoidosis)
9. Pulmonary pathologies (may include therapeutic or environmental agents, septic emboli)
10. Bowel pathologies (eg, inflammatory bowel disease, diverticulitis)
11. Cardiovascular pathologies (eg, prosthetic vascular graft, mycotic aneurysms, infective endocarditis involving native and prosthetic valves, cardiac implantable electronic devices, vasculitis)
12. Central nervous system pathologies (eg, encephalitis)
13. Musculoskeletal pathologies (may include infections of disc space, joint space, periprosthetic joint and other orthopedic hardware, osteomyelitis superimposed on existing bone pathology, osteomyelitis in patients with diabetes, and differentiating osteomyelitis from bone infarction, arthritis, sacroiliitis)
14. Renal pathologies (eg, interstitial nephritis, pyelonephritis)

The [ACR–SPR Practice Parameter for Imaging Pregnant or Potentially Pregnant Patients with Ionizing Radiation](#) [6] provides useful information on radiation risks to the fetus regardless of source. Information on managing pregnant or potentially pregnant patients undergoing nuclear medicine procedures is available from the International Commission on Radiological Protection [7,8]. The Advisory Committee on the Medical Uses of Isotopes (ACMUI) Sub-Committee on Nursing Mother Guidelines for the Medical Administration of Radioactive Materials recommends discontinuing breastfeeding for 4 hours after 18F-fluorine-18-2-fluoro-2-deoxy-D-glucose (FDG) administration, 24 hours after technetium-99m–labeled radiopharmaceuticals, 6 days for 111-In leukocytes,

and 28 days after gallium-67 citrate is injected [9]. Milk can be pumped and stored during the discontinuation period for future use as per ACMUI guidelines.

III. QUALIFICATIONS AND RESPONSIBILITIES OF PERSONNEL

See the [ACR–ACNM–SNMMI–SPR Practice Parameter for the Use of Radiopharmaceuticals in Diagnostic Procedures](#) [5].

IV. SPECIFICATIONS OF THE EXAMINATION

The written or electronic request for nuclear medicine imaging of infection and inflammation should provide sufficient information to demonstrate the medical necessity of the examination and allow for its proper performance and interpretation.

Documentation that satisfies medical necessity includes 1) signs and symptoms and/or 2) relevant history (including known diagnoses). Additional information regarding the specific reason for the examination or a provisional diagnosis would be helpful and may at times be needed to allow for the proper performance and interpretation of the examination.

The request for the examination must be originated by a physician or other appropriately licensed health care provider. The accompanying clinical information should be provided by a physician or other appropriately licensed health care provider familiar with the patient's clinical problem or question and consistent with the state's scope of practice requirements. (ACR Resolution 35 adopted in 2006 – revised in 2016, Resolution 12-b)

Radiopharmaceuticals and Imaging

1. FDG

Cellular uptake of FDG is governed by 3 mechanisms: passive diffusion, active transport by an Na- dependent glucose transporter, and via GLUT-1 through GLUT-13 transporters, with the GLUT- 1 through GLUT-13 transporters being the most important pathway in human cells and granulation tissue. Once inside the cell, FDG is phosphorylated by hexokinase to F-18 FDG-6 phosphate but is not metabolized [10].

