Society of Nuclear Medicine Procedure Guideline for ^{111}In-Leukocyte Scintigraphy for Suspected Infection/Inflammation

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I. Purpose

The purpose of this guideline is to assist nuclear medicine practitioners in recommending, performing, interpreting, and reporting the results of ^{111}In-labeled leukocyte (^{111}In-leukocyte) scintigraphy.

II. Background Information and Definitions

^{111}In-leukocyte scintigraphy is a diagnostic imaging test that displays the distribution of radiolabeled leukocytes in the body. Regional, whole-body, planar, and/or SPECT scintigrams of specific anatomic regions are obtained for suspected infection/inflammation.

In osteomyelitis, regional or whole-body bone scintigraphy may be used in conjunction with ^{111}In-leukocyte scintigraphy to detect sites of abnormal bone remodeling. Bone marrow scintigraphy using ^{99m}Tc-sulfur colloid can be a useful adjunct to assess marrow distribution at suspected osteomyelitis sites, particularly when the site is adjacent to orthopedic hardware and the neuropathic joint. Gallium scintigraphy is usually preferred in patients with (a) neutropenia or (b) nonsuppurative or lymphocyte-mediated infections. ^{99m}Tc-HMPAO (exametazime)-labeled leukocyte scintigraphy is a frequently used option for acute infections, particularly in pediatric patients.

III. Examples of Clinical or Research Applications

A. To detect sites of infection/ inflammation in patients with fever of unknown origin.
B. To localize an unknown source of sepsis and to detect additional site(s) of infection in patients with persistent or recurrent fever and a known infection site.
C. To survey for site(s) of abscess or infection in a febrile postoperative patient without localizing signs or symptoms. Fluid collections, ileus, bowel gas, fluid, and/or healing wounds reduce the specificity of CT and ultrasound.
D. To detect site(s) and extent of inflammatory bowel disease. ^{99m}Tc-labeled leukocytes may be preferable for this indication.

E. To detect and follow up osteomyelitis primarily when there is increased bone remodeling secondary to joint prostheses, nonunited fractures, or sites of metallic hardware from prior bone surgery.
F. To detect osteomyelitis in diabetic patients when degenerative or traumatic changes, neuropathic osteoarthropathy, or prior osteomyelitis have caused increased bone remodeling.
G. To detect osteomyelitis involving the skull in postoperative patients and for follow-up of therapy.
H. To detect mycotic aneurysms, vascular graft infections, and shunt infections.

IV. Procedure

A. Patient Preparation

Patients must be able to cooperate for whole-body or regional images, which may require 30–60 min for completion. No special preparation for the test is needed.

B. Information Pertinent to Performing the Procedure

Coordination of this procedure with the referring physician is essential. Clinical history and the results of prior tests are helpful, including: any history of surgery or trauma; the presence and location of surgical drains, skin or soft-tissue infection, and intravenous administration sites; and the presence of nasogastric and/or ostomy (tracheostomy, colostomy, feeding gastrostomy, etc.) tubes. Bone radiographs and other imaging studies may be very helpful in assessing the cause of abnormal ^{111}In-leukocyte localization in bone.

C. Precautions

Procedures and quality assurance for correct identification of patients and handling blood products are essential. The labeled leukocytes should be reinjected as soon as possible and preferably within 1–2 h after labeling. Use of central intravenous lines requires strict sterile technique.