Images obtained with positron emission tomography (PET) have a distinctly higher spatial resolution than those obtained with single photon emitting radiopharmaceuticals. Results are available within 1–2 hours after radiopharmaceutical administration. Some institutions may also use dual time point imaging in cases to help separate infectious/inflammatory uptake from malignant uptake. Physiologic FDG uptake in most normal organs is quite low (except brain, heart, and urinary tract where uptake is high), resulting in relatively high target-to-background ratios [11]. Under normal conditions, the bone marrow has a low glucose metabolism, potentially facilitating the differentiation of inflammatory or cellular infiltrates from hematopoietic marrow. Compared with infection, degenerative bone changes usually demonstrate only mildly increased FDG uptake. Patients should void immediately before being positioned on the PET/CT table for imaging. In special circumstances, intravenous hydration, diuretic administration, and/or bladder catheterization can be used to reduce radiation burden and artifacts related to accumulated physiologic radiopharmaceutical activity in the ureters and urinary bladder. For adults, the administered activity should be 5–20 mCi (185–740 MBq) of FDG. For children, the administered activity should be determined based on body weight and should be as low as reasonably achievable (ALARA). The typical pediatric range of administered activity of FDG is 0.10–0.14 mCi/kg (3.7–5.2 MBq/kg), with a minimum administered activity of 0.7 mCi (26 MBq) [12]. For additional details about FDG tumor imaging protocols, see the [ACR–ACNM–SNMMI–SPR Practice Parameter for Performing FDG-PET/CT in Oncology](#) [13].

FDG-PET/CT is frequently recommended and used for identification and/or management to include FUO, bacteremia, vasculitis, sarcoidosis, and musculoskeletal infection/inflammation. In many cases, it has become the radiopharmaceutical of choice [14]. The excellent sensitivity of FDG makes this radiopharmaceutical very useful in FUO, an entity with diverse infectious, inflammatory, and malignant etiologies. FDG is useful for detecting infective endocarditis, infections of cardiac implantable electronic devices and prosthetic vascular grafts, mycotic

aneurysms, lung abscesses, and intra-abdominal infections [15-17]. PET/CT can evaluate for septic embolic in cases of known infective endocarditis and for identifying the source and/or extent of infection related to bacteremia [18]. FDG is also useful for diagnosing musculoskeletal infection, especially of the spine [19]. Although FDG-PET/CT is sensitive for the detection of infection and inflammation, its ability to consistently distinguish among infection, inflammation, or tumor may be limited by nonspecific uptake in each of these conditions. The clinical and laboratory data in a specific case should be considered. Tissue sampling may be necessary to provide a definitive diagnosis [20,21].

2. Radiolabeled autologous leukocytes (indium-111 oxine or technetium-99m exametazime)

In vitro labeling of leukocytes is a process that requires isolation of the cells from the patient's blood. This process is performed by separation the leukocytes from plasma, labeling of the cells, resuspension of the labeled cells in plasma, and reinfusion as soon as possible after labeling. Although this process results in a high labeling efficiency, the majority of these labeled leukocytes are neutrophils [22].

It is imperative that the labeled leukocytes (as with any blood product) be administered only to the patient for whom they are intended. There must be a written policy for the handling of radiolabeled blood products to ensure that all samples are positively identified as to source and are administered only to the correct patient.

Labeled leukocyte imaging is useful in patients with FUO (especially when infection is a likely etiology), inflammatory bowel disease, postoperative infections, and cardiovascular infections including infective endocarditis and cardiac implantable electronic device infections. It is also useful for differentiating infection from tumor. It plays a role in musculoskeletal infections, except those involving the spine. Removal of dressings contaminated with wound drainage can reduce false-positive results. The correlation of labeled leukocyte images with bone marrow images, performed with technetium-99m sulfur colloid, improves the accuracy of the examination for diagnosing osteomyelitis [23-26].

Technetium-99m-labeled leukocytes are best suited for use in pediatric patients (due to a lower radiation dose to the spleen than with indium-111-labeled leukocytes) and for imaging acute inflammatory conditions, such as inflammatory bowel disease. Indium-111-labeled leukocytes may be preferable for more indolent conditions, such as periprosthetic joint infection [26].

It should be noted that patients with low leukocyte count might not be suitable for labeled leukocyte imaging because it will preclude adequate labeling. This may result in a suboptimal or nondiagnostic study. The patient's peripheral white blood cell count should be at least 3,000 cells/ μ L (preferably >5,000 cells/ μ L) for proper labeling [22,27].