D. Radiopharmaceutical

1. Leukocytes are obtained from 40–80 mL of venous blood in adults. In children, the amount of blood depends on patient size and circulating leukocyte count. The minimum volume of blood obtained is 10–15 mL. Circulating granulocyte counts should be a minimum of 3×10^6 cells/mL. Whole blood is normally obtained by direct venipuncture and mixed immediately with acid citrate dextrose or heparin. Leukocytes are labeled with ^{111}In-oxine by means of a variety of accepted methods.
2. Cell labeling should be performed by trained laboratory personnel and is performed in a laminar flow hood using sterile procedures. Care must be taken to ensure correct identification of patients and blood products. All patient and laboratory procedures should have an appropriate quality control program.
3. The radiolabeled leukocytes are administered via intravenous injection. A large-bore butterfly needle (18–20 gauge) is suggested. If an existing intravenous line is used for infusion, it should be flushed with normal saline before and after injection. Dextrose in water solutions should not be used, because these can cause clumping of labeled cells.
4. Radiolabeled leukocytes should be administered within 1–2 h of cell labeling. Labeled cells stored longer than 3 h have a significant loss of cell viability. Temperatures higher than 70°F tend to increase cell damage and should be avoided.
5. In adults, the administered activity is in the range of 10–20 MBq (0.3–0.5 mCi), and up to 40 MBq (1 mCi) is suggested in large patients. Doses are decreased in pediatric patients to 0.15–0.25 MBq/kg (0.007–0.0135 mCi/kg). Minimum administered activity is 1.85–2.3 MBq (0.05–0.06 mCi) and maximum administered activity is 18.5 MBq (0.5 mCi).
6. In adults, the injected ^{99m}Tc-sulfur colloid dose is in the range of 300–370 MBq (8–10 mCi) and 740–925 MBq (20–25 mCi) for ^{99m}Tc-diphosphonate.

E. Image Acquisition

1. Images are acquired at varying times depending upon the clinical situation, usually 1–4 or 16–30 h after injection. Delayed images should be obtained if the early images are negative. Planar images are usually acquired for 10–15 min. Imaging times of 15–20 min or longer may be needed in low count regions (e.g., distal limb in osteomyelitis).
2. Planar images are usually obtained using a large-field-of-view gamma camera, fitted with a medium-energy collimator. Energy windows of 15%–20% are centered over the 173- and 247-keV ^{111}In photopeaks.
3. Whole-body scans are acquired using single or dual large-field-of-view detector(s). Scanning times vary with the type of equipment but are generally 25–35 min (rate of 5–6 cm/min).
4. ^{99m}Tc-sulfur colloid imaging is usually performed after ^{111}In-leukocyte imaging if there is a question concerning bone marrow distribution. Imaging is delayed 30 min after injection, allowing sufficient time for satisfactory clearance of blood pool activity.

Radiation Dosimetry: Adults

Radiopharmaceuticals	Administered activity MBq (mCi)	Organ receiving the largest radiation dose mGy/MBq (rad/mCi)	Effective dose equivalent mSv/MBq (rem/mCi)
^{111}In-leukocytes [1]	10–18.5 iv (0.3–0.5)	5.5 Spleen (20)	0.59 (2.2)
^{99m}Tc-sulfur colloid [2]	300–370 iv (8–10)	0.077 Spleen (0.28)	0.014 (0.052)

[1] International Commission on Radiological Protection. *Radiation Dose to Patients from Radiopharmaceuticals.* ICRP Publication 53. London, UK: ICRP; 1988:256; normal liver.

[2] International Commission on Radiological Protection. *Radiation Dose to Patients from Radiopharmaceuticals.* ICRP Publication 53. London, UK: ICRP; 1988:180; normal liver.

Radiation Dosimetry: Children (5 Years Old)

Radiopharmaceuticals	Administered activity MBq/kg (mCi/kg)	Organ receiving the largest radiation dose mGy/MBq (rad/mCi)	Effective dose equivalent mSv/MBq (rem/mCi)
^{111}In-leukocytes [1]	0.15–0.25 iv (0.004–0.007)	17 Spleen (63)	1.8 (6.7)
^{99m}Tc-sulfur colloid [2]	4.0–5.3 iv (0.10–0.15)	0.25 Spleen (0.93)	0.041 (0.15)

[1] International Commission on Radiological Protection. *Radiation Dose to Patients from Radiopharmaceuticals.* ICRP Publication 53. London, UK: ICRP; 1988:256; normal liver.