Additional SPECT or SPECT/CT of relevant sites may also be useful in many cases (to improve localization and to differentiate between physiologic and pathologic uptake etiologies, etc) [23,28,29].

a. Indium-111 oxine-labeled leukocytes

Imaging usually is performed 18–30 hours after reinfusion of the labeled cells. However, the performance of early (1–3 hours) imaging, especially when inflammatory bowel disease is suspected, may be appropriate.

Administered activities of 0.3–0.5 mCi (11.1–18.5 MBq) may be given to adults. The administered activity for children, which should be based on body weight, is 0.0135 mCi/kg (0.25 MBq/kg), with a minimum of 0.06 mCi (2.3 MBq). The usual administered activity of indium-111-labeled leukocytes in children is 0.007–0.0135 mCi/kg (0.15–0.25 MBq/kg) [12].

Advantages of the indium-111 label include a very stable label and a normal biodistribution limited to the liver, spleen, and bone marrow. The 67-hour half-life of indium-111 allows for delayed imaging, which may be valuable for musculoskeletal infection. Complementary bone (technetium-99m methylene diphosphonate) or marrow (technetium-99m sulfur colloid) scintigraphy can be performed while the patient's cells are being labeled, as simultaneous dual radiopharmaceutical acquisitions, or immediately after completion of the indium-labeled leukocyte examination [26]. Disadvantages of the indium label

include less than ideal high photon energies, lower-resolution images, higher patient radiation absorbed doses, and the fact that an 18- to 30-hour interval between reinjection of labeled leukocytes and imaging is generally required [26].

b. Technetium-99m exametazime–labeled leukocytes

Images may be acquired as early as 0.5–3 hours and as late as 24 hours after reinjection of labeled leukocytes. The 6-hour physical half-life of technetium-99m effectively precludes imaging beyond 24 hours [26].

Hydrophilic technetium-99m complexes formed by radiopharmaceutical elution from leukocytes appear in the urinary tract shortly after injection and may appear in a normal bowel on images obtained as early as 3 hours after injection. Activity occasionally also is seen in the normal gallbladder [26].

Administered activity of 5–10 mCi (185–370 MBq) may be given to adults. The administered activity for children, which should be based on body weight, is 0.2 mCi/kg (7.4 MBq/kg), with a minimum of 2 mCi (37 MBq) [12].

Advantages of the technetium-99m label compared with the indium-111 label include a photon energy optimal for gamma camera imaging, higher-resolution images (which improves visualization of small-part anatomy, such as the hands and feet), lower patient radiation exposure, and the ability to detect abnormalities within a few hours after injection [26]. Technetium-99m imaging is also preferred over indium-111 imaging for the evaluation of intra-abdominal infection/inflammatory bowel disease. In this situation, it is imperative to start imaging early enough (30 minutes–2 hours) before physiological radiotracer excretion through the gastrointestinal tract occurs [22,27].

Disadvantages include urinary tract activity, which appears shortly after injection, and bowel activity, which appears by 3–4 hours after injection. The instability of the label and the short half-life of technetium-99m are disadvantages when delayed imaging beyond 24 hours is needed. Patients with musculoskeletal infection often require bone or marrow scintigraphy. When technetium-99m–labeled leukocytes are used, an interval of 48–72 hours is required between the labeled leukocyte and bone or bone marrow scans [25].

3, Gallium-67 citrate

Gallium-67 citrate in the carrier-free state, given intravenously, binds to plasma transferrin and is transported to inflamed and infected tissues where it traverses the porous capillary endothelium. Gallium uptake in infection may depend in part on bacterial uptake as well as macrophage binding and binding to the leukocyte-derived tissue lactoferrin.

A small amount of gallium probably is transported bound to circulating leukocytes. Gallium also accumulates in certain tumors (especially in lymphomas and lung carcinomas) and in traumatized tissue [30]. Gallium may be limited in its ability to distinguish infection from other inflammatory and neoplastic processes [20].

Imaging usually is performed 18–72 hours after radiopharmaceutical administration; however, if appropriate, imaging may be performed as early as 4 hours or as late as 7 days after injection. Imaging at multiple time points may be useful to reduce false-positive and false-negative studies related to bowel and renal activity [30]. Single-photon emission computed tomography (SPECT) and SPECT/CT of relevant sites also may be useful in cases [28].

Administered activities of 4.0–6.0 mCi (150–220 MBq) may be given to adults. The usual administered activity in children is 0.04–0.07 mCi/kg (1.5–2.6 MBq/kg) with a minimum administered activity of 0.25–0.5 mCi (9–18 MBq).

Bowel activity may obscure detail in the abdomen. Preparation of the colon using enemas and/or a mild laxative is of questionable value. For this reason, gallium-67 citrate may not be optimal for patients whose disease is in the abdomen. In patients with diminished plasma transferrin or iron overload, altered biodistribution may occur, resulting in impaired localization of sites of inflammation or infection.

Although gallium-67 citrate is not extensively used currently, it is useful for evaluating the patient with FUO; most opportunistic infections include pneumocystis jiroveci pneumonia and other pulmonary conditions (eg, drug toxicity, sarcoidosis, mycobacterium, early radiation pneumoconiosis, pneumoconioses, idiopathic pulmonary fibrosis, connective tissue disease); discitis/spinal osteomyelitis; skull base osteomyelitis/malignant otitis externa; interstitial nephritis; and vasculitis [31]. Although gallium-67 is superior to radiolabeled leukocytes for discitis/spinal osteomyelitis, tuberculosis, and some bacterial,

fungal, and chronic infections [30], it appears to be less sensitive and specific than FDG-PET/CT for FUO including fever caused by spinal infection. Also, FDG-PET/CT has better spatial resolution and lower radiation exposure and allows for faster imaging compared to gallium-67 [32-34]. Thus FDG-PET/CT is preferable to gallium-67 for most indications.

V. DOCUMENTATION

Reporting should be in accordance with the [ACR Practice Parameter for Communication of Diagnostic Imaging Findings](#) [35].

The report should include the radiopharmaceutical, administered activity, and route of administration as well as any other pharmaceuticals administered, along with dosage and route of administration.

VI. EQUIPMENT SPECIFICATIONS

Equipment performance monitoring should be in accordance with the [ACR–AAPM Technical Standard for Nuclear Medical Physics Performance Monitoring of Gamma Cameras](#) [36].

Please refer to the [ACR–ACNM–SNMMI–SPR Practice Parameter for Performing FDG-PET/CT in Oncology](#) for protocoling for this imaging modality [13].

A gamma camera equipped with a medium-energy collimator is used for imaging gallium-67 and indium-111 leukocytes, ideally with SPECT/CT capabilities. A low-energy, all-purpose/general all-purpose collimator or, preferably, a high-resolution collimator is used with technetium-99m leukocytes. Although a small-field-of-view (SFOV) camera (250–300 mm) may be used, the detector head must be shielded adequately if the radiopharmaceutical used is gallium-67 or indium-111. A large-field-of-view (LFOV) camera (=400 mm) head may be used, especially when imaging a large area of the body. Dual-head gamma cameras are commonly used.

For each of the 3 radiopharmaceuticals, images may be obtained either as multiple spot views or as whole-body surveys. The following techniques are suggested (assuming adult-administered activity):

<u>Gallium-67</u>	<u>SFOV Camera</u>	<u>LFOV Camera</u>
Spot images	50,000-300,000 counts	100,000-500,000 counts
Whole body		5 cm/min (40 min maximum)

SPECT: Data should be acquired for 20 to 25 seconds per angular sampling (50,000-80,000 counts per sample) over a 360° rotation using a 64 × 64 matrix.