[2] International Commission on Radiological Protection. *Radiation Dose to Patients from Radiopharmaceuticals.* ICRP Publication 53. London, UK: ICRP; 1988:180; normal liver.

a. Planar images of involved sites are obtained to assess pattern of bone marrow uptake.
b. Corresponding views of contralateral regions are useful for comparison.
c. A gamma camera fitted with a medium-energy collimator and a 15%–20% energy window over the ^{99m}Tc photopeak are used.
d. Ten-minute regional views are usually satisfactory (counts will vary depending on the region of interest).
e. Image intensity is adjusted to provide images comparable with ^{111}In-leukocyte images to facilitate comparison of relative uptake at sites of suspected infection.
f. Combined or simultaneous ^{99m}Tc-sulfur colloid/^{111}In-leukocyte scans can be obtained with additional views in difficult cases.

5. Simultaneous ^{111}In-leukocyte/^{99m}Tc-diphosphonate bone images can be obtained using a gamma camera that can acquire and discriminate the 140-keV ^{99m}Tc photons from the ^{111}In photons. Each ^{111}In-leukocyte/^{99m}Tc bone image is acquired using a medium-energy collimator for 50,000 counts in the ^{111}In window

or for 15 min, 4 h, and/or 16–30 h after injection of the ^{111}In-leukocytes.

a. A 15% window at the 140-keV ^{99m}Tc peak and a 15% window at the 247-keV ^{111}In photopeak are used if the ^{99m}Tc dose is injected on day 1 before ^{111}In-leukocyte imaging. Many centers also use a 10% or 15% window at the 173-keV ^{111}In photopeak for delayed ^{111}In-leukocyte images obtained on day 2 (18–30 h) after the ^{99m}Tc dose has been injected.
b. Combined images can also be obtained with older cameras that can acquire only 1 radioisotope at a time. Using a medium-energy collimator, a 10% window at the 140-keV ^{99m}Tc peak is used for a 5-min or 400,000-count bone image. Without moving the patient or camera, the window is changed to a 15%–20% window at the 247-keV ^{111}In peak, and a 50,000-count or 15-min ^{111}In-leukocyte image is acquired.

6. For the appendicular skeleton and other sites, such as the pelvis, hips, and calvarium, simultaneous ^{111}In-leukocyte/^{99m}Tc-sulfur colloid or ^{111}In-leukocyte/^{99m}Tc-diphosphonate SPECT imaging can be obtained to better assess the extent of bone or bone marrow involvement and to help differentiate soft-tissue from bone uptake. For evaluation of hip prostheses, ^{111}In-leukocyte/^{99m}Tc-sulfur colloid is superior to ^{111}In-leukocyte/^{99m}Tc-diphosphonate bone imaging in most cases.
   a. ^{111}In-leukocyte/bone SPECT scans are best obtained using dual- or triple-detector systems equipped with medium-energy collimators. The images are acquired in dual-isotope mode using the window settings as described previously in section IV.E.5.a.
   b. For 3-detector systems, projection images from the ^{99m}Tc and ^{111}In energy windows are obtained over 20–30 min (See the Society of Nuclear Medicine Procedure Guideline for General Imaging).

F. Interventions

In patients with suspected infected joint prostheses, aspiration of the involved joint should be avoided during the interval between injection and imaging to avoid bleeding and removal of localized ^{111}In-leukocyte activity.

G. Processing

See the Society of Nuclear Medicine Procedure Guideline for General Imaging for details.

H. Interpretation Criteria

Accurate interpretation of labeled leukocyte scintigraphy requires knowledge of the normal and abnormal variants of leukocyte localization.

1. Normal Findings
   ^{111}In-leukocyte distribution at 18–24 h is primarily confined to the reticuloendothelial system of the liver, spleen, bone marrow, and minimal activity in major blood vessels. No bowel or bladder activity is present. On images performed up to 4 h after injection, diffuse pulmonary activity is normally seen.
2. Inflammatory Bowel Disease
   a. Images obtained 0.5–1 and 2–3 h after injection are necessary to accurately assess the site(s) and extent of bowel involvement.
   b. Inflammatory bowel disease shows early regional or diffuse bowel localization with progression of activity along the bowel lumen over time as a result of ^{111}In-leukocyte accumulation. There is good correlation with site and inflammation activity index. Note: 99mTc-labeled leukocytes are preferred for evaluation of inflammatory bowel disease.
3. Abscess Detection
   One-third to one-half of sites are visualized by 4 h after injection and more than 90% of sites by 24 h. Uptake is usually equal to or greater than liver activity.
4. Osteomyelitis
   Focal ^{111}In-leukocyte accumulation that is greater than adjacent or contralateral background activity and corresponds to a bone site or, more specifically, to a site of increased bone radiopharmaceutical accumulation (but does not have to be of the same intensity) is indicative of osteomyelitis.
   a. In the presence of orthopedic hardware or prostheses, normal bone marrow is disrupted and displaced, making interpretations difficult in these regions. Comparison of ^{111}In-leukocyte localization with ^{99m}Tc-sulfur colloid uptake using combined or sequential ^{111}In-leukocyte/^{99m}Tc-colloid images is often necessary. Comparison with adjacent or contralateral regions can also be helpful.
   b. ^{111}In-leukocyte uptake is typically increased in the vicinity of infected orthopedic hardware and normal or decreased (as a result of displaced marrow) in the presence of normal or loose but noninfected prostheses. Infection is likely when there is abnormal ^{111}In-leukocyte localization without corresponding ^{99m}Tc-sulfur colloid bone marrow activity (discordant activity).
   c. Comparison with radiographs is often very helpful.

d. For SPECT images, a diagnosis of osteomyelitis is indicated when abnormal focal ^{111}In-leukocyte localization corresponds to abnormal bone uptake on 2 or more adjacent 6–8-mm tomographic slices and is identified in at least 1 plane. Soft-tissue infection is likely if the ^{111}In-leukocyte localization does not correspond to abnormal bone tracer uptake.

I. Reporting

The report should include the following information:

1. Indication for the study
2. Procedure
   a. Dose of radiopharmaceutical
   b. Time(s) of acquisition after injection
   c. Type of images (total body, regional, SPECT)
3. Findings
   a. Site(s) of abnormal localization
   b. Degree of localization compared with liver, bone, or bone marrow uptake and whether it increased over time if delayed images were obtained
4. Study limitations or confounding factors
5. Impression (e.g., positive, negative, indeterminate)
   a. The clinical significance of the findings
   b. If appropriate, differential clinical diagnoses

J. Quality Control

1. The labeling efficiency of ^{111}In-leukocytes may be determined by recentrifugation (approximately 450 g for 5 min) of the labeled leukocytes once they have been washed and resuspended in 5 mL of buffered saline. The supernatant is poured into a separate counting tube, and the leukocyte pellet is resuspended in 5 mL of cell-free plasma. Each tube is then counted in a dose calibrator. Labeling efficiency = (resuspended ^{111}In-leukocyte activity) / [(resuspended ^{111}In-leukocyte activity) + (supernatant activity)].
2. Leukocyte clumping may be checked by looking at a drop of ^{111}In-leukocyte suspension placed on a hemocytometer slide and viewing it under a microscope under low and medium power. There should be very little clumping present.
3. A rough estimate of the number of cells labeled can be made by visual examination of a representative sample on a hemocytometer slide. The average number of cells per 50-micron (small) square is then determined.
   No. cells/cm^3 (mL) = average number of cells/small square × (2×10^6).