<u>Indium-111 leukocytes</u>	<u>SFOV Camera</u>	<u>LFOV Camera</u>
Spot images	30,000-60,000 counts	50,000-100,000 counts
Whole body		5 cm/min (40 min maximum)

SPECT: Because of the low count rate, a dual or multidetector unit is recommended. For the head and body, data should be acquired for 25 to 30 seconds per angular sampling over a 360° rotation, using a 64 × 64 matrix. For the extremities, especially the feet, acquisition time should be increased to 45 to 60 seconds per angular sampling. Iterative reconstructions with collimator corrections specific to indium-111 improve image quality.

<u>Technetium-99m leukocytes</u>	<u>SFOV Camera</u>	<u>LFOV Camera</u>
Spot image	50,000-300,000 counts	100,000-500,000 counts
Whole body		5 cm/min (40 min maximum)

SPECT: Data should be acquired for 30 seconds per angular sampling using a 128 × 128 matrix over a 360° rotation. Iterative reconstruction with collimator corrections specific to technetium-99m, along with scatter and attenuation corrections may improve image quality.

VII. RADIATION SAFETY IN IMAGING

Radiologists, medical physicists, non-physician radiology providers, radiologic technologists, and all supervising physicians have a responsibility for safety in the workplace by keeping radiation exposure to staff, and to society as a whole, "as low as reasonably achievable" (ALARA) and to assure that radiation doses to individual patients are appropriate, taking into account the possible risk from radiation exposure and the diagnostic image quality necessary to achieve the clinical objective. All personnel who work with ionizing radiation must understand the key principles of occupational and public radiation protection (justification, optimization of protection, application of dose constraints and limits) and the principles of proper management of radiation dose to patients (justification, optimization including the use of dose reference levels). https://www-pub.iaea.org/MTCD/Publications/PDF/PUB1775_web.pdf

Facilities and their responsible staff should consult with the radiation safety officer to ensure that there are policies and procedures for the safe handling and administration of radiopharmaceuticals in accordance with ALARA principles. These policies and procedures must comply with all applicable radiation safety regulations and conditions of licensure imposed by the Nuclear Regulatory Commission (NRC) and by applicable state, local, or other relevant regulatory agencies and accrediting bodies, as appropriate. Quantities of radiopharmaceuticals should be tailored to the individual patient by prescription or protocol, using body habitus or other customized method when such guidance is available.

Nationally developed guidelines, such as the [ACR's Appropriateness Criteria](#)[®], should be used to help choose the most appropriate imaging procedures to prevent unnecessary radiation exposure.

Additional information regarding patient radiation safety in imaging is available from the following websites – Image Gently[®] for children (www.imagegently.org) and Image Wisely[®] for adults (www.imagewisely.org). These advocacy and awareness campaigns provide free educational materials for all stakeholders involved in imaging (patients, technologists, referring providers, medical physicists, and radiologists).

Radiation exposures or other dose indices should be periodically measured by a Qualified Medical Physicist in accordance with the applicable ACR Technical Standards. Monitoring or regular review of dose indices from patient imaging should be performed by comparing the facility's dose information with national benchmarks, such as the ACR Dose Index Registry and relevant publications relying on its data, applicable ACR Practice Parameters, NCRP Report No. 172, Reference Levels and Achievable Doses in Medical and Dental Imaging: Recommendations for the United States or the Conference of Radiation Control Program Director's National Evaluation of X-ray Trends; 2006, 2009, amended 2013, revised 2023 (Res. 2d).

VIII. QUALITY CONTROL AND IMPROVEMENT, SAFETY, INFECTION CONTROL, AND PATIENT EDUCATION

Policies and procedures related to quality, patient education, infection control, and safety should be developed and implemented in accordance with the ACR Policy on Quality Control and Improvement, Safety, Infection Control, and Patient Education appearing under the heading *Position Statement on QC & Improvement, Safety, Infection Control, and Patient Education* on the ACR website (<https://www.acr.org/Advocacy-and-Economics/ACR->

[Position-Statements/Quality-Control-and-Improvement](#)).

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