K. Sources of Error

1. Potential causes for focal ^{111}In-leukocyte soft-tissue localization other than infection: intravenous line localization, accessory spleen, acute bleeds, hematomas, inflammatory response to foreign body, neoplasm, localized bile collections, bowel inflammation, endometritis, vaginitis, myositis ossificans, bladder catheters, nasogastric and tracheostomy tubes, and recent infarcts. Rare cases of false-positive ^{111}In-leukocyte scans caused by increased numbers of labeled platelets have been reported.
2. Potential causes of false-negative ^{111}In-leukocyte studies: chronic abscess more than 3 wk of age, lymphocytic mediated infection (tuberculosis, sarcoidosis, granulomatous process, viral infection, etc.), hepatic or splenic abscesses, abscess adjacent to the liver or spleen, low-grade or chronic osteomyelitis, especially in the central skeleton, such as vertebral osteomyelitis. False-negative scans for detection of osteomyelitis can occur when the patient is imaged after being on intravenously administered antibiotics for several weeks. If intravenous antibiotics have been stopped for 2–4 wk before imaging, a false-negative scan is not likely to occur.
3. Bowel ^{111}In-leukocyte localization not caused by infection: irritative bowel lesion(s) such as stomas or from multiple enemas, gastrointestinal bleeding or infarction, fistula to bowel from an adjacent abscess, swallowed labeled cells (bronchitis, sinusitis, pneumonia).
4. Noninfectious causes of ^{111}In-leukocyte bone/joint localization: active rheumatoid or traumatic/degenerative arthritis, gouty arthritis, acute fractures (less than 2 mo), traumatic or neuropathic arthropathy, acute bone infarcts, foreign body reaction. Rarely neoplasms such as lymphoma, adjacent soft tissue inflammation such as myositis, or active heterotopic bone formation can cause ^{111}In-leukocyte uptake.
5. Errors in interpretation in suspected osteomyelitis cases can be minimized by obtaining ^{99m}Tc-sulfur colloid marrow studies in cases where ^{111}In-leukocyte images are indeterminate (neither clearly positive nor negative).
   a. Concordant ^{111}In-leukocyte and ^{99m}Tc-sulfur colloid marrow uptake is normal, whereas a discordant pattern, with ^{111}In- leukocyte uptake without corresponding marrow uptake, is highly suspicious for infection.
   b. Simultaneous acquisition of ^{111}In-leukocyte/^{99m}Tc-diphosphonate bone images helps distinguish adjacent soft-tissue in-

fection from bone infection, increasing the specificity for osteomyelitis.

6. Extensive soft tissue surrounding bone may give the appearance of underlying bone involvement. (In this circumstance SPECT may be helpful.)
7. If a 20–30-mCi dose of ^{99m}Tc bone tracer is injected on the same day as the ^{111}In-leukocyte images, the intense ^{99m}Tc activity can produce photon overload in the lower ^{111}In window, which may cause a corresponding false-positive focus. Use of the lower ^{111}In window should be avoided if ^{99m}Tc bone tracer is injected just before ^{111}In-leukocyte imaging. Similarly, on the delayed images, intense ^{111}In activity may scatter into the ^{99m}Tc window. The contribution that scatter makes to the final image varies from camera to camera and should be evaluated.
8. False-positive scan interpretations can occur in patients with very active soft-tissue infection adjacent to a thin and/or relatively vascular bone, such as the maxilla, mandible, or pelvis.
9. Causes for abnormally decreased ^{111}In-leukocyte accumulation:
   a. Osteomyelitis of the spine will often appear as focal decreased uptake compared with adjacent bone marrow.
   b. Decreased uptake can also be seen in severely hypovascular/avascular sites (e.g., cysts). Implants (e.g., prostheses and pacemakers) can also have this appearance.

V. Issues Requiring Further Clarification

A. Relative efficacy of gallium, ^{99m}Tc-leukocyte, ^{99m}Tc-fanolesomab and ^{111}In-leukocyte scintigraphy in different clinical settings.

VI. Concise Bibliography

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